Research Article

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Combination Aspirin and/or Calcium Chemoprevention with Colonoscopy in Colorectal Cancer Prevention: Cost-effectiveness Analyses

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Abstract

Background: Clinical and cohort studies have shown that low-dose aspirin and calcium are effective low-risk strategies for primary prevention of colorectal cancer (CRC). We compared the cost-effectiveness of aspirin and calcium chemoprevention used with colonoscopy for primary prevention of CRCs.

Methods: Markov chain Monte Carlo simulations for a population of 100,000 persons, with a colonoscopy compliance rate of 50%, were used for the analysis. If adenomas were detected, colonoscopy was repeated every 4 years until no adenomas were evident. Data sources included adenoma transition rates, initial adenoma and CRC incidences, and treatment complication rates from existing literature. Age-adjusted U.S. standard population mortality rates were used and costs were from Medicare reimbursement data. The target population was U.S. adults, undergoing CRC screening from ages 50 to 75 years.

Results: Outcomes included incremental cost-effectiveness ratios (ICER), life-years saved (LYS), and cancer-free years saved (CFYS). The ICER per LYS for colonoscopy alone dominated compared with no screening. Compared with colonoscopy alone, colonoscopies with aspirin (ICER = $12,950/LYS) or calcium (ICER = $13,041/LYS) were the next most cost-effective strategies. ICERs per CFYS were $3,061 and $2,317 for aspirin and calcium, respectively, when added to colonoscopy. Sensitivity analyses indicated that initial prevalence of adenomas was a main determinant of prevention cost-effectiveness.

Conclusion: Low-dose aspirin or calcium supplementation may be beneficial when added to colonoscopy, for optimum CRC prevention, at small incremental costs.

Impact: Cost-effectiveness analyses suggest that aspirin and calcium in combination with colonoscopies are cost-effective for CRC prevention in average-risk populations. *Cancer Epidemiol Biomarkers Prev; 22(3); 399–405. ©2012 AACR.*

Introduction

Aspirin and calcium both have been studied extensively for their possible roles in the chemoprevention of colorectal cancer (CRC) and have recently been reviewed by us and others (1–3). Both agents have been considered in strategies alone and with colonoscopy for increasing screening effectiveness (1) which serves to detect CRC by early identification of adenomatous polyps, removal by polypectomy, and follow-up with surveillance colonoscopy according to published guidelines (4). However, despite the increased effectiveness (1) associated with the use of aspirin and/or calcium in the primary prevention of CRCs, it is not presently recommended as an evidence-based prevention strategy. The U.S. Preventive Services Task Force (USPSTF) last evaluated the use of aspirin for prevention of CRCs in 2007 (5) and determined that "aspirin appears to be effective at reducing the incidence of colonic adenoma and colorectal cancer . . .[but]. . . further evaluation of the cost-effectiveness of chemoprevention compared with, and in combination with, a screening strategy is required." (5). Recent data show that low-dose aspirin (75–81 mg/d) is effective for CRC prevention in the average-risk population (6) and dramatically reduces the incidence of complications associated with high-dose aspirin therapy. The cost-effectiveness of low-dose aspirin chemoprevention (7), and calcium supplementation alone (8), have been reviewed recently by our team (1) and have indicated that both aspirin at 81 mg/d and calcium at 1,200 mg/d are cost-effective strategies for primary prevention alone and also in the context of colonoscopy screening.

The USPSTF guidelines for CRC screening recommend colonoscopy every 10 years starting at 50 years of age until 75 years (5), and when an advanced or multiple adenomatous polyps have been detected, surveillance

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colonoscopy is recommended every 3 to 5 years as mentioned above (4). This strategy is effective at reducing the incidence and mortality from CRCs, as seen in the mortality analyses from the National Polyp Study (9), where they reported a 53% reduction in mortality from CRCs with this strategy. However, in the United States, use of colonoscopy by the general population older than 50 years is less than 50% according to AHRQ data (10) and also for any endoscopy as reported by the American Cancer Society (11). A recent randomized controlled trial (RCT) reported that the rate of participation in a group of asymptomatic eligible adults offered one-time colonoscopy screening was only 24.6% (12). Thus, although colonoscopy is the most effective screening strategy for decreasing CRC mortality, much of the population does not participate in this strategy and, alternatively, less invasive prevention strategies become more attractive. This information led us to conduct a cost-effectiveness analysis with the following objective: to evaluate the use of low-dose aspirin, calcium supplementation and colonoscopy to reduce CRC incidence and mortality, using real-world rates of colonoscopy compliance, instead of the 100% compliance rate assumed in previous cost-effectiveness analyses of colonoscopy and primary chemoprevention (7, 8, 13, 14).

Materials and Methods

Our analysis was designed to address the primary outcomes of (i) how does the actual population-based compliance rate of colonoscopy screening (documented at 50% or less) affect its overall efficacy in preventing CRCs and (ii) the addition of low-dose aspirin for ages 50 to 60 years only, calcium for ages 50 to 75 years, or both to colonoscopy screening a cost-effective CRC prevention strategy?

General assumptions of the Markov process

The cost-effectiveness of primary CRC prevention with low-dose aspirin and calcium, in combination with colonoscopy screening, were compared using Markov Monte Carlo simulation. This method allows tracking of patient-level outcomes where probabilistic risk factors are incorporated at annual intervals. The initial population simulates 100,000 patient outcomes who are initially 50 years of age. Simulated outcomes are based on each of the 4 interventions which include (i) colonoscopy alone, (ii) colonoscopy with aspirin, (iii) colonoscopy with calcium, and (iv) colonoscopy, aspirin, and calcium chemoprevention. All inputs for effectiveness of the different strategies have been determined from previous RCTs of the use of these agents for chemoprevention of CRC (15–17). Each of these interventions is compared with a baseline scenario where no screening intervention is used. In the initial stage, individuals are identified as compliant or noncompliant with regard to colonoscopy, based on a random draw from a Bernoulli distribution with a probability of 0.50. This rate is consistent with actual U.S. population compliance (10, 11). In addition, aspirin intervention includes daily doses of 81 mg from age 50 to 60 years, whereas calcium intervention includes 1,200 mg of elemental calcium (carbonate form) daily from ages 50 to 75 years. Ages 50 to 60 years were chosen for aspirin chemoprevention because the lowest rate of aspirin-related complications occur in this age group (18) and protection from CRCs by using aspirin extends for 10 years following aspirin use (6). If no polyps are identified on initial colonoscopy screening at age 50 years, then colonoscopy is not repeated until 10 years after initial colonoscopy. The possible outcomes of colonoscopy screening are no polyps, adenomas, or CRCs. Complications are assumed to occur from colonoscopy 0.3% of the time and result in an added average cost of $20,000 per event (7). Of those who have complications during colonoscopy, there is a 5.5% mortality rate (7). If an adenomatous polyp is discovered, colonoscopy is repeated every 4 years [average between the recommended 3–5 years (<4)] until adenomatous polyps are no longer identified. Patients in a Markov state can also develop CRC based upon established rates of advancing through the following states: (i) no polyps, (ii) low-grade adenoma, (iii) high-grade adenoma, and (iv) CRCs. The effectiveness of colonoscopy is dependent on the efficacy of colonoscopy plus polypectomy to prevent CRCs. The population in each transition state is also subject to natural attrition by the annual age–specific death rate of the U.S. population (19). The study was not submitted to an Institutional Review Board for review because all data were taken only from previously published data sources and no new clinical data were used in the study. No existing clinical data sources were used and all patients were simulated.

Transition probabilities

The transition probabilities of moving from state to state are inputs to the model and are taken from existing literature. Three types of compliance rate probabilities are built into the model, the initial compliance rates with colonoscopy guidelines, the compliance rates for surveillance colonoscopy if adenomas are found, and the compliance rates for use of the chemopreventive agents, aspirin and calcium. We used the following compliance rate inputs: 50% for compliance with initial colonoscopy guidelines (10, 11), 58.4% for compliance with surveillance colonoscopy following polypectomy (20), and 80% compliance each for aspirin and calcium (15, 16). This differs from other cost-effectiveness analyses in that 100% compliance with colonoscopy and aspirin or calcium use was assumed in all other studies (7, 8, 13, 14). The prevalence of any adenoma at initial colonoscopy at age 50 was 36.6 years (21), with 27.0% for low-grade polyps (21), 9.6% for a high-grade polyp (21), and 1.0% for CRCs (21). The adenoma development rate per year is 17.1% with no chemoprevention (7), and the metachronous adenoma rate was set at 10.4% for aspirin, 13.7% for calcium, and 6.8% for aspirin plus calcium chemoprevention, based upon rates of adenoma prevention from RCTs (15–17). The Markov model used the metachronous rate to

determine the number of polypectomies and surveillance colonoscopies. The conversion rates of adenomas were 1.5% and 1.8% probability of developing a high-grade polyp from a low-grade and CRC development from a high-grade polyp per year, respectively (8). The baseline efficacy of colonoscopy alone assumed that 82.2% of small adenomas and 95.4% of high-grade adenomas were detected (8). All models were simulated using TreeAge Pro Healthcare 2011 (TreeAge Software, Inc.).

Effectiveness and costs

The effectiveness of colonoscopy screening and chemoprevention was measured in terms of cancer-free years saved (CFYS). The CFYS variable is found to be more robust to simulations when compared to life-years saved (LYS) for cancer prevention strategies. We find CFYS more informative than LYS in our study, as more than half of our simulated observations die from natural causes while relatively fewer develop CRCs. The life-years lost accumulate for each 1-year cycle, and the number of LYS are determined by the difference in life-years lost from cancer-related deaths between a model with screening and/or chemoprevention with 1 with any of the 3 scenarios for chemoprevention and a no-screening strategy.

Screening costs were determined by 2011 Medicare reimbursement rates by CPT (Current Procedural Terminology) code for colonoscopy and polypectomy at University Medical Center, Lubbock, TX (22). The yearly costs of aspirin and calcium were determined from a pharmacy website (23). The average cost of CRC treatment is based on (8) and is $75,930 per individual case. Complication rates for colonoscopy procedures and aspirin use [perforations, upper gastrointestinal bleeds (UGB), and deaths from complications], as well as weighted costs for CRC treatments were calculated from existing literature sources (7, 8, 13, 14) All future costs were discounted at an annual rate of 3% (24). All inputs, ranges, and their references are listed in Table 1.

Results

Reference case scenario

As shown in Table 2, in the no-screening scenario, 9,363 CRC cases and 2,817 CRC-related deaths occurred in the simulated cohort of 100,000 subjects, resulting in the loss of 17,787 life-years at a cost related only to expenditures for CRC care, with an average cost of US$4629 per person. Table 2 also shows the outcomes of modeling the four strategies to prevent CRCs in a 50% compliant population with regard to initial colonoscopy screening. Chemoprevention strategies using aspirin, calcium with an 80% compliance rate for each, or both with colonoscopy all resulted in decreased CRC incidence and mortality. Colonoscopy alone resulted in a 25% decrease in incidence, followed by colonoscopy with calcium, at 26%, colonoscopy with aspirin, at 28% and colonoscopy with both aspirin and calcium chemoprevention at 32%. Data are also shown for reduction in CRC-related mortality with each scenario compared with no screening, ranging from 23% to 28%.

Costs

Colonoscopy screening alone resulted in a decreased cost for CRC treatment, relative to no screening. This resulted in an overall cost per person of US$4114, discounted at a rate of 3% (Table 2). With aspirin and/or calcium chemoprevention added to colonoscopy, the increased costs per person included cost of the agent, and the costs of complications in the case of aspirin, included in all strategies containing aspirin (Table 1).

Incremental cost-effectiveness ratios

The incremental cost-effectiveness ratios (ICER) values for colonoscopy and colonoscopy with chemoprevention are shown in Table 2. The comparisons between strategies 1 and 2 are calculated only for nondominated strategies. A strategy is said to dominate another when the cost is lower and there are additional LYS or CFYS. The main comparison is between strategy 1 and the no-screening option, with colonoscopy alone dominating compared with no screening. The ICERs for aspirin + colonoscopy, calcium + colonoscopy, and for aspirin + calcium + colonoscopy were $12,950, $13,041, and $26,269, respectively, per LYS. This shows the highest cost-effectiveness for colonoscopy alone, but aspirin + colonoscopy, calcium + colonoscopy, and aspirin + calcium + colonoscopy are more effective in terms of LYS but also cost-effective in that they both fall below an ICER of $50,000 per LYS that has been used by others (13, 25), as a willingness-to-pay threshold to differentiate an efficient strategy from an inefficient one. ICERs for CFYS are also shown in Table 2.

Sensitivity analysis

As simulation results rely on assumptions, a sensitivity analysis was developed that shows the potential effects of realistic adjustments in our parameters. First, we examined the sensitivity of our results to changes in adenoma transition probabilities from low- to high-grade to CRCs. We conducted a 2-way analysis assuming a low transition rate scenario (1.0%, 1.5%, and 1.0%; refs. 74, 8, 24) and a high scenario (17.1%, 5.5%, and 1.8%; refs. 7, 8). The ICERs associated with these results change dramatically given the range in transition rates. For example, under high adenoma transition rates, all treatments dominate the no-screening option. Under higher adenoma transition rates, the efficacies from calcium and/or aspirin treatments become more important in preventing CRC and maintaining low cost of treatment. Conversely, under lower rates, the use of colonoscopy becomes more effective, relative to other treatments at preventing cancer occurrence.

Second, we ran a 1-way sensitivity analysis regarding the rate of complications from low-dose aspirin to impact users with a range of 0.56% to 1.10% (7) based on relatively new evidence showing a lower low-dose aspirin complication rate (26, 27). When this low complication rate

Table 1. Inputs to the cost-effectiveness model

Treatment costs, US$	Baseline (range)	References
Annual aspirin treatment (81 mg/d)	24 (3–24)	13,23
Annual calcium treatment (1,200 mg/d)	63 (23–63)	8,23
Colonoscopy	745	22
Colonoscopy with polypectomy	1,001	22
Complication costs, US$		
Average cost of CRC treatment	75,930	8[a]
Colonoscopy complication	20,000	7
Aspirin-related complication	12,000	7[b]
Initial population assumptions		
Age at initial colonoscopy	50	5
Percentage with no polyps	62.4 (50.0–75.0)[c]	21
Adenoma prevalence at 50 y (%)	36.6 (24.3–48.7)[c]	21
Percentage with low-grade polyp	27.0 (17.9–35.9)[c]	21
Percentage with high-grade polyp	9.6 (6.4–12.8)[c]	21
Percentage with CRC	1.0 (0.7–1.3)[c]	21
Compliance rates, %		
Colonoscopy	50.00 (24.6–100)	10 (11,7)
Aspirin	80.00	15
Calcium	80.00	14,16
Surveillance colonoscopy follow-up at 5 y	58.40	20
Probabilities (%)		
Complication from colonoscopy	0.3	8,7
Death from colonoscopy complication	5.5	7
Complication from aspirin use per y	1.1 (0.56–1.1)	7,26
Death from low-dose aspirin use complication	0.1	13
Death from unresectable CRC/y	42.0	7
Effectiveness of CRC prevention strategies		
Aspirin	40%	6
Calcium	20%	8
Aspirin + calcium	60%	17

[a]Cost calculated from weighted values for cost of treatment per CRC stage, weighted by prevalence of stage at diagnosis.
[b]Cost calculated for aspirin complications from a weighted cost for type of complication.
[c]Numbers generated for the symmetric sensitivity analysis.

scenario is used, the death rate from aspirin complications decreases by 4.4% in scenarios containing aspirin treatments. This reduction in aspirin-related complications has a substantial impact on the cost effectiveness. Relative to no screening, the ICER is reduced from $12,950 to $2,223. When we consider the impact on cancer-free ICERs, we see that relative to COL the ratio is reduced from $33,891 to $20,370.

Third, we examined a 2-way sensitivity analysis concerning the initial percentage of population without adenomas at age 50 years using a range of 50.0% to 75.0%. In the upper percentage scenario, the cancer rate decreased for all treatments. Average cost per person is reduced by 13% to 19% for all treatments with COL and no-screening scenarios having the largest reductions. Impacts from the lower scenario are relatively symmetric to the upper scenario. A lowered initial prevalence of adenomas drives the higher cost-effectiveness of all treatments.

Fourth, we evaluated a 1-way sensitivity analysis regarding the cost of aspirin and calcium supplements and reduced the cost to $3 and $23, respectively, as compared with the base case of $24 and $63. This resulted in a reduced average cost per person by $184 (3.5%) for aspirin + COL, $622 (12.3%) for calcium + COL, and $795 (13.1%) for aspirin + Ca + COL. Lowering the cost of aspirin and calcium makes them a more cost-effective tool in preventing CRCs.

Finally, we conducted a 2-way sensitivity analysis regarding the colonoscopy compliance rates given symmetric upper (75%) and lower scenarios (25%). Assuming the lower compliance rate, cancer rates increase by 16.3% with COL, whereas for the other treatment scenarios, the rate increases by 16.8% to 16.9%. The largest impact of higher colonoscopy compliance is found to be on the aspirin and calcium treatments, which is not surprising given their complementary relationship. In this scenario,

Table 2. Outcomes of strategies to prevent CRC for a cohort of 100,000 subjects invited to screening

Outcome	No screening	COL	Aspirin + COL	Calcium + COL	Aspirin + Ca+ COL
CRC cases (*n*)	9,363	7,029	6,728	6,909	6,413
CRC cases prevented (*n*)	—	2,334	2,635	2,454	2,950
CRC prevention rate (%)	—	25	28	26	32
CRC deaths (*n*)	2,817	2,165	2,114	2,145	2,023
CRC death prevention rate (%)	—	23	25	24	28
LYS, y	—	4,175	4,915	3,130	5,567
CFYS, y	—	17,399	20,796	17,618	23,420
Strategy cost (US$ per person)	—	509	819	1496	1,785
Care for CRCs (US$ per person)	3,589	2,658	2,478	2,534	2,369
Total (US$ per person)	4,629	4,114	5,266	5037	6,092
ICER (US$ per LYS)	—	−12,330[a]	12,950	13,041	26,269
ICER (US$ per CFYS)	—	−2,959[a]	3,061	2317	6,244

Abbreviations: CRC, colorectal cancer; ICER, incremental cost effectiveness ratio; LYS, life-years saved; CFYS, cancer-free life years saved.

[a]When a strategy was more effective and less costly than no screening (no screening being dominated), savings per person instead of the ICER was provided.

average costs per person decreases from 3.9%-5.9% for all scenarios with the largest reduction to the COL scenario, where the average cost is reduced by an average of $241 (5.9%) per person. This effort would have additional cost savings in populations where aspirin and calcium regimens were used ranging from a reduction in costs by $237 to $271 (3.9%–5.4%).

Discussion

The primary outcomes of this analysis show that colonoscopy, even at only 50% compliance in the population, is still the most cost-effective in terms of both LYS and CFYS. The addition of low-dose aspirin from age 50 to 60 years to colonoscopy is the most cost-effective chemoprevention strategy, in terms of LYS, although COL still dominates the ICERs compared with no screening. Colonoscopy with calcium chemoprevention is the most cost-effective in terms of CFYS and a little less in LYS terms. Colonoscopy with both aspirin for 10 years, and calcium chemoprevention for 25 years is the most effective in terms of both CFYS, and LYS. The ICERs for all strategies compared with the no-screening scenario show in Table 2 that colonoscopy with aspirin and colonoscopy with calcium were the most cost-effective in terms of LYS and CFYS. Therefore, chemoprevention with low-dose aspirin for 10 years or less and/or calcium for 25 years are all cost-effective strategies to prevent CRCs, when combined with colonoscopy. These results showing the positive effect of low-dose aspirin chemoprevention are consistent with those found in (13). In addition, we conducted sensitivity analyses on a number of key variables, and while these analyses showed changing impacts from the different variables, the basic outcome of the results do not change.

The screening model assumptions used in our study differ from most other cost-effectiveness studies that have been published previously (7, 8, 13, 14) in that real-world compliance statistics were used with a compliance of only 50%, and a combination chemoprevention scenario was included as an adjuvant strategy with colonoscopy screening. According to our simulation, the addition of low-dose aspirin for only 10 years to colonoscopy was better than colonoscopy alone in terms of LYS and CFYS, and thus was the most cost-effective chemoprevention strategy (Table 2). It can be argued that CFYS is a better outcome for comparison and evaluation of cancer prevention strategies because the ultimate goals of prevention are to have more years without a diagnosis of CRCs. Although classic cost-effectiveness analyses (7, 8, 13, 14, 24) use LYS as the sole denominator for ICER statistics, we propose that the use of CFYS is more appropriate for cancer prevention strategies because LYS is more influenced by additional mortality factors, especially in an aging population. It is also appears that CFYS is more robust in simulation studies, as greater than half the population dies of causes unrelated to CRCs, whereas the CRC-related death rate is substantially smaller. This leads to a larger variability in results when using LYS as natural deaths are simulated. In an aging population, the longer the population remains cancer-free, the greater the likelihood that competing mortalities may become dominant in the estimation of LYS.

Our data may be difficult to compare with previous cost-effectiveness studies, in that we have realistically represented the population as only 50% compliant with the guidelines for colonoscopy screening, as opposed to 100%. This decreased compliance results in lower prevention rates, deaths, decreased prevention costs, and

increased CRC costs per person compared with studies with 100% compliance, and in our own sensitivity analyses. As an example, in the analysis by Hassan and colleagues (13), colonoscopy alone has a 68% CRC prevention rate compared with our analysis which resulted in a 25% CRC prevention rate, with 50% compliance, with the strategy stopping at the age of 75 years. The 80% compliance with aspirin and/or calcium chemoprevention likewise resulted in lower cancer prevention rates than would be seen with the 100% compliance assumed by Hassan and colleagues (13). Unlike the Hassan and colleagues articles, we did not apply the estimates of CRC prevention obtained by the pooling of cardiovascular trials to our simulated cohort but used those prevention estimates for aspirin and calcium chemoprevention obtained by the original RCTs conducted by Baron and colleagues (15, 16), and Grau (17), as listed in Table 1. However, like Hassan and colleagues (13), we used an average-risk population in our model. Thus, our goal was to establish the cost-effectiveness of aspirin for a 10-year period in the general population as a cost-effective strategy for the prevention of CRCs along with colonoscopy early detection.

There are limitations with the present study. We did not include the indirect costs of CRCs in the analysis, nor did we include the suboptimal efficacy of colonoscopy screening for proximal CRC, which now appears to be a key target of aspirin chemoprevention (13, 28). However, we did use realistic effects of aspirin and calcium in data derived from RCTs of adenoma recurrence and on CRC incidence and mortality (Table 1). In addition, we did not include as inputs to our model, the additional deaths prevented from cardiovascular disease, other cancers (29), preventive effects of calcium supplementation on fracture risk (30), and other competing causes of mortality that could also have been prevented by aspirin and calcium. The potential economic value of these scenarios has not yet been modeled in their aggregate effects.

Another possible limitation to our analysis is the apparent discrepancy between the numbers of cancers in the no-screening scenario, which are higher than Surveillance Epidemiology and End Results (SEER) data for lifetime probability of developing CRCs. This difference is likely because SEER probabilities are based upon actual cancer outcomes which should differ significantly from the input assumptions into our Markov simulation. SEER data for developing CRCs are derived after the effects of all CRC screening strategies (as well as a significant current population use of aspirin), not just colonoscopy. Also, there is a significant population use of aspirin and calcium for other purposes (e.g., heart disease and osteoporosis). Our baseline data on cancer cases and costs are derived from expected outcomes of a population for whom no strategy at all is used for early detection and no aspirin or calcium chemoprevention occurs.

There have been recent high-profile articles promoting the inclusion of aspirin in evidence-based guidelines for the prevention of CRCs (1, 2, 31). The accumulated evidence from long-term experience with CRC incidence decline in those on cardiovascular disease prevention trials with low-dose aspirin (28, 29), as well as the recent cost-effectiveness analyses on aspirin (7, 14) and calcium (14) in combination with current recommendations, provide evidence to support a new review from both the USPSTF and ACS policy groups. However, the specifics of the resulting recommendation, such as the dose; target population group, stratification by high or low risk for adenoma or CRCs based on lifestyle variables or waist circumference; and the duration of aspirin and calcium chemoprevention may require further determination. In such a carefully developed approach, colonoscopy recommendations could be supplemented with chemoprevention, resulting in more CRCs prevented and lives saved for a small increased cost. This key decision should be based on the reality that despite its relative efficacy in preventing CRCs, colonoscopy is significantly underused in our population and that its efficacy may be cost-effectively increased by an appropriate chemoprevention regimen. The impact of the present study derives from the use and the growing acceptance of using cost-effectiveness analyses to compare multiple chemoprevention strategies combined with early detection with the hope of optimizing CRC prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B.C. Pence, E.J. Belasco, C.P. Lyford
Development of methodology: B.C. Pence, E.J. Belasco, C.P. Lyford
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.C. Pence
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.C. Pence, E.J. Belasco, C.P. Lyford
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.C. Pence
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