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Can calcium chemoprevention of adenoma recurrence substitute or serve as an adjunct for colonoscopic surveillance?

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Objectives: The aim of this study was to examine the potential cost-effectiveness of calcium chemoprevention post-polypectomy as a substitute or adjunct for surveillance.
Methods: We constructed a Markov model of post-polypectomy adenoma recurrence and colorectal cancer (CRC) development, calibrated to data from prospective chemoprevention trials of fiber, calcium, antioxidants, and aspirin. We modeled four scenarios for 50-year-old patients immediately after polypectomy: (i) natural history with no further intervention; (ii) elemental calcium 1,200 mg/day from age 50–80; (iii) surveillance colonoscopy from age 50–80 every 5 years, or 3 years for large adenoma; (iv) calcium + surveillance. Patients were followed up until age 100 or death.
Results: Calcium was cost-effective compared to natural history ($49,900/life-year gained). However, surveillance was significantly more effective than calcium (18.729 versus 18.654 life-years/patient; 76 percent versus 14 percent reduction in CRC incidence) at an incremental cost of $15,900/life-year gained. Calcium + surveillance yielded a very small benefit (0.0003 incremental life-years/patient) compared with surveillance alone, at a substantial incremental cost of $3,090,000/life-year gained.
Conclusion: Post-polypectomy calcium chemoprevention is unlikely to be a reasonable substitute for surveillance. It may be cost-effective in patients unwilling or unable to undergo surveillance.

Keywords: Calcium, Chemoprevention, Colorectal cancer

Despite screening programs, colorectal cancer (CRC) remains the second leading cause of cancer-related death in the United States (19;20;39;40). It is estimated that 70–90 percent of CRCs arise from adenomatous polyps (11;22). Because the adenoma recurrence rate after polypectomy is approximately 40–50 percent (8;37;62), the prevention of recurrent adenomas could contribute significantly to reducing CRC incidence.

Major international differences in CRC incidence rates suggest that chemopreventive factors, including nutritional

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factors, may modulate the risk of this cancer (16;32;53). An ideal chemopreventive agent would decrease the risk of cancer while being safe and affordable. Two of the best-studied chemopreventive agents are nonsteroidal anti-inflammatory drugs (NSAIDs) (5;49) and calcium (4;52). The effect of NSAIDs may be mediated at least in part by inhibition of cyclooxygenase-2 (2). Previous cost-effectiveness analyses suggest that potential complications with aspirin make it an unattractive substitute or adjunct for screening (25;56). Analyses undertaken before the cardiovascular toxicity of cyclooxygenase-2 inhibitors was appreciated concluded that using these agents as adjuncts or substitutes for screening or surveillance would be cost-prohibitive (3;26).

In epidemiological studies, calcium appears to reduce the risk of CRC (34;41), possibly by binding bile and fatty acids or by inhibiting colonic epithelial cell proliferation (29;31). Supplementation with calcium at 3 g/day for 48 months reduced adenoma recurrence by 24 percent versus placebo ($p < .05$) in a randomized trial.(4) In our meta-analysis (52), we concluded that supplemental calcium at 3–4 g/day appears to reduce the incidence of recurrent adenoma by 22 percent versus placebo over 3–4 years. In a recent report from the Women's Health Initiative (WHI), no reduction in CRC risk was found in women supplemented with 1 g of calcium carbonate and 400 IU of vitamin D3 per day over a 7-year period, casting doubt on calcium's chemopreventive potential (60). However, several factors could have contributed to the negative results of the WHI study, including the doses of calcium used, which were one-third of those used in adenoma chemopreventive trials; the relatively high intake of calcium in the placebo group; the average CRC risk of the population studied; the relatively short duration of follow-up for a cancer end point; and overlapping interventions.

Calcium supplementation in doses of up to 1.2 g of elemental calcium per day is well-tolerated. Side effects are rare and usually mild, including nausea, bloating, and constipation. Allergic reactions have not been noted, the most serious side effects are milk alkali syndrome and nephrolithiasis, and mortality has not been reported. There are no compelling data that adverse outcomes differ between calcium treatment and placebo (4).

Calcium may be an attractive agent for post-polypectomy chemoprevention given its safety,, and low cost. Our aims were to explore whether calcium supplementation could be a cost-effective adjunct or substitute for surveillance after polypectomy.

METHODS

Literature Review

We searched MEDLINE through March 2006 for English language literature that provided data on CRC, screening, surveillance, adenoma prevention and recurrence, and calcium chemoprevention. Model inputs were based on literature reviews (Table 1).

Decision Analytic Model: General Description

A decision analytic Markov model was constructed in TreeAge Pro 2006 (TreeAge Software Inc., Williamston, MA) to simulate the natural history of adenomas and CRC in a population of adenoma-bearing individuals starting at age 50 years. Chemoprevention, surveillance colonoscopy, or their combination is then superimposed on the natural history model (Supplementary Figure 1, which can be viewed online at www.journals.cambridge.org/thc).

The model structure is similar to that of our model of CRC screening in the general U.S. population (25–27;54), but the fundamental differences are the calibration of the new model to post-polypectomy data and inclusion of variable surveillance intervals determined by adenoma characteristics. The model tracks the most advanced colorectal neoplastic lesion per person in a hypothetical cohort. The principal health states in the model are: normal; small ($<$10 mm) adenomatous polyp; large ($\geq$10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead. We assumed that cancer progresses from localized to regional (2 years in each state) to disseminated (6;7;35). In the Natural History model, CRCs can be diagnosed with colonoscopy only once they lead to symptoms. Diagnosed CRCs are treated, resulting in stage-specific survival (25–28;54). Beginning at age 50 years, adenoma-bearing persons progress through the model for fifty 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect U.S. life table data (36).

Calibration of Post-polypectomy Natural History Parameters

We derived annual transition probabilities between health states (e.g., normal to small polyp; large polyp to localized CRC) to reproduce the prevalence and size distribution of adenomas found at surveillance colonoscopy in the National Polyp Study (65;66) and the placebo arms of chemoprevention trials (1;4;5;18;38;50;51), and the CRC incidence found in the chemoprevention trials (47). We made several assumptions. First, the trials used to calibrate the model reported relatively high adenoma prevalence at year 1 compared with the smaller incremental increases in later years, forcing the assumption that some polyps observed at year 1 had been missed at year 0, instead of all arising *de novo*, which is consistent with data that colonoscopy does not have perfect sensitivity (42;45). Second, we assumed that the reported polyp prevalence in the trials was a function of a higher true prevalence and a certain miss rate, determined by the sensitivity of colonoscopy. Third, in chemoprevention trials, 27–30 percent of adenomas at entry were large (33;47),

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Table 1. Inputs in the Cost-Effectiveness Model

Variable	Base Case Value (Range)	Reference
Clinical[a]		
Adenoma prevalence after screening colonoscopy at age 50 (missed adenomas), %	22.4	(5;4;1;18;47;33)
Small adenoma, %	17.8	(5;4;1;18;47;33)
Large adenoma, %	4.6	(5;4;1;18;47;33)
Cancer prevalence after screening colonoscopy at age 50 (missed cancer), %		
Localized CRC, %	0.16	(5;4;65;50;47)
Regional CRC, %	0.12	(5;4;65;50;47)
Disseminated CRC, %	0	(5;4;65;50;47
Annual transition rate to small adenoma from no adenoma, given history of small adenoma, %	9	(5;4;65;66;18)
Annual transition rate to small adenoma from no adenoma, given history of large adenoma, %	33	(5;4;65;66;18)
Annual transition rate to large adenoma from small adenoma, %	1.5	(5;4;65;1;18;46)
Annual transition rate to cancer from large adenoma, %	1.8	(5;49;4;65;1;18;47)
Symptomatic presentation of localized cancer, %	22/y over 2y	(46)
Symptomatic presentation of regional cancer, %	40/y over 2y	(46)
Mortality rate from treated localized cancer, %	1.74/y in first 5y	(46)
Mortality rate from treated regional caner, %	8.6/y in first 5y	(46)
Mean survival from distant cancer, y	1.9	(46)
Mortality rate from cancer treatment, %	2	(62;63)
Relative risk of any adenoma at 3 years with calcium chemoprevention compared with natural history	0.80	(4;52)
Relative risk of large adenoma at 3 years with calcium chemoprevention compared with natural history	0.65	(4;52)
Colonoscopy sensitivity for cancer, %	95 (90–97)	(63;61)
Colonoscopy sensitivity for large adenoma, %	90 (85–95)	(63;61)
Colonoscopy sensitivity for small adenoma, %[b]	85 (80–90)	(63;61)
Colonoscopy major complication rate, %	0.1 (0.05–0.5)	(63;61)
Colonoscopy mortality rate, %	0.01 (0.005–0.03)	(63;61)
Cost, $ [c]		
Colonoscopy	940 (710–1,350)	(25;26;65;15;61)
Colonoscopy with lesion removal	1,375 (990–2,030)	(25;26;65;15;61)
Calcium per year	53 (23–255)	(44;43)
Endoscopy complication	29,000 (16,000 – 43,000)	(62;25;26;15;13)
Colorectal cancer care by stage		
Localized	52,000 (40,000–64,000)	(62;25;26;9;12;14;57)
Regional	78,000 (66,000 – 90,000)	(62;25;26;9;12;14;57)
Distant	81,000 (69,000 – 93,000)	(25;26;9;12;14;57;61)

[a]Derived from epidemiologic and autopsy data.
[b]Sensitivity for small adenoma set at (1-specificity).
[c]Derived from Centers for Medicare and Medicaid Services and published data.

and we assumed that the size distribution of polyps at year 1 was a function of this distribution at entry and the sensitivity of colonoscopy for small or large polyps. Fourth, we assumed that most CRCs arose through the sequence of small polyp to large polyp to localized CRC, but we also included CRCs that arose without an identifiable polypoid precursor.

Through an iterative process, we derived values for small and large polyp prevalence after colonoscopy at year 0 and annual rate of *de novo* polyp formation (i.e., the transition probability from normal to small polyp) that yielded polyp prevalence at years 1 and 3 in the range of that observed in the trials used to calibrate the model, after accounting for the imperfect sensitivity of colonoscopy for determining true prevalence. The process yielded small and large polyp prevalence after colonoscopy at year 0 of 18 percent and 5 percent, respectively, and an annual transition rate from normal to small polyp of 14 percent. We used our previously derived annual transition probability for small to large polyp of 1.5 percent, which is used in our CRC screening model (27;28;54) that is calibrated to the age-specific prevalence at autopsy of small and large adenomatous polyps.

The model's predicted adenoma prevalence at colonoscopy of 30 percent at year 1 and of 44 percent at year 3 after polypectomy at year 0 are consistent with the results of post-polypectomy surveillance colonoscopy first performed

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at year 1 or year 3 in the studies used to calibrate the model (4;5;18;65;66). The model predicted that 11–15 percent of adenomas detected every year would be large, which is consistent with the 8–16 percent reported in the National Polyp Study and chemoprevention trials (5;50;65;66).

Having calibrated the natural history model for small and large adenoma, we next calibrated the model to CRC incidence. In the chemoprevention trials, CRC incidence was 3.79 per 1,000 person-years in year 1, and 0.96 per 1,000 person-years from the year 1 colonoscopy through year 4 colonoscopy (47). As with adenomas, we assumed that the higher CRC rate in the first interval was due to CRC missed during the initial colonoscopy. For calibration purposes, we included some missed CRC at entry and aimed to calibrate the model for an annual CRC incidence as determined by colonoscopy with 95 percent sensitivity for CRC at year 4 of approximately 0.96 per 1,000 persons (47).

We have previously derived annual transition probabilities from normal to localized CRC without a polypoid precursor for our CRC screening model (27;28;54). Using these probabilities for the base case, the inputs for small and large adenoma as derived above, and an iterative process, we determined that an annual transition rate from large polyp to localized CRC of 1.8 percent yielded an overall CRC rate at year 4 colonoscopy of 0.95 per 1,000 person-years, which is consistent with the data we chose to calibrate the model (47). Next, by running a model simulation in which CRC could not arise without an adenoma, we determined that, in the base case, approximately 10 percent of all CRCs arose without a polypoid precursor. We accepted this as reasonable in this polyp-bearing population.

Natural History after Initial Polypectomy

In the Natural History strategy, all patients underwent colonoscopy with polypectomy of any detected polyps at year 0 before entering the simulation. Thereafter, colonoscopy was performed only to diagnose symptomatic CRC and no chemoprevention was given.

Effect of CRC Surveillance

We superimposed surveillance on the natural history model. As in the Natural History strategy, all patients underwent colonoscopy with polypectomy before entering the simulation. Thereafter, colonoscopy was performed every 5 years, or every 3 years after removal of a large polyp, from age 50 to 80 years (64). CRCs could be diagnosed during surveillance colonoscopy as well as after leading to symptoms.

Effect of Calcium Chemoprevention

Calcium 1.2 g elemental/day was superimposed on the Natural History strategy (calcium as a substitute for surveillance) and on the surveillance strategy (as an adjunct to surveillance). In the base case, the model was calibrated to yield a relative risk of adenoma recurrence at 3 years of 0.80 with calcium compared with no chemoprevention (4;52). This was achieved by assuming an annual relative risk of new adenoma of 0.75 and an annual relative risk of progression from small to large adenoma of 0.83 with calcium compared with no chemoprevention. These assumptions yielded a relative risk of large adenoma of 0.65 at 3 years with calcium compared with no chemoprevention, which is also consistent with the literature (52). We assumed calcium was safe and did not incur any additional costs for complications.

Cost Inputs

Procedure cost estimates ranged from those derived from Medicare fee schedules (including professional fees and procedural reimbursement) to those reported from a health maintenance organization in a previous decision analysis (15;24–26;55;59;63). The cost of calcium has not changed from 2005 to 2008 (30;43;44). For the various preparations of calcium available at a dose of 1.2 g/day, the yearly median cost was $53 (range $23–$255; mean $64) (43;44). For the base case, we used the median cost of $53. In sensitivity analysis, we considered a broad range of costs, including the minimum and maximum costs for calcium (Table 2). Complication costs were derived from relevant diagnostic-related groups (13;25;26). Costs for care of stage-specific colon cancer were taken from published reports (9;12;14;25;26;57). Costs were updated to 2006 dollars using the medical services component of the consumer price index. Indirect costs were not included. We performed analyses from the perspective of a third party payer.

Model Outputs: Clinical and Economic Outcomes and Cost-Effectiveness

For each strategy, the model yielded the number of CRC cases by stage, deaths by cause, and average life-years and costs per person. Life-years and costs were discounted at 3 percent annually. If one strategy afforded more life-years than another at a higher expense, an incremental cost-effectiveness ratio was calculated, yielding cost per life-year saved. Systematic sensitivity analyses were performed on the model's inputs. These results are shown only for the critical variables whose values significantly affected the results (Table 2).

RESULTS

Base Case: Clinical Outcomes

Compared with Natural History, all strategies reduced CRC incidence and mortality and increased life expectancy (Table 2). Under Natural History, a cohort of 100,000 persons experienced 7,759 CRC cases. Calcium supplementation alone decreased CRC incidence by 14 percent to 6,672. Surveillance decreased CRC incidence by 76 percent to 1,844 cases. The addition of calcium to surveillance decreased CRC

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Table 2. Base Case Clinical and Economic Results and Incremental Cost-Effectiveness Ratios

	Natural History	Calcium Supplementation	Surveillance	Surveillance and Calcium Supplementation
CRC cases per 100,000 persons from age 50 to 80 years	7,759	6,672	1,844	1,725
CRC stage				
Local	40%	39%	56%	55%
Regional	38%	38%	32%	33%
Distant	23%	23%	12%	12%
Life-years/person[a]	18.642	18.654	18.729	18.729
Cost/person[a]	$2,796	$3,392	$4,579	$5,426
Incremental life-years gained per 100,000 persons compared to				
Natural History	—	1,194	8,654	8,682
Calcium Supplementation	—	—	7,461	7,488
Surveillance	—	—	—	27
Increment cost per life-year gained compared to:				
Natural History	—	$49,900	$20,600	$30,300
Calcium Supplementation	—	—	$15,900	$27,200
Surveillance	—	—	—	$3,090,000

Note. Strategy in top row is more effective and less costly than strategy in left column to which it is being compared
[a]Discounted at 3% per year.
CRC, colorectal cancer.

cases 2 percent further to 1,725 cases. Surveillance shifted cases toward earlier stages at diagnosis, consistent with the literature (Supplementary Figure 2, which can be viewed online at www.journals.cambridge.org/thc).

Base Case: Economic Outcomes

Supplementary Figure 3 (which can be viewed online at www.journals.cambridge.org/thc) shows itemized discounted costs under each strategy in the base case in the general population. Compared with Natural History ($2,796/person), calcium supplementation ($3,392/person) increased total cost by 21 percent, and surveillance ($4,580/person) increased total cost by 64 percent. When calcium was added to surveillance, total cost increased to $5,426/person, or 94 percent higher than under Natural History. Under Natural History and with calcium supplementation, most of the cost was attributable to CRC care. Under the two strategies including colonoscopic surveillance, CRC care costs were decreased significantly, and most of the total cost was attributable to the cost of surveillance.

Base Case: Cost-Effectiveness

Table 2 shows the incremental cost-effectiveness ratio for the four strategies. Calcium had an acceptable incremental cost-effectiveness ratio when compared with Natural History ($49,900/life-year gained). However, surveillance had a lower incremental cost-effectiveness ratio when compared with calcium ($15,900/life-year gained), resulting in extended dominance over calcium. Calcium yielded a small benefit in life-years as an adjunct to surveillance at a substantial incremental cost of $3,090,000/life-year gained. In contrast, adding surveillance in persons already on calcium cost $27,200/life-year gained.

Sensitivity Analyses

Cost-effectiveness estimates were most dependent on the magnitude of calcium's chemoprotective effect and the cost of calcium. Other variables had minimal impact on the results (Table 3).

Figure 1 demonstrates the effect of varying the annual relative risk of adenoma recurrence with calcium compared with no chemoprevention. Over the plausible range of chemopreventive effect, surveillance remained a reasonable option compared with calcium supplementation alone. Compared with calcium alone, surveillance cost $14,000 to $17,800/life-year gained as the calcium effect decreased from minor chemoprevention with an annual relative risk of adenoma recurrence of 0.95 to the most optimistic assumption of an annual relative risk of 0.60, which corresponds to a 0.67 relative risk of any adenoma and 0.52 relative risk of large adenoma at 3 years. In contrast, the addition of calcium to surveillance remained a very costly intervention even under the most optimistic assumption for calcium chemoprevention, costing $2,350,000/life year gained when the annual relative risk of adenoma recurrence was 0.60.

Supplementary Figure 4 (which can be viewed online at www.journals.cambridge.org/thc) shows the effect of varying the annual cost of calcium. Even at very low cost for calcium, surveillance remained cost-effective compared with calcium supplementation alone. Calcium as an adjunct to surveillance reached a cost of under $50,000/life-year gained

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Table 3. Incremental Cost-Effectiveness Ratios in One-Way Sensitivity Analyses

Variable	Value in Sensitivity Analysis	Calcium versus Natural History	Surveillance versus Calcium	Calcium/Surveillance versus Surveillance
Colonoscopy sensitivity for cancer, %	90	$46,400	$15,200	$2,160,000
	97	$51,500	$16,200	$3,700,000
Colonoscopy sensitivity for large adenoma, %	85	$49,900	$16,400	$2,340,000
	95	$49,900	$15,500	$4,470,000
Colonoscopy sensitivity for small adenoma, %	80	$49,900	$15,800	$2,780,000
	90	$49,900	$16,100	$3,500,000
Colonoscopy major complication rate, %	0.05	$50,000	$15,300	$3,090,000
	0.5	$49,800	$20,900	$3,090,000
Colonoscopy mortality rate, %	0.005	$49,900	$15,400	$3,120,000
	0.03	$49,900	$18,200	$2,950,000
Colonoscopy cost, $	710	$50,200	$5,990	$3,100,000
	1,350	$49,600	$33,600	$3,080,000
Colonoscopy with lesion removal cost, $	990	$50,100	$8,090	$3,350,000
	2,030	$49,700	$29,200	$2,660,000
Calcium per year cost, $	23	$4,640	$23,200	$1,100,000
	255	$355,000	Calcium is dominated	$16,500,000
Endoscopy complication cost, $	16,000	$50,000	$15,400	$3,090,000
	43,000	$49,900	$16,500	$3,090,000
Colorectal cancer care costs	0.5-fold of base case	$52,500	$17,100	$3,120,000
	2-fold of base case	$38,900	$9,200	$3,010,000

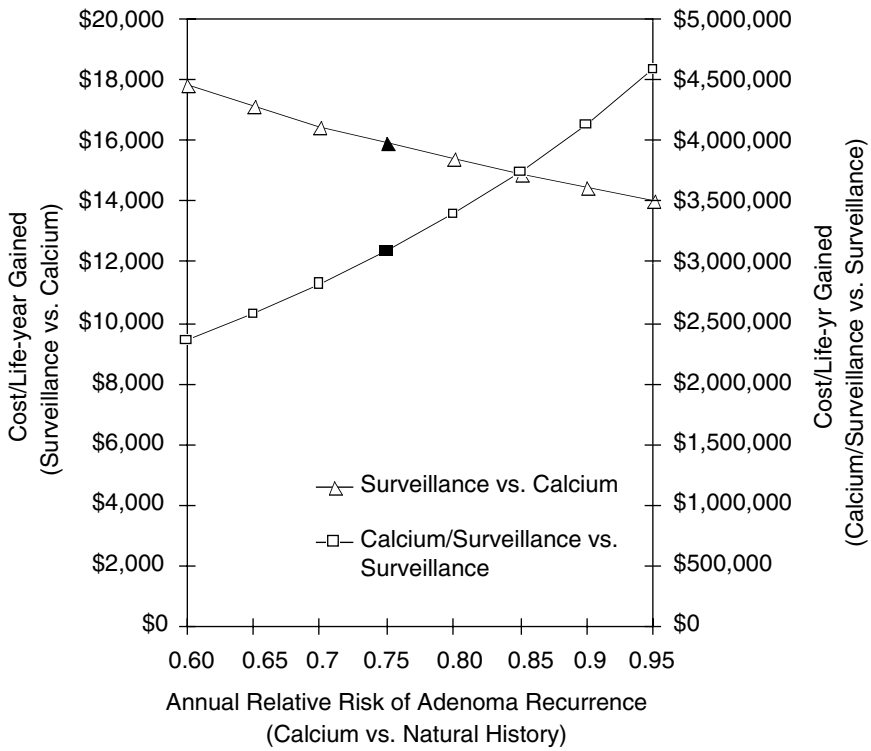

Figure 1. Influence of varying the annual relative risk of adenoma recurrence with calcium versus natural history on the cost/life-year gained for surveillance versus calcium supplementation, and calcium + surveillance versus surveillance alone. Solid points represent the base case.

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at an annual calcium cost of $7. However, this attractive incremental cost-effectiveness ratio is associated with a relatively small increase in effectiveness (Table 3).

DISCUSSION

Mounting evidence from epidemiological studies and several large randomized controlled trials have shown that calcium supplementation may be an effective strategy for preventing and reducing recurrence of colorectal adenomas. Because most CRCs arise from adenomas, calcium chemoprevention may be a reasonable clinical strategy. Whereas calcium supplementation appears to be quite safe, it is prudent to investigate whether calcium chemoprevention of CRC could constitute an effective or cost-effective strategy before considering it as a public health intervention. In doing so, it is mandatory to consider what the optimum target population might be. Given that the randomized trials have evaluated calcium supplementation in individuals with prior adenoma on colonoscopy, a group at higher risk for recurrence than the average population, we focused our analyses on a hypothetical cohort of individuals found to have an adenoma on screening colonoscopy at age 50 years.

Should physicians be recommending, or even prescribing, calcium supplements to their adenoma-bearing patients after polypectomy? Our analyses suggest that surveillance is likely to be much more effective than calcium chemoprevention alone, and that surveillance remains an acceptable intervention in terms of cost-effectiveness over a wide range of calcium chemopreventive effect and calcium cost. Calcium as an adjunct to surveillance may provide a relatively modest improvement in life-expectancy, but this may be achieved at a very substantial cost per life-year gained.

Surveillance colonoscopy is predicted to be a very effective strategy in persons with a history of adenoma. To compete with surveillance, one might postulate that a chemopreventive agent would have to have efficacy approaching a 75–80 percent risk reduction. To enjoy widespread use, it would probably also require a very low cost. As demonstrated in our base case, inexpensive chemoprevention can carry a very high cost/life-year gained as an adjunct to surveillance if it reduces adenoma recurrence risk by only 20–35 percent.

In our simulation, compared with no surveillance or chemoprevention, calcium supplementation was cost-effective by traditional standards. However, because surveillance was much more effective and was a cost-effective alternative, calcium supplementation cannot be recommended as a substitute for surveillance. For adenoma-bearing individuals who have undergone initial polypectomy but are then unable or unwilling to undergo surveillance colonoscopy, calcium supplementation may be a viable and cost-effective strategy.

Our results are similar to those of cost-effectiveness analyses of other chemopreventive agents, such as aspirin and cyclooxygenase-2 inhibitors (3;25;26;56). Collectively, no single chemopreventive agent has been shown to be superior to screening or surveillance. However, the promise of chemoprevention still holds. Ongoing trials of chemopreventive agents may provide encouraging evidence regarding effectiveness. For instance, combinations of chemopreventive agents such as calcium plus aspirin (17) and calcium plus vitamin D (17;58;67) may increase effectiveness. Currently, a national trial of vitamin D and calcium supplementation is under way to evaluate reduction in recurrence of adenomas (http://crisp.cit.nih.gov/crisp/crisp_lib.query).

Adherence is an important consideration. The estimates we present are for persons who adhere fully with long-term chemoprevention and/or surveillance. Thus, they are optimistic estimates on a population-wide basis. Nationally, adherence to CRC screening is disappointing, and surveillance adherence is not well characterized. Adherence to calcium supplementation outside of a clinical trial is not known. Reduced adherence to calcium supplementation may yield a disproportionate decrease in its efficacy without decreasing cost as much, and hence, low adherence may further disfavor calcium supplementation.

In our analysis, we modeled the use of supplemental calcium. However, another approach to increasing daily intake of calcium is from dietary sources. In theory, the individual cost could be less if calcium is part of foods that also provide nutrients and calories, such as dairy, fruits, and vegetables. However, widespread dietary changes in the population are very difficult to achieve. Two studies addressing the cost of achieving a target amount of calcium intake found that calcium carbonate supplements, generic or brand name, are the least expensive source of calcium (21;23).

In the current analysis, we have not considered other beneficial effects of calcium on health, such as increasing bone density and preventing fractures, particularly among the elderly, and women, and potentially lowering of blood pressure. The benefit on bone health is supported by data from the Women's Health Initiative showing that calcium and vitamin D supplementation increase bone mass and decrease risk of fractures in those with good compliance. In other analyses, calcium supplementation has been deemed a cost-effective strategy in prevention of vertebral fractures in postmenopausal women (47) and women treated with glucocorticoids (10). In such patients, calcium may have the additional benefit of reducing adenoma recurrence, but our results suggest that surveillance colonoscopy should still be pursued if appropriate.

Strengths of our analysis include the calibration of the natural history model to data from chemoprevention trials and systematic review of the effect of calcium on adenomas. Our model accounts for missed adenomas during colonoscopy, reflecting the reality for surveillance in everyday practice. We used a wide range of values in our sensitivity analysis for all clinical and economic parameters.

Our study has several limitations. Because our model focuses on post-polypectomy surveillance, it applies to

individuals who are at higher risk for adenomas adenoma formation and CRC. Our quantitative estimates cannot be applied to average risk individuals, but given the lower adenoma risk in these persons, we anticipate that calcium supplementation is also unlikely to be a reasonable substitute for screening. An important consideration is that our model allows for CRC prevention by calcium through its decrease in adenoma recurrence risk. Epidemiological studies suggest that calcium may reduce the risk of CRC (34;41) but a study from the Women's Health Initiative did not support this conclusion (26). It remains to be clarified whether the Women's Health Initiative study could have failed to detect a true effect of long-term calcium use on cancer as an outcome. Our estimates on calcium's potential effectiveness as a chemopreventive agent rely on the assumption that reduction of adenoma recurrence risk will translate into CRC risk reduction. Our sensitivity analyses were one-way deterministic sensitivity analyses.

In summary, calcium supplementation is unlikely to be a reasonable substitute for surveillance after polypectomy. As an adjunct to surveillance, it may add little in terms of CRC risk reduction or increase in life expectancy. Despite its low cost, it is likely to carry a high cost/life-year gained as an adjunct to surveillance. In those who are unwilling or unable to undergo surveillance, calcium supplementation may be a viable option. In the future, combinations of chemopreventive agents may prove to be viable interventions for CRC prevention if they have reasonable effectiveness at a low cost, with excellent safety and long-term adherence.

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