Aspirin as an Adjunct to Screening for Prevention of Sporadic Colorectal Cancer

A Cost-Effectiveness Analysis

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Background: **Aspirin may decrease colorectal cancer incidence, but its role as an adjunct to or substitute for screening has not been evaluated.**

Objective: **To examine the potential cost-effectiveness of aspirin chemoprophylaxis in relation to screening.**

Design: **Markov model.**

Data Sources: **Literature on colorectal cancer epidemiology, screening, costs, and aspirin chemoprevention (1980–1999).**

Target Population: **General U.S. population.**

Time Horizon: **50 to 80 years of age.**

Perspective: **Third-party payer.**

Intervention: **Aspirin therapy in patients screened with sigmoidoscopy every 5 years and fecal occult blood testing every year (FS/FOBT) or colonoscopy every 10 years (COLO).**

Outcome Measures: **Discounted cost per life-year gained.**

Results of Base-Case Analysis: **When a 30% reduction in colorectal cancer risk was assumed, aspirin increased costs and decreased life-years because of related complications as an adjunct to FS/FOBT and cost $149 161 per life-year gained as an adjunct to COLO. In patients already taking aspirin, screening with FS/FOBT or COLO cost less than $31 000 per life-year gained.**

Results of Sensitivity Analysis: **Cost-effectiveness estimates depended highly on the magnitude of colorectal cancer risk reduction with aspirin, aspirin-related complication rates, and the screening adherence rate in the population. However, when the model's inputs were varied over wide ranges, aspirin chemoprophylaxis remained generally non–cost-effective for patients who adhere to screening.**

Conclusions: **In patients undergoing colorectal cancer screening, aspirin use should not be based on potential chemoprevention. Aspirin chemoprophylaxis alone cannot be considered a substitute for colorectal cancer screening. Public policy should focus on improving screening adherence, even in patients who are already taking aspirin.**

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Colorectal cancer is the second leading cause of cancer-related death in the United States, with 129 400 new cases and 56 600 deaths estimated to have occurred in 1999 (1). Most cases of colorectal cancer arise from adenomatous polyps (2). Screening has been shown to decrease colorectal cancer incidence and mortality rates (3, 4), and various decision analyses support its cost-effectiveness (5–10). Despite demonstrated clinical and economic benefits, however, use of screening tests is low (11–13). In a large population-based study, 19.8% of respondents reported having fecal occult blood testing during the preceding year and 30.4% reported having sigmoidoscopy–proctoscopy during the preceding 5 years; 9.5% had had both tests (13).

In a national strategy to decrease the burden of colorectal cancer, aspirin chemoprevention is a potentially powerful adjunct to screening. Numerous case–control (14–21) and cohort studies (22–26) support the hypothesis that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the incidence of colorectal adenoma and colorectal cancer and the mortality rate from colorectal cancer by 30% to 65%. Many animal models show that NSAIDs have an antitumor effect in the colon (27). However, the Physicians' Health Study, a randomized study of male physicians that was not designed to examine colorectal cancer specifically, found no decrease in colorectal cancer incidence when 325 mg of aspirin on alternate days was compared with placebo (28). These results may conflict because of the specific dose and duration used and the patients studied.

Aspirin is of proven benefit in secondary prevention of cardiovascular morbidity and death (29) and in primary prevention of myocardial infarction in men (30). However, its use for primary cardiovascular prevention remains controversial, in part because mortality preven-

tion is unproven and no randomized studies in women exist (29). Although it is well recognized that aspirin may cause major complications (30–35), prophylactic aspirin is prescribed on the basis of cardiovascular considerations. In contrast, aspirin is unlikely to be prescribed for colorectal cancer prevention until better estimates of its benefits and risks become available.

Since such data are unlikely to be available for the general U.S. population in the near future, we constructed a decision analytic model to explore the incremental clinical and economic effects of aspirin when it is added to an accepted screening program for sporadic colorectal cancer. Accepted screening programs consisted of flexible sigmoidoscopy every 5 years and yearly fecal occult blood testing (FS/FOBT) (8, 36) or screening colonoscopy every 10 years (COLO), an emerging alternative screening strategy (7–10, 37). Our primary aim was to clarify whether aspirin chemoprevention might prove to be a cost-effective adjunct to screening. In secondary analyses, we examined the potential role of aspirin chemoprevention in an unscreened population and the effects of screening when added to existing aspirin use.

METHODS

Literature Review

We searched MEDLINE from 1980 to 1999 for English-language literature that provided data on colorectal cancer, screening, aspirin chemoprevention, and aspirin-related complications. Model inputs were based on the literature search and on rigorous literature reviews by a multidisciplinary expert panel from the Agency for Health Care Policy and Research (8) and by the Office of Technology Assessment (7) (**Table 1**).

Decision Analytic Model

We created a Markov model using DATA 3.0 (TreeAge Software Inc., Williamstown, Massachusetts); Excel 2000 (Microsoft Corp., Redmond, Washington) was used for analysis. The Markov model estimated the clinical and economic consequences of six strategies: natural history (no aspirin or screening), FS/FOBT, COLO, aspirin alone (ASA), FS/FOBT and aspirin (FS/FOBT/ASA), and colonoscopy and aspirin (COLO/ASA). Beginning at 50 years of age, patients progressed through the model for 30 1-year cycles; principal states were normal, polyp, cancer (localized, regional, or distant), and dead. The Markov model is discussed in detail in the Appendix. To reflect the effect of aspirin in the general population and not in an individual, we varied the percentage of persons in the population who adhered to screening. Using population-based data (13), we selected a screening adherence rate of 25% to reflect current practice. The general population, men, and women were examined separately.

Natural History of Sporadic Colorectal Cancer

We constructed a model of the natural history of sporadic colorectal cancer in patients at average risk for the disease. Epidemiologic data on colorectal cancer were derived from the Surveillance, Epidemiology, and End Results (SEER) program (38). According to results of autopsy studies, adenomatous polyp prevalence was assumed to increase from 15% at 50 years of age to 47% at 75 years of age (16% to 54% in men; 15% to 40% in women) (39–41). We assumed that 90% of tumors develop from polyps and that cancer progresses from localized to regional (2 years in each state) to disseminated, with symptomatic presentation by stage as reflected in SEER data. Age-specific transition probabilities were calculated between normal, polyp, and cancer to yield polyp and cancer rates derived from the literature. Age-specific non–colorectal cancer mortality rates were derived from U.S. life tables (46).

Effect of Colorectal Cancer Screening

We selected FS/FOBT as an accepted strategy endorsed by published guidelines (8, 36). In the model, any positive test result was followed by colonoscopy and, if necessary, polypectomy. If the results of colonoscopy were normal, screening resumed in 10 years. After an adenoma was detected, surveillance colonoscopy was performed every 5 years. Although specific patients with high-risk or low-risk adenomas may undergo surveillance at different intervals, we chose 5 years to reflect the average surveillance interval for the population. Colonoscopy was performed at cancer diagnosis and 3 years and every 5 years thereafter (8). As long as results of screening tests remained negative, FS/FOBT was continued.

Emerging data from clinical studies and decision analyses suggest that colonoscopy is a cost-effective screening tool (7–10, 37). Therefore, COLO was examined as an alternative screening strategy. In the model, colonoscopy was performed every 10 years as long as no

Table 1. **Inputs in the Cost-Effectiveness Model**

Variable	Base-Case Value (Range)*	References
Clinical		
Colorectal cancer incidence without adenoma per 100 000 person-years†	Age and gender-specific, 6–86	7, 38–41
Colorectal cancer incidence with adenoma per 100 000 person-years†	Age and gender-specific, 299–876	7, 38–41
Symptomatic presentation of localized cancer, %†	22/y over 2 y	38
Symptomatic presentation of regional cancer, %†	40/y over 2 y	38
Mortality rate from treated localized cancer, %†	1.74/y in first 5 y	38
Mortality rate from treated regional cancer, %†	8.6/y in first 5 y	38
Mean survival with distant cancer, *y*†	1.9	38
Mortality rate from cancer treatment, %	2	7, 8
Fecal occult blood test sensitivity for cancer, %	40 (30–60)	7, 8
Fecal occult blood test sensitivity for polyp, %	10 (5–15)	7, 8
Fecal occult blood test specificity, %‡	92 (87–97)	7, 8
Polyps or cancer within reach of sigmoidoscope, %	50	7, 8
Sigmoidoscopy sensitivity for polyp or cancer within reach of sigmoidoscope, %	90 (80–95)	7, 8
Colonoscopy sensitivity for polyp, %	90 (85–95)	7, 8
Colonoscopy sensitivity for cancer, %	95 (90–97)	7, 8
Sigmoidoscopy specificity, %	95 (90–99)	7, 8
Colonoscopy major complication rate, %	0.1 (0.05–0.5)	7, 8
Sigmoidoscopy major complication rate, %	0.01 (0.005–0.02)	7, 8
Colonoscopy mortality rate, %	0.01 (0.005–0.03)	7, 8
Sigmoidoscopy mortality rate, %	0.001 (0.0005–0.002)	7, 8
Reduction in colorectal cancer incidence with aspirin, %	30 (5–55)	14–26
Rate of major aspirin-related complication per 10 000 person-years		30–35
Persons <65 y	2 (0.5–5)	
Persons ≥65 y	16 (4–40)	
Mortality rate given major aspirin-related complication, %	5 (2–8)	42–44
Cost, *$*		
Fecal occult blood testing	10 (5–15)	8
Flexible sigmoidoscopy	206 (76–336)	Medicare
Flexible sigmoidoscopy with biopsy	377 (165–589)	Medicare
Colonoscopy	623 (288–958)	Medicare
Colonoscopy with biopsy	901 (433–1369)	Medicare
Endoscopy complication	24 000 (18 000–30 000)	45
Colorectal cancer care by stage		8
Localized	24 000 (14 000–34 000)	
Regional	31 000 (21 000–41 000)	
Distant	40 000 (30 000–50 000)	
Aspirin per person-year	4 (2–6)	–§
Major aspirin complication	15 000 (10 000–20 000)	45

* Range in the Monte Carlo analysis.
† Derived from epidemiologic data in references, assuming 90% of cancer cases arise from adenomas.
‡ Specificity = (1 − false-positive rate in persons without polyp or cancer).
§ Retail cost at University of Michigan pharmacy, Ann Arbor, Michigan.

adenoma or cancer was detected. Surveillance after adenoma detection was the same as that described for FS/FOBT.

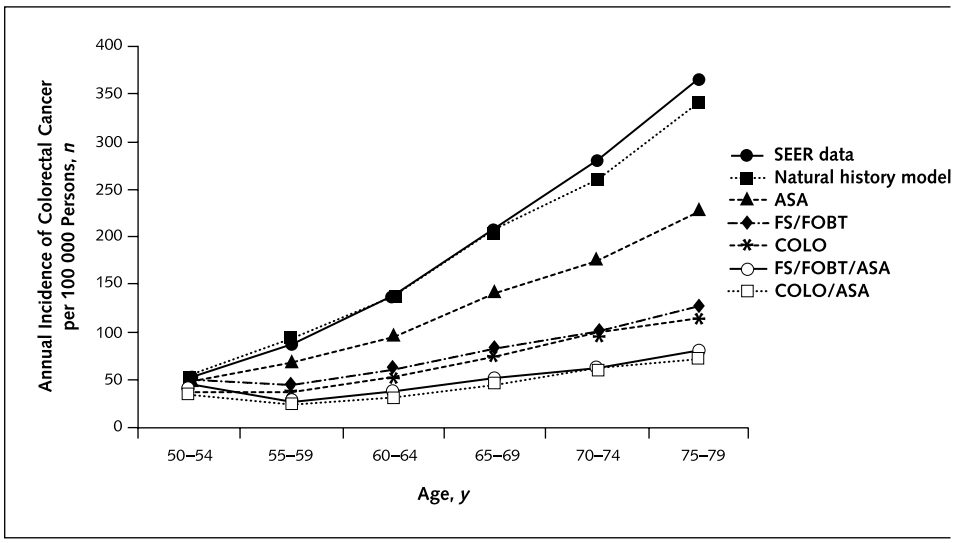
Effect of Aspirin

Aspirin, 325 mg/d, was added to the screening and natural history strategies. In the base case, aspirin was estimated to reduce colorectal cancer risk by 30% through equal reductions in adenoma incidence and progression to cancer (14–26).

Aspirin may increase occult gastrointestinal blood loss (47–53), which could affect the FS/FOBT strategy. In the base case, we assumed that aspirin did not affect fecal occult blood testing because increases in blood loss have been reported only with high doses (48–53) and low doses have been reported to have no effect on fecal occult blood testing (54–56). The protective effect of NSAIDs is not explained by earlier detection of adenomas or cancer (19, 26); however, increased sensitivity and decreased specificity of FS/FOBT in patients receiving aspirin were assessed in the sensitivity analysis.

In the model, aspirin-related complications were followed by aspirin withdrawal and return to baseline risk for colorectal cancer. Using data from trials of low-

Figure 1. **Colorectal cancer incidence by age.**



The natural history model closely reproduces data from the Surveillance, Epidemiology, and End Results (*SEER*) program. In the model, aspirin chemoprevention, colorectal cancer screening, and screening and aspirin combined led to progressively lower cancer rates. ASA = aspirin; COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.

dose aspirin, we calculated rates of excess serious complications in patients taking aspirin. The rates were 1.4 per 10 000 person-years in patients younger than 65 years of age and 28 to 40 per 10 000 person-years in older patients with cerebrovascular disease (30, 32–34). The 1-year prevalence of serious gastrointestinal NSAID-related complications is estimated to increase eightfold after 65 years of age (31). Thus, we selected a base-case rate of 2 per 10 000 person-years before 65 years of age and 16 per 10 000 person-years thereafter for serious aspirin-related complications. We modeled mortality rates of 2% to 8% after a serious aspirin-related complication (42–44).

We did not include changes in cardiovascular outcomes in the base case for several reasons. First, the role of aspirin in primary cardiovascular prevention is controversial, largely because prevention of death is unproven (29). A recent decision analysis suggested that aspirin may be harmful in cohorts at low risk for cardiovascular events and may be only minimally beneficial as risk increases (57). Second, aspirin may increase the incidence of hemorrhagic stroke (30), and the balance of risks and benefits is unknown, particularly in women (29). Third, in patients with cardiovascular indications for aspirin, a potential effect on colon cancer is unlikely to affect prescribing decisions. Thus, we chose to examine the incremental benefit of colorectal cancer screening in a population already receiving aspirin. In the sensitivity analysis, we examined the effect of aspirin by assuming that it reduced cardiovascular mortality. Cardiovascular death accounts for 30% to 42% of deaths, depending on age (46).

Costs

Procedure costs were derived from Medicare fee schedules and include professional fees and median procedure reimbursement. We used the wholesale cost of aspirin at the University of Michigan pharmacy, Ann Arbor, Michigan. Complication costs were derived from relevant diagnostic related groups (45). Costs for care of stage-specific colon cancer were taken from reports to the National Cancer Institute (7). All costs are in 1998 U.S. dollars (**Table 1**).

Outcomes

Colorectal cancer cases by stage, deaths by cause, average life-years after age 50 years, total costs, and itemized costs were determined for each strategy. Costs and life-years were discounted at an annual rate of 3% (58).

If one strategy afforded more life-years than another at higher expense, an incremental cost-effectiveness ratio was calculated, yielding cost per life-year saved. Sensitiv-

ity analysis was performed by using two methods. First, in a Monte Carlo simulation (DATA 3.5.7, TreeAge Software, Inc.), many inputs were varied simultaneously and randomly for 3500 iterations, yielding estimates for the variability in cost-effectiveness ratios that arises when variables in the model are allowed to take on distributions (Appendix). Variable ranges are shown in **Table 1**. Second, systematic sensitivity analyses were performed on the model's inputs. The results are shown only for the critical variables whose values significantly affected the results.

Role of the Funding Sources

No funding agency had any role in the design, conduct, or reporting of this study.

RESULTS

Aspirin as an Adjunct to Screening

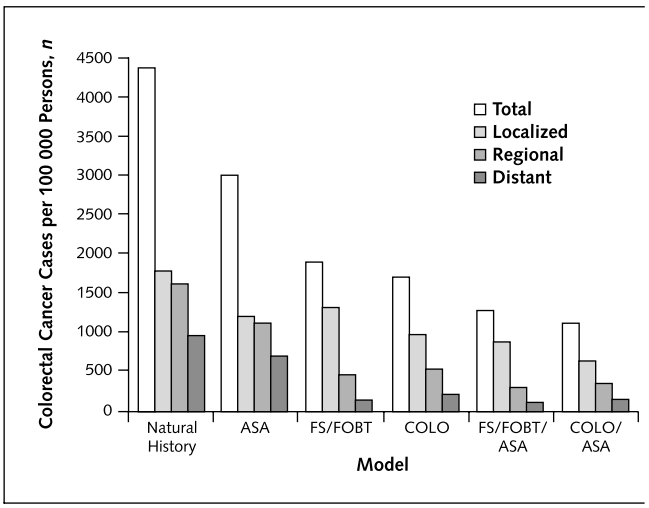
Clinical Outcomes

Figure 1 shows the incidence of colorectal cancer by age in the general population compared with our base case and validates our natural history model. In the base case, colorectal cancer incidence decreased by approximately 65% with FS/FOBT or COLO and by approximately 75% with FS/FOBT/ASA or COLO/ASA.

The cases of colorectal cancer diagnosed in a general population cohort and their stages at diagnosis are shown in **Figure 2** for the base case. Compared with natural history, screening significantly reduced total cases of colorectal cancer (4361 per 100 000 persons with no intervention, 1895 per 100 000 persons with FS/FOBT, and 1693 per 100 000 persons with COLO). The addition of aspirin therapy to screening further reduced cancer incidence (1258 cases per 100 000 persons with FS/FOBT/ASA and 1109 per 100 000 persons with COLO/ASA). Screening shifted cases toward earlier stages at diagnosis, consistent with data from screening studies (59).

Table 2 shows deaths and mean survival under different strategies in the base case in the general population. Compared with no screening, FS/FOBT or COLO markedly reduced colorectal cancer mortality and caused few screening-related deaths. When aspirin was used in persons adhering to either form of screening, the additional decrease in cancer deaths was essentially offset by aspirin-related deaths. Adding aspirin therapy yielded a net reduction in deaths when 25% of the population was screened; however, this benefit was significantly smaller than the benefit of increasing screening adherence.

Figure 2. **Cancer cases by stage.**



In our model, total cases of cancer diagnosed from 50 to 80 years of age decreased progressively with aspirin, screening, and aspirin and screening. Aspirin decreased case number without altering stage, while screening decreased case number and led to diagnosis at earlier stages. ASA = aspirin; COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.

Economic Outcomes

Figure 3 shows itemized discounted costs under each strategy in the base case in the general population. Compared with natural history ($830 per person), FS/FOBT and COLO increased costs approximately 2.5-fold ($2005 per person and $2125 per person). When aspirin therapy was added to FS/FOBT or COLO, overall costs increased approximately 5% ($2105 per person and $2237 per person).

Cost-Effectiveness in the Base Case

The strategies of FS/FOBT and COLO had acceptable incremental cost-effectiveness ratios compared with no screening (**Table 3**). The effect of screening without aspirin was similar in men and women. The strategy FS/FOBT cost $15 451 per life-year in men and $18 639 per life-year in women; COLO cost $18 626 per life-year in men and $22 329 per life-year in women.

Table 3 shows the incremental cost-effectiveness ratios for the addition of aspirin therapy to screening.

Table 2. **Clinical Outcomes for a Cohort of 100 000 Persons, 50 to 80 Years of Age, in the General Population***

Variable	Cancer Deaths	Screening Deaths	Aspirin Deaths	Other Deaths	Total Deaths	Mean Discounted Life-Years per Person
	←		*n*		→	
All persons screened						
FS/FOBT	394	44	0	47 089	47 527	18.773
FS/FOBT/ASA	267	43	129	47 134	47 573	18.771
COLO	442	55	0	47 092	47 589	18.768
COLO/ASA	276	54	129	47 141	47 600	18.769
25% of persons screened, 75% not screened						
FS/FOBT	1317	11	0	46 737	48 064	18.721
FS/FOBT/ASA	917	11	129	46 887	47 994	18.734
COLO	1329	14	0	46 737	48 080	18.719
COLO/ASA	920	14	129	46 889	47 951	18.734
No persons screened						
Natural history	1624	0	0	46 619	48 243	18.703
ASA	1134	0	129	46 805	48 068	18.722

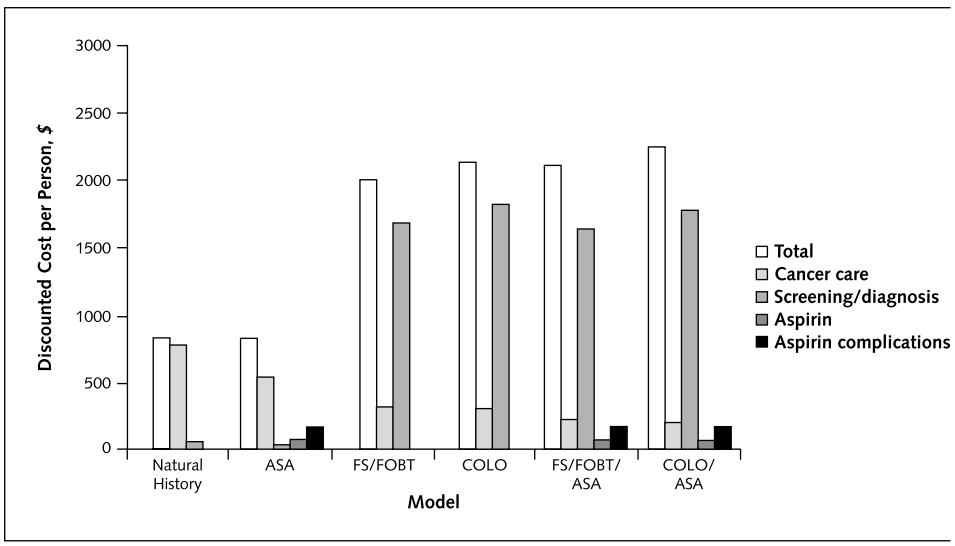
* ASA = aspirin; COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.

Aspirin increased costs and decreased life-years because of related complications as an adjunct to FS/FOBT and yielded a small benefit in life-years as an adjunct to COLO (**Table 2**) at a substantial incremental cost ($149 161 per life-year). Differences in the cost-effectiveness ratios for sex-specific screening remained relatively small when aspirin therapy was started. Women had slightly higher values and men had slightly lower values than those shown for the general population in **Table 3**.

Cost-Effectiveness in the Sensitivity Analysis

In Monte Carlo simulation, the median incremental cost-effectiveness ratios for FS/FOBT and COLO compared with no intervention were, respectively, $17 668 per life-year (interquartile range, $14 497 to $21 143 per life-year [98% of values within $7506 to $28 500 per life-year]) and $22 649 per life-year (interquartile range, $16 525 to $28 861 per life-year [98% of values within $8466 to $37 436 per life-year]). The addition of aspirin therapy to FS/FOBT increased costs and de-

Figure 3. **Discounted costs per person.**



Total cost per person increased minimally for aspirin use alone. Screening significantly reduced the costs for cancer care but increased the total cost per person approximately 2.5-fold. The cost of aspirin-related complications accounts for most aspirin-related costs. ASA = aspirin; COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.

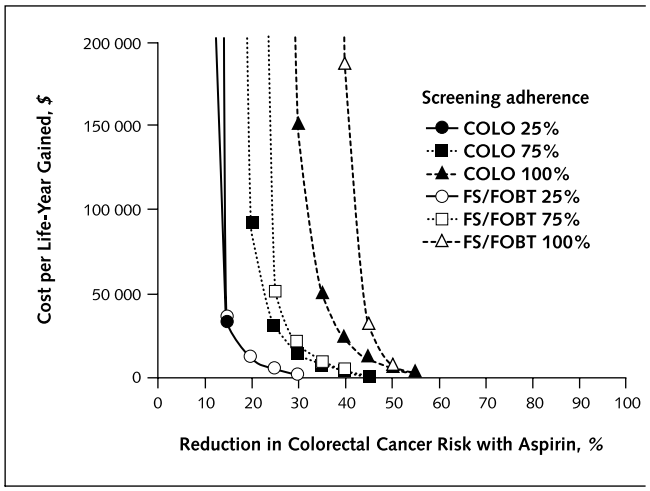
creased life-years (that is, FS/FOBT dominated FS/FOBT/ASA) in 68% of iterations and decreased costs and increased life-years (FS/FOBT/ASA dominated FS/FOBT) in 12% of iterations. In the remaining 20% of iterations, the median incremental cost-effectiveness ratio was $38 530 per life-year (interquartile range, $13 999 to $111 974 per life-year [80% of values within $4516 to $309 222 per life-year]). Similarly, COLO dominated COLO/ASA in 55% of iterations, and COLO/ASA dominated COLO in 10% of iterations. In the remaining 35% of iterations, the median incremental cost-effectiveness ratio for adding aspirin therapy to COLO was $35 031 per life-year (interquartile range, $11 907 to $99 874 per life-year [80% of values within $4353 to $294 329 per life-year]).

Cost-effectiveness estimates were highly dependent on the magnitude of aspirin's chemopreventive effect, the rate of screening adherence in the population, and aspirin-related complications rates. **Figure 4** demonstrates the effect of adding aspirin therapy to screening while systematically varying its chemopreventive effect and the rate of screening adherence. **Figure 5** shows the effect of adding aspirin therapy to COLO at different aspirin-related complication rates. The results for the addition of aspirin therapy to FS/FOBT were nearly identical (data not shown). The incremental cost-effectiveness ratio for adding aspirin therapy to screening underwent a sharp transition from very high values to lower values at all levels of population screening adherence (**Figure 4**). As population screening adherence or aspirin-related complications increased, aspirin's chemopreventive benefit had to be progressively greater to make therapy cost-effective (**Figures 4** and **5**).

We examined the effect of aspirin as an adjunct to screening if it decreased cardiovascular death as well as colorectal cancer incidence. If aspirin decreased cardiovascular mortality rates by 0.1% and colorectal cancer incidence by 30%, aspirin would increase costs and decrease life-years when added to FS/FOBT but would cost $57 682 per life-year when added to COLO. If aspirin decreased cardiovascular mortality rates by 1% and colorectal cancer incidence by 30%, the addition of aspirin therapy to FS/FOBT or COLO would cost $10 039 per life-year or $8976 per life-year, respectively.

Finally, we examined the effect of increased sensitivity and decreased specificity for fecal occult blood testing in patients taking aspirin. These changes did not significantly affect the results. When sensitivities for cancer or polyps were as extreme as 70% and 20%, respectively, and when specificity was as low as 85%, the addition of aspirin therapy to FS/FOBT slightly decreased colorectal cancer mortality rates, slightly increased screening-related mortality rates, and marginally increased costs. The net result remained a loss of life-years and an increase in costs, as in the base case.

Figure 4. **Sensitivity analysis of reduction in colorectal cancer risk by aspirin use and screening adherence in the population.**

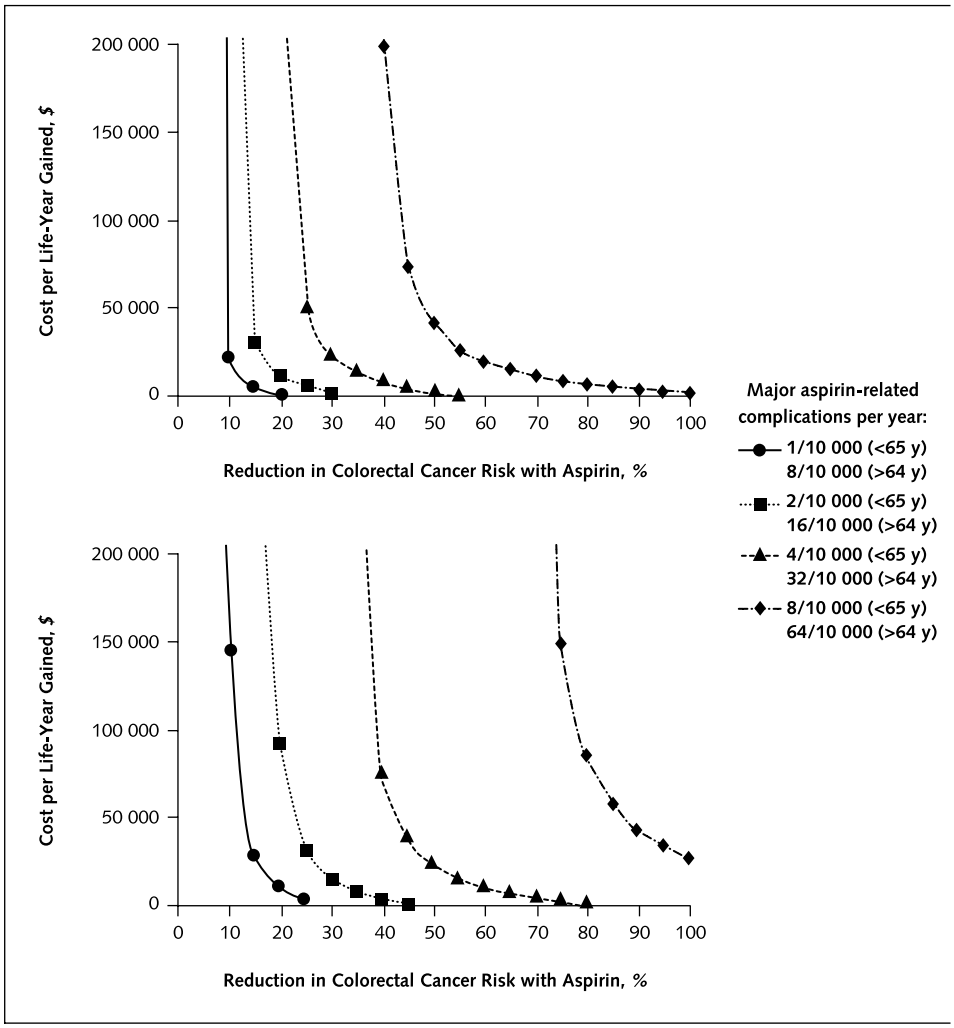


The incremental cost-effectiveness ratio for adding aspirin therapy to screening changed sharply from very high values to lower values at all levels of screening adherence. As adherence increased, aspirin's chemopreventive benefit was required to be progressively greater to make the addition of aspirin therapy cost-effective. COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.

Addition of Screening to Aspirin Alone

Because many people are currently not screened, we investigated aspirin chemoprevention alone. Given a 30% reduction in colorectal cancer with ASA in the base case (**Figure 1**), fewer cases of colorectal cancer occurred with ASA (2996 per 100 000) than with no intervention; however, this strategy led to more cases of colorectal cancer than either screening strategy (**Figure 2**). The strategy of ASA decreased colorectal cancer deaths compared with natural history, but this benefit was partially offset by aspirin-related deaths (**Table 2**). Cost per person was slightly lower with ASA ($817) than with no intervention ($830) (**Figure 3**). Therefore, in the base case, ASA was dominant compared with no intervention

Figure 5. **Sensitivity analysis of reduction in colorectal cancer risk and related complication rates when aspirin therapy is added to colonoscopy.**



Screening adherence rates were 25% (*top*) and 75% (*bottom*). As screening adherence or aspirin-related complications increased, aspirin's chemopreventive benefit was required to be progressively greater to make the addition of aspirin cost-effective.

Table 3. **Base-Case Incremental Cost-Effectiveness Ratios***

Strategy 1	Cost-Effectiveness Ratios for Strategy 2, *$ per Life-Year*				
	ASA	FS/FOBT	COLO	FS/FOBT/ASA	COLO/ASA
No aspirin or screening	Dominated†	16 844	20 172	–	–
ASA	0	–	–	26 315	30 822
FS/FOBT	–	0	–	Dominated‡	–
COLO	–	–	0	–	149 161

* Incremental cost-effectiveness ratio = (total costs of strategy 2 − total costs of strategy 1)/(life-years of strategy 2 − life-years of strategy 1). ASA = aspirin; COLO = colonoscopy every 10 years; FS/FOBT = flexible sigmoidoscopy every 5 years and annual fecal occult blood testing.
† Strategy 2 is more effective and less costly than strategy 1.
‡ Strategy 2 is less effective and more costly than strategy 1.

(**Table 3**). In Monte Carlo simulation, ASA dominated natural history in 38% of iterations and natural history dominated ASA in 12% of iterations. In the remaining 50% of iterations, the median incremental cost-effectiveness ratio for adding aspirin therapy to natural history was $8973 per life-year (interquartile range, $3401 to $25 715 per life-year [80% of values within $1169 to $79 527 per life-year]). However, ASA was significantly less effective than FS/FOBT or COLO (**Figures 1** and **2**, **Table 2**), both of which incurred costs less than $25 000 per life-year when compared with natural history (**Table 3**).

Because aspirin is commonly used for prevention of cardiovascular disease, we considered the effect of screening in persons already using aspirin. In the base case, adding FS/FOBT or COLO to existing aspirin use cost less than $31 000 per life-year gained (**Table 3**). If aspirin reduced colorectal cancer incidence by 60%, the addition of FS/FOBT or COLO to aspirin therapy would cost $48 970 per life-year or $56 203 per life-year, respectively. In Monte Carlo simulation, the median incremental cost-effectiveness ratios for the addition of FS/FOBT to ASA and COLO to ASA were $27 798 per life-year (interquartile range, $21 566 to $35 413 per life-year [90% of values within $14 980 to $49 241 per life-year]) and $35 014 per life-year (interquartile range, $25 785 to $45 923 per life-year [90% of values within $16 481 to $66 451 per life-year]), respectively.

DISCUSSION

We constructed a computer simulation to estimate the contribution of aspirin chemoprophylaxis to a national strategy for reducing death from sporadic colorectal cancer. We examined the effects of adding aspirin therapy to the combination of screening sigmoidoscopy and fecal occult blood testing, as well as to the emerging alternative of screening colonoscopy, as a function of aspirin's colorectal cancer risk reduction, its complication risks, and the rate of adherence to screening. Moreover, we investigated the potential effects of aspirin alone and of screening in persons already using aspirin. Our principal conclusion is that decisions to add aspirin therapy to screening should be driven primarily by potential cardiovascular benefits, not by colorectal cancer chemoprevention. Our secondary conclusions are as important: Aspirin therapy cannot be considered a substitute for screening, and screening should be pursued in patients already taking aspirin. These conclusions apply to both men and women. Our results have important implications for public policy as well as for individual patients and physicians.

Our model suggests the cost-effectiveness of adding aspirin therapy to screening depends greatly on the precise magnitude of aspirin's effect on colorectal cancer risk, the rate of aspirin-related complications, and the rate of screening adherence in the population. The dramatic change in the cost per life-year with small changes in aspirin's colorectal cancer risk reduction (**Figure 4**) highlights the need for further controlled studies to determine more precisely the magnitude of the aspirin effect.

In a population that adheres to screening, adding aspirin therapy for cancer chemoprevention is not likely to be cost-effective. Aspirin would need to reduce risk for colorectal cancer by 40% to 80%, and rates of aspirin-related complications would need to be low (**Figures 4** and **5**). However, if aspirin decreased the cardiovascular mortality rate by 0.1% or more in addition to decreasing colorectal cancer risk by 30%, aspirin use in a screened population may be cost-effective. If aspirin affected the performance of fecal occult blood testing, its impact would probably not change significantly; this is consistent with observations that earlier detection of adenomas or cancer does not seem to explain the protective effect of NSAIDs (19, 26).

Aspirin chemoprevention seems cost-effective in an unscreened population. However, it is much less effective than screening, which is highly cost-effective. Furthermore, although aspirin may be cost-effective if it decreases colorectal cancer risk by about 15% when 25% of the population adheres to screening (**Figures 4** and **5**), increasing screening adherence reduces colorectal cancer mortality much more dramatically than universal aspirin use. Thus, aspirin cannot be considered a substitute for screening. Moreover, the addition of screening to existing aspirin use remains cost-effective even if aspirin yields very significant cancer chemoprevention.

Under all circumstances, the complication rate with aspirin was an important determinant of cost-effectiveness (**Figure 5**). Therefore, safer chemoprevention remains an attractive option. Cyclooxygenase-2 inhibitors, for example, may prove efficacious and safer but may

also be more costly. Their cost-effectiveness will depend on the precise magnitude of their efficacy in chemoprevention, complication rate, and cost.

Although evaluating the cost-effectiveness of screening was not our principal aim, our results complement recent studies. Our model's estimates of the clinical and economic impact of screening agree with previous clinical studies and decision analyses (3, 5–10, 59, 60). One recent decision analytic model found screening colonoscopy to be superior to fecal occult blood testing alone or sigmoidoscopy alone (9). This result can be replicated in our model (data not shown). However, our model suggests that the combination of fecal occult blood testing and sigmoidoscopy is similar to screening colonoscopy, assuming fecal occult blood testing and sigmoidoscopy are complementary tests. Another recent analysis suggests that screening colonoscopy and the combination of fecal occult blood testing and sigmoidoscopy may be similarly cost-effective (10). Furthermore, a recent clinical trial supports the conclusion that colonoscopic screening is effective (37). Calls for insurance coverage of screening colonoscopy are growing (61, 62). Because screening colonoscopy requires adherence every 10 years and the combination of fecal occult blood testing and sigmoidoscopy requires yearly adherence, colonoscopy may be the more attractive alternative.

Several potential biases must be recognized in our analysis. First, although we considered a range of screening adherence rates, we assumed that the benefits and risks of long-term aspirin use are generally applied to the entire population. This may have biased our results against or in favor of aspirin. However, in our model, aspirin-related reduction in colorectal cancer risk can be viewed as combining efficacy and adherence: An overall 20% risk reduction can reflect 20% risk reduction with 100% adherence or 40% risk reduction with 50% adherence. Interactions between aspirin and screening adherence rates, however, are beyond the scope of the model. Second, the analysis that included aspirin-related reduction in cardiovascular mortality rates did not consider cardiovascular disease expenditures. The consequences of this limitation are difficult to assess because costs directly related to cardiovascular deaths could decrease while longer-term costs for chronic cardiovascular disease could increase.

Our model may be helpful in formulating public policy on colorectal cancer prevention, but it can also be informative to individual patients and physicians. For a patient adhering to screening, current evidence does not support the addition of aspirin therapy for colorectal cancer chemoprophylaxis. The decision to take aspirin should be driven by other considerations, including prevention of cardiovascular disease. Colorectal cancer screening has great potential benefit for unscreened patients. It is important to note that the recommendation for screening should not be affected by whether the patient is taking aspirin and that aspirin should not be considered a reasonable alternative to screening.

Our model suggests that the addition of aspirin therapy in a population adhering to screening is not likely to be beneficial for colorectal cancer prevention. Aspirin use should be based on other clinical considerations. While aspirin alone may be of some benefit in colorectal cancer prevention, it cannot substitute for screening. As suggested by our results and many previous investigations, screening is highly cost-effective and remained so in our model for patients already taking aspirin, even when aspirin was assumed to confer a high degree of colorectal cancer chemoprevention. Therefore, we strongly believe that public policy efforts for colorectal cancer prevention must focus on improving screening adherence. To patients and physicians, it must be clear that even if aspirin is proven to help prevent sporadic colorectal cancer, its use is not a substitute for colorectal cancer screening.

Appendix: Markov Model and Monte Carlo Simulation

The complete Markov model begins with a single decision node, followed by six Markov nodes. Each Markov node is the root node for one of the six strategies (natural history, ASA, FS/FOBT, COLO, FS/FOBT/ASA, and COLO/ASA). The probabilities of existing in the principal Markov states at baseline (50 years of age) were derived from the literature used to construct the model. For the general population of men and women, these probabilities were polyp, 0.15; undiagnosed localized cancer, 0.0009; undiagnosed regional cancer, 0.00049; undiagnosed distant cancer, 0.00011; and normal, 0.8485.

The natural history model is illustrated in the **Appendix Figure.** To construct the natural history model for the general population, age-specific transition probabilities from normal to polyp were derived to yield a progressive increase in polyp prevalence, from 15% at 50 years of age to 47% at 75 years of age. These transition probabilities ranged from 0.011 per year at 50 to

60 years of age to 0.019 per year at 70 years of age and older. Assuming that 90% of colorectal cancer cases arise from polyps, age-specific transition probabilities from polyp to cancer and normal to cancer were derived (**Table 1**) to yield the age-specific rates for colorectal cancer incidence found in the SEER data. Rates of symptomatic presentation with localized or regional cancer were derived to reflect the stage distribution in the SEER data (**Table 1**). Age-specific probabilities of non–colorectal cancer death were derived from U.S. life tables (range, 0.0047 per year at 50 years of age to 0.060 per year at 80 years of age). Sex-specific probabilities were derived by using the same methods. The addition of aspirin therapy or screening to the natural history model is described in the Methods section.

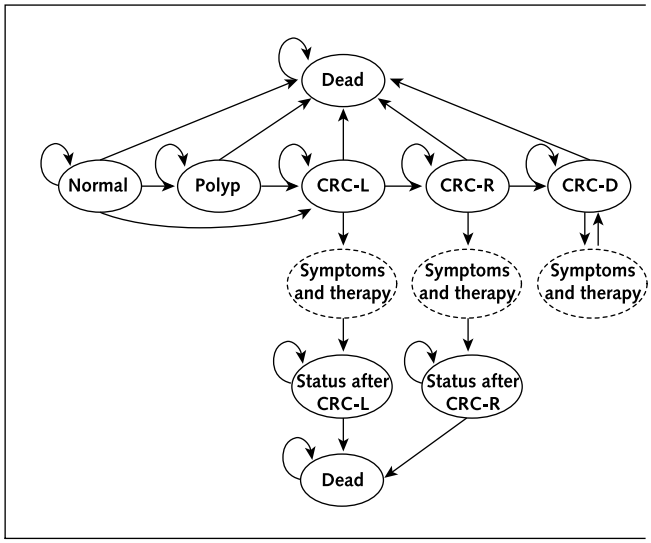
The probabilities of existing in the principal Markov states at baseline and the transition probabilities for the natural history model were never varied. For the purposes of the model, therefore, the population under study was assumed to be infinitely large and to reflect epidemiologic characteristics of the general U.S. population.

For the Monte Carlo simulation, the six Markov nodes emanated from a single decision node; this allowed the total costs and life-years for the six strategies to be evaluated simultaneously with the same set of values for the model variables in each specific iteration. During each of 3500 iterations, each variable from **Table 1** that is listed with a range in the Monte Carlo analysis took on a randomly selected value from within its range. Because limited data exist on the distribution of each variable, we made a conservative assumption and selected flat distributions for all. That is, each value within a variable's range was assumed to be equally likely (for example, a sensitivity of 30% to 60% for cancer for the fecal occult blood test [**Table 1**]).

During each Monte Carlo iteration, the "expected value" for each strategy's cost and effectiveness was calculated in DATA 3.5.7. This "expected value" reflects the mean value per person in an infinitely large population. Because in each iteration the underlying natural history variables were held constant, the estimates of variability produced by the Monte Carlo simulation reflect only the variability from assuming that costs and probabilities with ranges in **Table 1** (such as the performance characteristics of screening tests) take on a certain distribution. Uncertainty of population sampling did not contribute to the reported variability because, in each iteration, an infinitely large cohort with the same characteristics (the natural history variables) was assessed.

The expected values for each strategy's cost and effectiveness from each iteration were imported into Excel 2000. For each iteration, for each pair of strategies being compared, it was determined whether one strategy was dominant (more effective and less costly). If not, an incremental cost-effectiveness ratio was calculated. These incremental cost-effectiveness ratios are meaningful because the expected values for cost and effectiveness for all six strategies were assessed with exactly the same model inputs in each iteration. The percentage of iterations in which a strategy dominated or was dominated by its comparator strategy was calculated. Data were imported into SAS 6.12 (SAS Institute, Inc., Cary, North Carolina) for analysis of the distributions of the incremental cost-effectiveness ratios in those iterations in which this ratio could be calculated. Thus, the results of the Monte Carlo simulation for each pair of strategies compared are reported as the percentage of iterations in which one or another strategy was dominant and the distribution of the incremental cost-effectiveness ratio in that percentage of iterations in which no strategy was dominant.

Appendix Figure. **Markov states in the natural history model.**



The ovals with solid borders represent the principal Markov states of normal, polyp, localized colorectal cancer (*CRC-L*), regional colorectal cancer (*CRC-R*), distant colorectal cancer (*CRC-D*), and dead. The Markov states for patients who survived treatment for cancer (status after CRC-L and status after CRC-R) are also shown. The ovals without solid borders represent intermediate states associated with the symptomatic presentation of cancer. As shown, patients could remain in the same Markov state or transition to dead at the end of every cycle. Normal patients may develop a polyp or CRC-L. Polyps may progress to CRC-L. Cancer cases progressed from localized to regional to distant unless symptoms led to diagnosis and treatment. If this occurred, patients entered postcancer surveillance in status after CRC-L and status after CRC-R.

For simplicity, the addition of aspirin therapy and the screening strategies are not depicted. Aspirin decreased the transition probabilities from normal to polyp or CRC-L, and from polyp to CRC-L. In addition, aspirin-related complications, including death, may arise in any Markov state. When the screening strategies were modeled, states analogous to the principal states depicted were created with modifiers to track an individual's history (status after normal results on fecal occult blood testing, sigmoidoscopy, or colonoscopy or status after polypectomy). These modifiers determined screening and surveillance intervals and tests.

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