ORIGINAL ARTICLE

A Randomized Trial of Aspirin to Prevent Colorectal Adenomas

John A. Baron, M.D., Bernard F. Cole, Ph.D., Robert S. Sandler, M.D., Robert W. Haile, Dr.Ph., Dennis Ahnen, M.D., Robert Bresalier, M.D., Gail McKeown-Eyssen, Ph.D., Robert W. Summers, M.D., Richard Rothstein, M.D., Carol A. Burke, M.D., Dale C. Snover, M.D., Timothy R. Church, Ph.D., John I. Allen, M.D., Michael Beach, M.D., Ph.D., Gerald J. Beck, Ph.D., John H. Bond, M.D., Tim Byers, M.D., E. Robert Greenberg, M.D., Jack S. Mandel, Ph.D., Norman Marcon, M.D., Leila A. Mott, M.S., Loretta Pearson, M.Phil., Fred Saibil, M.D., and Rosalind U. van Stolk, M.D.

ABSTRACT

BACKGROUND

Laboratory and epidemiologic data suggest that aspirin has an antineoplastic effect in the large bowel.

METHODS

We performed a randomized, double-blind trial of aspirin as a chemopreventive agent against colorectal adenomas. We randomly assigned 1121 patients with a recent history of histologically documented adenomas to receive placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients) daily. According to the protocol, follow-up colonoscopy was to be performed approximately three years after the qualifying endoscopy. We compared the groups with respect to the risk of one or more neoplasms (adenomas or colorectal cancer) at least one year after randomization using generalized linear models to compute risk ratios and 95 percent confidence intervals.

RESULTS

Reported adherence to study medications and avoidance of nonsteroidal antiinflammatory drugs were excellent. Follow-up colonoscopy was performed at least one year after randomization in 1084 patients (97 percent). The incidence of one or more adenomas was 47 percent in the placebo group, 38 percent in the group given 81 mg of aspirin per day, and 45 percent in the group given 325 mg of aspirin per day (global P=0.04). Unadjusted relative risks of any adenoma (as compared with the placebo group) were 0.81 in the 81-mg group (95 percent confidence interval, 0.69 to 0.96) and 0.96 in the 325-mg group (95 percent confidence interval, 0.81 to 1.13). For advanced neoplasms (adenomas measuring at least 1 cm in diameter or with tubulovillous or villous features, severe dysplasia, or invasive cancer), the respective relative risks were 0.59 (95 percent confidence interval, 0.38 to 0.92) and 0.83 (95 percent confidence interval, 0.55 to 1.23).

CONCLUSIONS

Low-dose aspirin has a moderate chemopreventive effect on adenomas in the large bowel.

From the Norris Cotton Cancer Center, Dartmouth–Hitchcock Medical Center, Lebanon, N.H. (J.A.B., B.F.C., E.R.G.); Dartmouth Medical School, Hanover, N.H. (J.A.B., R.R., M.B., E.R.G., L.A.M., L.P.); the University of North Carolina School of Medicine, Chapel Hill (R.S.S.); the University of Southern California School of Medicine, Los Angeles (R.W.H.); the Veterans Affairs Medical Center, Denver (D.A.); the University of Colorado School of Medicine, Denver (D.A., T.B.); Henry Ford Health Sciences Center, Detroit (R.B.); the University of Toronto, Toronto (G.M.-E., N.M., F.S.); the Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City (R.W.S.); the Cleveland Clinic Foundation, Cleveland (C.A.B., R.U.S., G.J.B.); Fairview Southdale Hospital, Minneapolis (D.C.S.); the University of Minnesota, Minneapolis (T.R.C.); the University of Minnesota School of Medicine, Minneapolis (J.I.A., J.H.B.); Minnesota Gastroenterology, Minneapolis (J.I.A.); the Veterans Affairs Medical Center, Minneapolis (J.H.B.); and the Rollins School of Public Health, Emory University, Atlanta (J.S.M.). Address reprint requests to Dr. Baron at Biostatistics and Epidemiology, Evergreen Center, 46 Centerra Pkwy., Lebanon, NH 03766, or at john.a.baron@dartmouth.edu.

N Engl J Med 2003;348:891-9.

THERE IS CONSIDERABLE EVIDENCE that nonsteroidal antiinflammatory drugs (NSAIDs), particularly aspirin, reduce the risk of colorectal cancer and adenomas. Both epidemiologic studies and experimental studies in animals have demonstrated the anticarcinogenic effects of these drugs,[1,2] and randomized trials in patients with familial adenomatous polyposis have shown that the NSAIDs sulindac and celecoxib can cause regression of adenomas.[3-6]

Adenomas are precursors of most colorectal cancers. The epidemiology of adenomas closely resembles that of colorectal cancer itself,[7,8] and prevention of adenomas will most likely also prevent colorectal cancer. However, since observational data alone generally cannot establish chemopreventive efficacy, we conducted a randomized trial of aspirin for the prevention of colorectal adenomas.

METHODS

DESIGN OF THE STUDY

The Aspirin/Folate Polyp Prevention Study is a randomized, double-blind, placebo-controlled trial of the efficacy of oral aspirin, folic acid, or both to prevent colorectal adenomas. The study has a three-by-two factorial design, comparing 81 mg and 325 mg of aspirin per day with placebo and comparing 1 mg of folic acid per day with placebo. The trial was initially designed to investigate only aspirin, but soon after recruitment began, the study was extended to examine folate also. One hundred patients who were randomly assigned to receive aspirin or placebo could not be included in the factorial design for folate, but they are in the analyses of aspirin presented here. This report focuses solely on aspirin; the folate intervention is ongoing. The trial involves nine clinical centers (see the Appendix). Human-subjects committees at each study center approved the study protocol. An independent data and safety monitoring committee reviews the study semiannually.

RECRUITMENT, RANDOMIZATION, AND TREATMENT

The staff of the clinical centers reviewed colonoscopy and pathology records to identify potential participants. Eligible patients had at least one of the following: one or more histologically confirmed colorectal adenomas removed within 3 months before recruitment, one or more histologically confirmed adenomas removed within 16 months before recruitment and a lifetime history of two or more confirmed adenomas, or a histologically confirmed adenoma at least 1 cm in diameter removed within 16 months before recruitment. We also required each patient to have undergone a complete colonoscopy within three months before recruitment and to have no known colorectal polyps remaining. Eligible patients were between 21 and 80 years old, were in good health, and were recommended to undergo colonoscopic follow-up three years after the qualifying examination.

Exclusion criteria included a history of a familial colorectal cancer syndrome, invasive large-bowel cancer, malabsorption syndromes, any condition that could potentially be worsened by supplemental aspirin or folic acid, and any condition commonly treated with aspirin, NSAIDs, or folate (e.g., recurrent arthritis, atherosclerotic vascular disease, and folic acid deficiency). Our recruitment goal in the initial aspirin protocol was 1000 randomized patients, a number that would give the study 80 percent power (with a 5 percent type I error) to detect an absolute difference in the rate of recurrence of adenoma of 40 percent, given a 40 percent risk of recurrence in the placebo group.

Recruitment extended from July 1994 until March 1998. After providing written informed consent, the patients began a three-month run-in period during which they received 325 mg of aspirin per day to assess adherence to therapy and tolerance of aspirin. Patients who reported taking at least 80 percent of the tablets, who wished to continue participating, and who were judged to be suitable, underwent randomization. Blocked randomization with the use of computer-generated random numbers was stratified according to study center, sex, and age (60 years or younger vs. older than 60 years). Study tablets were distributed primarily in calendar packs, with each blister containing three tablets: 325 mg of aspirin (or identical-appearing cellulose–sucrose placebo), 81 mg of aspirin (or placebo), and 1 mg of folic acid (or placebo). The study was double-blind: treatment assignments were not revealed to the patients or to any staff members except the statistical analyst and the pharmacy technician.

FOLLOW-UP

Patients were regularly counseled regarding the avoidance of aspirin and other NSAIDs. Acetaminophen was distributed for the treatment of minor febrile illnesses and pain. Every four months, the patients received questionnaires regarding their

adherence to study treatment; their use of medications, over-the-counter drugs, and nutritional supplements; and the occurrence of symptoms, illnesses, and hospitalizations. Lists of brand names and chemical names of available over-the-counter and prescription NSAIDs were included in the questionnaires, and patients were asked whether they had taken any of the listed drugs.

According to the protocol, patients were to undergo a complete surveillance colonoscopy 34 to 40 months after the qualifying examination. At each colonoscopy, the endoscopist recorded the estimated size and location of all polyps and mucosal lesions that were suggestive of neoplasia, according to usual clinical practice. Each lesion was removed and examined histologically at the clinical center and by the study pathologist. Polyps were classified as neoplastic (adenomatous) or nonneoplastic (e.g., hyperplastic) by the study pathologist.

The primary study outcome was the proportion of patients in whom one or more colorectal adenomas were detected during the period from one year after randomization through the anticipated surveillance follow-up examination. If a surveillance colonoscopy was not performed during the interval specified by the protocol, the last examination at least one year after randomization, on or before September 28, 2001, was used as the follow-up examination. Prespecified secondary outcomes were the numbers of colorectal adenomas and advanced lesions, defined as tubulovillous adenomas (25 to 75 percent villous features), villous adenomas (more than 75 percent villous), large adenomas (at least 1 cm in diameter), severe dysplasia, or invasive cancer. Separate analyses were also conducted of lesions in the left side of the colorectum (descending colon, sigmoid colon, and rectum) and the right side of the colorectum (the remainder of the bowel).

STATISTICAL ANALYSIS

Because folic acid intervention is continuing, this analysis compares the aspirin groups irrespective of folic acid treatment. Patients who underwent a follow-up endoscopy at least one year after randomization were included in the analyses. The predefined primary statistical analysis was a chi-square test with 2 degrees of freedom for a contingency table comparing the risk of one or more new adenomas in the three groups. Crude risk ratios and 95 percent confidence intervals were used to compare the aspirin groups with the placebo group. Adjusted risk ratios were obtained from log-linear models in which age, sex, the clinical center, the number of lifetime adenomas, and the duration of follow-up were covariates. Among patients in the full three-by-two factorial trial, a blinded analysis with further adjustment for folate-treatment assignment yielded results similar to those presented. The possibility that base-line characteristics modified treatment effects was assessed with the use of interaction terms in the log-linear model. Other clinical end points were compared with the use of Fisher's exact test. Poisson regression was used to estimate ratios of recurrent adenomas according to the treatment group; these results were similar to those in the risk analysis and are not presented. According to the protocol, we did not plan to stop the study early for

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Placebo (N=372)	81 mg of Aspirin (N=377)	325 mg of Aspirin (N=372)
Age — yr	57.4±9.9	57.3±9.9	57.7±9.1
Male sex — no. (%)	233 (62.6)	244 (64.7)	235 (63.2)
Race or ethnic group — no. (%)			
Non-Hispanic white	307 (82.5)	329 (87.3)	322 (86.6)
Non-Hispanic black	27 (7.3)	22 (5.8)	19 (5.1)
Hispanic	27 (7.3)	16 (4.2)	18 (4.8)
Asian, Pacific Islander, or other	11 (3.0)	10 (2.6)	13 (3.5)
Body-mass index†	27.3±4.4	27.3±4.4	27.7±4.7
Current cigarette smoker — no. (%)	53 (14.3)	59 (15.7)	55 (15.9)
Colorectal cancer in first-degree relative — no. (%)	105 (28.2)	111 (29.4)	125 (33.6)
No. of reported adenomas before randomization	2.4±2.2	2.2±2.0	2.4±2.4
Qualified for study with history of 1 adenoma — no. (%)	166 (44.9)	177 (47.1)	171 (46.1)
Qualified for study with adenoma ≥1 cm — no. (%)	124 (33.3)	108 (28.6)	127 (34.1)
No. of adenomas on examinations qualifying for study entry	1.6±1.0	1.6±1.0	1.6±1.0
Estimated diameter of largest qualifying adenoma — cm	0.7±0.5	0.7±0.5	0.7±0.5
Dietary calcium intake — mg/day	780±436	737±366	759±463
Dietary folate intake — μg/day	328±161	313±158	319±151

* Plus–minus values are means ±SD. Data on smoking status were missing for 5 patients, data on body-mass index, reported adenomas before randomization, and qualification for the study with history of one adenoma were missing for 4 patients, and data on dietary information were missing for 55 patients.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

efficacy. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Of the 1409 eligible patients who began the run-in period, 1121 underwent randomization: 372 were assigned to receive placebo, 377 to receive 81 mg of aspirin per day, and 372 to receive 325 mg of aspirin per day. Of the 288 patients who did not undergo randomization, 1 died, 73 had bleeding or another possible adverse event, 62 were unable to avoid taking drugs prohibited by the study, 47 were found to be ineligible for reasons related to the folate component of the study (e.g., anemia), 28 had intercurrent illness, 34 were noncompliant, 17 were ineligible for other reasons, and 26 declined to continue. The numbers of patients randomized ranged from 97 to 157 among the clinical centers. There were no significant differences among the groups in the demographic, lifestyle, or clinical characteristics that we assessed (Table 1).

A total of 1084 randomized patients (96.7 percent) underwent a follow-up examination (Table 2), and the entire large-bowel mucosa was well visualized in 1049 (96.8 percent). Reported compliance with the study protocol was excellent and was similar among the groups (Table 3). During the first year of participation, 94.1 percent of patients reported taking virtually all study tablets, and another 3.7 percent reported taking at least half. Even in the year before the final follow-up colonoscopy, 88.3 percent of patients reported taking 90 percent or more of the study tablets and another 5.3 percent at least half. Patients were also successful in avoiding nonprotocol use of aspirin and other NSAIDs. During the first year, 73.7 percent of patients reported no use of NSAIDs; only 3.8 percent reported taking NSAIDs on more than four days a month, on average. In the year before the follow-up examination, these proportions were 66.4 percent and 9.3 percent, respectively.

Among the 1084 patients who had a follow-up examination, 670 had a total of 1812 polyps of some sort. Fifty-eight of 664 polyps in patients in the placebo group (8.7 percent) were lost or not removed, as were 47 of 497 in the group given 81 mg of aspirin (9.5 percent) and 41 of 651 in the group given 325 mg of aspirin (6.3 percent). At least one colorectal adenoma was diagnosed in 47.1 percent of patients in the placebo group, 38.3 percent of patients in the group given 81 mg of aspirin per day, and 45.1 percent of those taking 325 mg of aspirin per day (global P=0.04) (Table 4). The crude relative risk (for the comparison with placebo) was 0.81 in the 81-mg group (95 percent confidence interval, 0.69 to 0.96) and 0.96 in the 325-mg group (95 percent confidence interval, 0.81 to 1.13) (P for the differ-ence=0.06). The unadjusted relative risk for the two aspirin groups combined was 0.88 (95 percent confidence interval, 0.77 to 1.02). The multivariate relative risks were similar (Table 4).

Table 2. Follow-up of Patients.

Variable	Placebo (N=372)	81 mg of Aspirin (N=377)	325 mg of Aspirin (N=372)
Died — no. (%)	3 (0.8)	3 (0.8)	4 (1.1)
No follow-up examination — no. (%)	5 (1.3)	7 (1.9)	13 (3.5)
Follow-up examination only in 1st yr after randomization — no. (%)	1 (0.3)	1 (0.3)	0
Follow-up examination at least 1 yr after randomization — no. (%)			
Total no. evaluated	363	366	355
Within specified interval	318 (87.6)	332 (90.7)	309 (87.0)
Early follow-up examination	10 (2.8)	10 (2.7)	9 (2.5)
Late follow-up examination	35 (9.6)	24 (6.6)	37 (10.4)
Entire large-bowel mucosa well visualized	349 (96.1)	357 (97.5)	343 (96.6)
Interim endoscopy*	12 (3.3)	12 (3.3)	18 (5.1)
Duration of follow-up — mo†	32.9±4.2	32.5±3.4	32.8±3.7

* Interim endoscopy was performed after randomization but before the surveillance examination.
† Values are means ±SD.

Table 3. Self-Reported Compliance with Study Treatment and Avoidance of Nonsteroidal Antiinflammatory Drugs (NSAIDs), According to Treatment Assignment and Study Year.*

Variable	Placebo	81 mg of Aspirin	325 mg of Aspirin
	number of patients/total number (percent)		
Compliance with study treatment			
Year 1			
6–7 days/wk	333/358 (93.0)	338/357 (94.7)	332/351 (94.6)
3–5 days/wk	19/358 (5.3)	9/357 (2.5)	11/351 (3.1)
<3 days/wk	6/358 (1.7)	10/357 (2.8)	8/351 (2.3)
Year 2			
6–7 days/wk	315/353 (89.2)	324/358 (90.5)	317/349 (90.8)
3–5 days/wk	18/353 (5.1)	17/358 (4.7)	16/349 (4.6)
<3 days/wk	20/353 (5.7)	17/358 (4.7)	16/349 (4.6)
Year preceding follow-up examination			
6–7 days/wk	298/342 (87.1)	317/353 (89.8)	301/342 (88.0)
3–5 days/wk	15/342 (4.4)	20/353 (5.7)	20/342 (5.8)
<3 days/wk	29/342 (8.5)	16/353 (4.5)	21/342 (6.1)
Nonprotocol use of NSAIDs			
Year 1			
None	259/359 (72.1)	269/361 (74.5)	262/352 (74.4)
1–4 days/mo	86/359 (24.0)	77/361 (21.3)	78/352 (22.2)
>4 days/mo	14/359 (3.9)	15/361 (4.2)	12/352 (3.4)
Year 2			
None	246/356 (69.1)	250/362 (69.1)	251/352 (71.3)
1–4 days/mo	87/356 (24.4)	87/362 (24.0)	75/352 (21.3)
>4 days/mo	23/356 (6.5)	25/362 (6.9)	26/352 (7.4)
Year preceding follow-up examination			
None	227/351 (64.7)	248/359 (69.1)	226/346 (65.3)
1 day/mo	91/351 (25.9)	79/359 (22.0)	87/346 (25.1)
>4 days/mo	33/351 (9.4)	32/359 (8.9)	33/346 (9.5)

* Only patients who underwent a follow-up examination at least one year after randomization are included in this analysis. Table entries are based on the numbers of patients who responded to interval questionnaires regarding compliance.

Findings varied according to the type of lesion. The unadjusted risk ratios for advanced lesions were 0.59 (95 percent confidence interval, 0.38 to 0.92) for the 81-mg group and 0.83 (95 percent confidence interval, 0.55 to 1.23) for the 325-mg group (P for the difference=0.15). Colorectal cancer was diagnosed in one patient in the placebo group, two in the 81-mg group, and three in the 325-mg group (P=0.71). Findings were similar with respect to adenomas in the right side and the left side of the colorectum; restriction of the analysis to adenomas detected during planned surveillance colonoscopies yielded virtually identical results.

The reduced risk of advanced lesions with low-dose aspirin was more apparent among women than among men (P=0.02 for the interaction of treatment group and sex) and among patients younger than the median age (57 years at randomization) (P for the interaction=0.06). The adjusted risk ratio for the detection of at least one advanced adenoma in the group given 81 mg of aspirin per day was 0.18 (95 percent confidence interval, 0.06 to 0.60) among women and 0.37 (95 percent confidence interval, 0.19 to 0.73) among younger patients.

There were a small number of serious medical events (Table 5). The risks of death and serious bleeding were similar among the groups. Hospitalization, cancer, and myocardial infarction occurred somewhat more frequently in the aspirin groups than in the placebo group, but the differences were compatible with chance. Seven patients had a stroke (all nonfatal): two in the group given 81 mg of aspirin per day and five in the group given 325 mg of aspirin per day (P for heterogeneity=0.06). One stroke (in a patient in the group given 81 mg of aspirin)

Table 4. Risk of Recurrent Adenoma after Randomization.*

Variable	No. with Adenoma/ Total no. (%)	Crude Relative Risk (95% CI)	P Value†	Adjusted Relative Risk (95% CI)‡	P Value†
Any adenoma					
Placebo	171/363 (47.1)	1.00§		1.00§	
Aspirin	300/721 (41.6)	0.88 (0.77–1.02)		0.89 (0.77–1.03)	
81 mg/day	140/366 (38.3)	0.81 (0.69–0.96)		0.83 (0.70–0.98)	
325 mg/day	160/355 (45.1)	0.96 (0.81–1.13)	0.06	0.95 (0.80–1.12)	0.14
Advanced lesion					
Placebo	47/363 (12.9)	1.00§		1.00§	
Aspirin	66/721 (9.2)	0.71 (0.50–1.00)		0.70 (0.49–0.99)	
81 mg/day	28/366 (7.7)	0.59 (0.38–0.92)		0.58 (0.37–0.90)	
325 mg/day	38/355 (10.7)	0.83 (0.55–1.23)	0.15	0.83 (0.55–1.23)	0.13
Tubular adenoma (<1 cm)					
Placebo	143/363 (39.4)	1.00§		1.00§	
Aspirin	262/721 (36.3)	0.92 (0.79–1.08)		0.93 (0.79–1.10)	
81 mg/day	121/366 (33.1)	0.84 (0.69–1.02)		0.87 (0.72–1.05)	
325 mg/day	141/355 (39.7)	1.01 (0.84–1.21)	0.06	1.00 (0.83–1.20)	0.16

* CI denotes confidence interval.
† P values are for the difference between the group given 81 mg of aspirin per day and the group given 325 mg of aspirin per day.
‡ Risk ratios have been adjusted for age, sex, center, lifetime number of adenomas, and duration of follow-up.
§ This group served as the reference group.

was judged to be hemorrhagic after a review of the medical records.

DISCUSSION

In this randomized, double-blind clinical trial, we found that aspirin reduced the risk of recurrent adenomas among patients with a recent history of adenoma. The effect was moderate, however: a 19 percent relative reduction in the risk of one or more adenomas in the group given 81 mg of aspirin per day, a nonsignificant reduction of 4 percent in the group given 325 mg of aspirin per day, and a nonsignificant reduction of 12 percent for both aspirin groups combined. The reduction in the risk of advanced lesions (as compared with placebo) was more substantial: more than 40 percent in the group given 81 mg of aspirin per day.

Extensive observational data strongly suggest that persistent aspirin use reduces the risk of colorectal neoplasia.[1,2] Although 10 to 20 years of treatment seem to be required to lower the risk of colorectal cancer,[9] our data and those of Sandler et al.,[10] which appear elsewhere in this issue of the *Journal*, suggest that a few years of aspirin use can reduce adenoma recurrence. Virtually all studies indicate that the reduction in the risk of colorectal cancer or adenomas dissipates after aspirin therapy is stopped.[2] In a secondary analysis of a clinical trial focused on cardiovascular disease, aspirin had no significant effect on colorectal neoplasia.[11] However, the study did not include uniform surveillance for adenomas, and treatment was for a median of only five years — too brief a period for an effect on colorectal cancer to become evident.

The mechanisms by which aspirin reduces the risk of colorectal neoplasia are not clear. All NSAIDs disrupt the synthesis of prostaglandins by inhibiting cyclooxygenase enzymes. Cyclooxygenase-2 is thought to be the isoform most commonly implicated in carcinogenesis, but at the doses we used, aspirin has little activity against this isoform.[12] Nonetheless, aspirin may suppress the expression of cyclooxygenase-2,[13] and it may also have antineoplastic effects that are unrelated to cyclooxygenase.[14,15] Our finding that aspirin was associated with more substantial reductions in the risk of advanced lesions than in that of nonadvanced lesions suggests that the effects of aspirin may be greater in later stages of the adenoma–carcinoma sequence,

such as during progression from small tubular adenomas to larger or villous adenomas.

The possibility of overlooked adenomas may have affected our findings, since 15 to 25 percent of small polyps may be missed in a single colonoscopy.[16,17] Aspirin could cause these polyps to regress, as sulindac and celecoxib have been shown to do in patients with familial adenomatous polyposis,[3-6] and such regression could have been part of the effect we observed. However, if aspirin did not affect these polyps, their presence most likely would have had a conservative effect on our estimates, since randomization would have balanced the numbers of missed lesions in the groups. The duration of treatment may also have been important: longer treatment might have resulted in more pronounced effects.

Aspirin increases the risk of bleeding,[2,18,19] but in the low doses we used, this was not a substantial problem. In part because we excluded patients with known atherosclerotic disease, there were relatively few serious adverse events. There was an increase in the risk of stroke among patients who were randomly assigned to receive aspirin (P=0.06), a finding consistent with the results of previous studies of populations at low cardiovascular risk.[20]

It is not clear why a dose of 81 mg of aspirin per day, but not 325 mg, reduced the risk of adenomas in our study. In observational studies, the effect of NSAIDs on colorectal neoplasia has not depended very strongly on the dose,[10,21,22] but there has been virtually no comparison in epidemiologic studies of the doses of aspirin we used. The 81-mg dose and the 325-mg dose appear to suppress colorectal prostaglandin levels to a similar extent[23-25] and thus may have equivalent chemopreventive potency through cyclooxygenase-related mechanisms. Perhaps the most likely explanation for our finding is that a low threshold dose is required for chemoprotection and that the differences in effects between the low dose and the high dose were the result of chance. However, prostaglandin E_2 may protect the large-bowel mucosa from inflammatory damage[26,27] and several prostanoids may have anticarcinogenic effects,[28] so excessive prostanoid suppression could have deleterious effects on carcinogenesis.

It is also not clear why our results regarding the 325-mg dose of aspirin differ from those reported by Sandler et al.[10] Chance is certainly one possibility, as is the difference in populations. Our study included primarily patients at a moderately elevated risk of colorectal cancer, indicated by their history of colorectal adenomas, whereas Sandler et al. studied only patients with a history of colorectal cancer. Differences in the definition of end points could also be a factor. Our findings with respect to advanced adenomas were similar to the findings of Sandler et al. for all adenomas, but they found no effect of aspirin on lesions judged to be advanced. Neither study included patients without a history of colorectal neoplasia; such patients may have a different response to aspirin.

Our findings, together with those of Sandler et al., indicate that aspirin reduces the risk of colorectal adenomas among patients with a history of colorectal adenomas or cancer. However, broad recommendations for the use of aspirin as a chemopreventive agent are premature and must be considered in the context of possible toxic effects as well as the potential benefits already provided by periodic surveillance colonoscopy.[29,30] Also, evidence that aspirin and other NSAIDs prevent colorectal cancer itself is currently derived only from observational studies. A clinical trial of aspirin or another NSAID for the primary prevention of colorectal cancer would be desirable, but difficult, because of the large numbers of patients and long follow-up required and the ethical requirement to monitor patients for adenomas (and excise them). A trial of the effect of aspirin on recurrent cancer, second primary cancers,

Table 5. Incidence of Serious Adverse Events after Randomization.

Adverse Event	Placebo (N=372)	81 mg of Aspirin (N=377)	325 mg of Aspirin (N=372)	P Value*
	no. of patients			
Death	3	3	4	0.93
Hospitalization	44	61	57	0.20
Noncolorectal cancer	6	14	9	0.21
Colorectal cancer	1	2	3	0.71
Myocardial infarction	1	2	5	0.24
Coronary revascularization	4	3	5	0.76
Stroke	0	2	5	0.06
Serious bleeding†				
Gastrointestinal	3	2	4	0.65
Genitourinary	2	6	2	0.24

* P values are for the differences among the three groups.
† Serious bleeding was defined as bleeding leading to hospitalization or surgical intervention.

or both among patients with resected colorectal cancer might be more feasible. Nonetheless, our findings of a beneficial effect of aspirin on the risk of adenoma provide a basis for optimism regarding the development of NSAIDs as effective chemopreventive therapy against colorectal cancer.

Supported by a grant (CA 59005) from the National Institutes of Health. Aspirin and placebo tablets were generously provided by the Bayer Corporation.

Drs. Baron, Sandler, Ahnen, Bresalier, and Greenberg have reported serving as paid consultants to Merck. Dr. Ahnen is a consultant to Cell Pathways, Inc. Dr. Baron has reported serving as a consultant to Bayer. Dr. Rothstein has reported serving as a consultant to AstraZeneca. Dr. Baron has reported being paid by Pharmacia for lecturing. Dr. Marcon has reported being paid by AstraZeneca for lecturing. Dr. Rothstein has reported being paid by AstraZeneca, Merck, Pfizer, TAP, and Esai for lecturing. Drs. Burke, Greenberg, Sandler, and Rothstein have reported receiving grant support from Merck. Dr. Baron has equity interests in Pfizer and Merck. Dr. Beck has equity interests in Amgen, Pfizer, and Eli Lilly. Dr. Mandel has equity interests in Amgen. Ms. Mott has equity interests in Wyeth. Ms. Pearson has equity interests in Merck.

We are indebted to the patients for their cooperation and enthusiasm.

APPENDIX

The Aspirin/Folate Polyp Prevention Study Group also includes the following: **Investigators:** *Cleveland Clinic Foundation* — R. Cameron (University Suburban Health Center Physicians), J. Church; *University of Colorado Health Sciences Center* — L. Richman, R. Reveille, and R. Roller (Rocky Mountain Gastroenterology Associates); J. Levine and J. Singleton (University Hospital); P. Baker, P. Hanna, D. Hruza, L. Morton, and J. Sabel (South Denver Endoscopy); R. Hansen, N. Bilir, and A. Triebling (Arapahoe Gastroenterology); W. Brown and J. Deutsch (Denver Veterans Affairs Medical Center); J. Egan and P. McNally (Fitzsimons Army Medical Center); *Dartmouth–Hitchcock Medical Center* — A. Barchowsky, T. Morgan, and D. Nierenberg (Dartmouth–Hitchcock Medical Center); G. Fiarman (Lahey Clinic); D. Howell (Portland Gastroenterology Associates); P. Moses (University of Vermont College of Medicine); A. Robinson (Claremont, N.H.), S. Rosenberg (Beth Israel Deaconess); A. Warner (Lahey Clinic); *Henry Ford Health Sciences Center* — F. Arlow, S. Batra, M. Blumenkehl, A. Dekovich, M. Ibrahim, Y. Muszkat, R. Murphy, Y. Siddiqui, J. Swetech, S. Watts, and M. Zonca; *University of Iowa College of Medicine* — D. Abramson, D. Purdy, R. Silber, and G. Weinman (Gastroenterologists, P.C.I., Cedar Rapids); N. Dusdieker (Internists, P.C., Cedar Rapids); J. Ewing and B. O'Meara (Gastroenterology Associates of Iowa City); K. Gannamaneni, K. Gorrepati, and R. Movva (Gastroenterology Consultants, Moline); *University of Minnesota* — the physicians of Minnesota Gastroenterology, P.A.; *University of North Carolina School of Medicine* — M. Delissio and M. Pike (Cary Gastroenterology Associates); S. Levinson (Chapel Hill Internal Medicine); R. McCall and M. Pate (Mid-Carolina Gastroenterology); R. Schwarz (Raleigh Medical Group); *University of Southern California* — Z. Azar, B. Batra, D. Berkowitz, and E. Lever (Kaiser-Bellflower); C. Conteas, D. Gerety, and T. Teller (Kaiser-Sunset); *University of Toronto* — E.J. Irvine and B. Salena (McMaster University Hamilton Health Sciences Centre); L. Cohen, M.A. Cooper, T. Devlin, D. Hemphill, E. Hurowitz, E. Lin, H. Price, and S. Stafford (Sunnybrook and Women's College Health Sciences Centre); G. Kandel, P. Kortan, and G. Haber (St. Michael's Hospital); **Data and Safety Monitoring Board:** W. Willett (Harvard University), F. Giardiello (Johns Hopkins University School of Medicine), J. Lachin (George Washington University), and L.J. Roberts (Vanderbilt University School of Medicine); **Polyp Prevention Studies Coordinating Center:** B. Beaulieu, D. Carmichael, K. Chambers, P. Courtney, J. Dykes, S. Ewell, J. Hebb, J. Mullaly, S. Pierson, S. Raymond, S. Rovell-Rixx, and B. Thomas; **Coordinators:** *Cleveland Clinic Foundation* — J. Bauman and H. Hasson; *University of Colorado Health Sciences Center* — S. Frederick, S. Rein, and B. Ciminelli; *Dartmouth–Hitchcock Medical Center* — E. Brow, D. Chamberlain, L. Hallock, M. Hynes, L. Wetteman, and K. Wood; *Henry Ford Health Sciences Center* — L. Muffler and B. Zonka; *University of Iowa College of Medicine* — D. Finke and R. Thompson; *University of Minnesota* — J. Blomquist and S. Waldemar; *University of North Carolina School of Medicine* — A. Aileo and B. Schliebe; *University of Southern California* — J. Cowen, S. Gerety, L. Gerstmann, A. Gupta, P. Harmon, C. Hinck, A. Montes, and N. Uk; *University of Toronto* — N. Bassett, V. Jazmaji, M. Khatchadourian, M. Morgan, S. Pearen, C. Ross, and L. Vernich.

REFERENCES

1. Arber N. Do NSAIDs prevent colorectal cancer? Can J Gastroenterol 2000;14:299-307.
2. IARC handbooks of cancer prevention. Vol. 1. Non-steroidal anti-inflammatory drugs. Lyons, France: International Agency for Research on Cancer, 1997.
3. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313-6.
4. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 1991;101:635-9.
5. Ladenheim J, Garcia G, Titzer D, et al. Effect of sulindac on sporadic colonic polyps. Gastroenterology 1995;108:1083-7.
6. Steinbach G, Lynch PM, Phillips RKS, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946-52.
7. Peipins LA, Sandler RS. Epidemiology of colorectal adenomas. Epidemiol Rev 1994; 16:273-97.
8. Neugut AI, Jacobson JS, DeVivo I. Epidemiology of colorectal adenomatous polyps. Cancer Epidemiol Biomarkers Prev 1993;2: 159-76.
9. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med 1994;121:241-6.
10. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348: 883-90.
11. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst 1993;85:1220-4.
12. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis. J Natl Cancer Inst 1998;90:1529-36.
13. Xu XM, Sansores-Garcia L, Chen XM, Matijevic-Aleksic N, Du M, Wu KK. Suppression of inducible cyclooxygenase 2 gene transcription by aspirin and sodium salicylate. Proc Natl Acad Sci U S A 1999;96:5292-7.
14. Gupta RA, Dubois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer 2001; 1:11-21.
15. Shiff SJ, Rigas B. The role of cyclooxygenase inhibition in the antineoplastic effects of nonsteroidal antiinflammatory drugs (NSAIDs). J Exp Med 1999;190:445-50.
16. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-8.
17. Hixson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. Gastrointest Endosc 1991;37:125-7.
18. Hawkey CJ. Nonsteroidal anti-inflammatory drug gastropathy. Gastroenterology 2000;119:521-35.
19. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ 2000;321:1183-7.

20. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106. [Erratum, BMJ 1994;308:1540.]
21. Smalley W, Ray WA, Daugherty J, Griffin MR. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;159:161-6.
22. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer 1998;82:2326-33.
23. Sample D, Wargovich M, Fischer SM, et al. A dose-finding study of aspirin for chemoprevention utilizing rectal mucosal prostaglandin E(2) levels as a biomarker. Cancer Epidemiol Biomarkers Prev 2002;11:275-9.
24. Ruffin MTIV, Krishnan K, Rock CL, et al. Suppression of human colorectal mucosal prostaglandins: determining the lowest effective aspirin dose. J Natl Cancer Inst 1997;89:1152-60.
25. Barnes CJ, Hamby-Mason RL, Hardman WE, Cameron IL, Speeg KV, Lee M. Effect of aspirin on prostaglandin E2 formation and transforming growth factor alpha expression in human rectal mucosa from individuals with a history of adenomatous polyps of the colon. Cancer Epidemiol Biomarkers Prev 1999;8:311-5.
26. Kabashima K, Saji T, Murata T, et al. The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. J Clin Invest 2002;109:883-93.
27. Krause W, DuBois RN. Eicosanoids and the large intestine. Prostaglandins Other Lipid Mediat 2000;61:145-61.
28. Shureiqi I, Lippman SM. Lipoxygenase modulation to reverse carcinogenesis. Cancer Res 2001;61:6307-12.
29. Provenzale D. The cost-effectiveness of aspirin for chemoprevention of colorectal cancer. Gastroenterology 2002;122:230-3.
30. Ladabaum U, Chopra CL, Huang G, Scheiman JM, Chernew ME, Fendrick AM. Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2001;135:769-81.