

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 31, 2006

VOL. 355 NO. 9

## Celecoxib for the Prevention of Sporadic Colorectal Adenomas

Monica M. Bertagnolli, M.D., Craig J. Eagle, M.D., Ann G. Zauber, Ph.D., Mark Redston, M.D., Scott D. Solomon, M.D., KyungMann Kim, Ph.D., Jie Tang, M.S., Rebecca B. Rosenstein, Ph.D., Janet Wittes, Ph.D., Donald Corle, M.S., Timothy M. Hess, M.S., G. Mabel Woloj, Ph.D., Frédéric Boisserie, William F. Anderson, M.D., M.P.H., Jaye L. Viner, M.D., M.P.H., Donya Bagheri, M.S., D.A.B.T., John Burn, M.D., Daniel C. Chung, M.D., Thomas Dewar, M.D., T. Raymond Foley, M.D., Neville Hoffman, M.D., Finlay Macrae, M.D., Ronald E. Pruitt, M.D., John R. Saltzman, M.D., Bruce Salzberg, M.D., Thomas Sylwestrowicz, M.D., Gary B. Gordon, M.D., Ph.D., and Ernest T. Hawk, M.D., M.P.H., for the APC Study Investigators\*

### ABSTRACT

#### BACKGROUND

Studies showing that drugs that inhibit cyclooxygenase-2 (COX-2) reduce the number of colorectal adenomas in animals and patients with familial adenomatous polyposis suggest that COX-2 inhibitors may also prevent sporadic colorectal neoplasia.

#### METHODS

We randomly assigned patients who had adenomas removed before study entry to receive placebo (679 patients) or 200 mg (685 patients) or 400 mg (671 patients) of celecoxib twice daily. Randomization was stratified for the use of low-dose aspirin. Follow-up colonoscopies were performed at one and three years after randomization. The occurrence of newly detected colorectal adenomas was compared among the groups with the life-table extension of the Mantel–Haenszel test.

#### RESULTS

Follow-up colonoscopies were completed at year 1 in 89.5 percent of randomized patients, and at year 3 in 75.7 percent. The estimated cumulative incidence of the detection of one or more adenomas by year 3 was 60.7 percent for patients receiving placebo, as compared with 43.2 percent for those receiving 200 mg of celecoxib twice a day (risk ratio, 0.67; 95 percent confidence interval, 0.59 to 0.77;  $P < 0.001$ ) and 37.5 percent for those receiving 400 mg of celecoxib twice a day (risk ratio, 0.55; 95 percent confidence interval, 0.48 to 0.64;  $P < 0.001$ ). Serious adverse events occurred in 18.8 percent of patients in the placebo group, as compared with 20.4 percent of those in the low-dose celecoxib group (risk ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3;  $P = 0.5$ ) and 23.0 percent of those in the high-dose group (risk ratio, 1.2; 95 percent confidence interval, 1.0 to 1.5;  $P = 0.06$ ). As compared with placebo, celecoxib was associated with an increased risk of cardiovascular events (risk ratio for the low dose, 2.6; 95 percent confidence interval, 1.1 to 6.1; and risk ratio for the high dose, 3.4; 95 percent confidence interval, 1.5 to 7.9).

#### CONCLUSIONS

These findings indicate that celecoxib is an effective agent for the prevention of colorectal adenomas but, because of potential cardiovascular events, cannot be routinely recommended for this indication. (ClinicalTrials.gov number, NCT00005094.)

From Brigham and Women's Hospital, Boston (M.M.B., M.R., S.D.S., J.R.S.); Pfizer, New York (C.J.E., J.T., R.B.R., G.M.W., F.B.); Memorial Sloan-Kettering Cancer Center, New York (A.G.Z.); the University of Wisconsin, Madison (K.K., T.M.H.); the Statistics Collaborative, Washington, D.C. (J.W.); the National Cancer Institute, Bethesda, Md. (D.C., W.F.A., J.L.V., E.T.H.); CCS Associates, Mountain View, Calif. (D.B.); the University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom (J.B.); Massachusetts General Hospital, Boston (D.C.C.); Harris Methodist Hospital Fort Worth, Fort Worth, Tex. (T.D.); Regional Gastroenterology Associates of Lancaster, Lancaster, Pa. (T.R.F.); Sir Charles Gairdner Hospital, Perth, Australia (N.H.); the Royal Melbourne Hospital, Melbourne, Australia (F.M.); Nashville Medical Research Institute, Nashville (R.E.P.); Atlanta Gastroenterology Associates, Atlanta (B.S.); St. Paul's Hospital, University of Saskatchewan, Saskatoon, Canada (T.S.); and G.D. Searle, Skokie, Ill. (G.B.G.). Address reprint requests to Dr. Bertagnolli at the Division of Surgical Oncology, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mbertagnolli@partners.org.

\*Investigators participating in the Adenoma Prevention with Celecoxib (APC) study are listed in the Appendix.

N Engl J Med 2006;355:873-84.

Copyright © 2006 Massachusetts Medical Society.

**C**OLORECTAL CANCER IS A COMMON MALIGNANT condition, responsible for approximately 150,000 new patients and approximately 55,000 deaths per year in the United States alone.<sup>1</sup> Despite these statistics, colorectal cancer is one of the most preventable cancers. Most colorectal cancers develop from precursor adenomas, which can be identified and removed during a screening colonoscopy. This procedure may lower the rates of death due to colorectal cancer by as much as 30 to 40 percent.<sup>2</sup> The aim of chemoprevention is to use pharmacologic agents to augment the benefits of colonoscopic polypectomy by inhibiting early stages of tumorigenesis, thereby preventing malignant transformation of precursor adenomas.

A remarkable concordance of data from more than 40 observational studies suggests that nonsteroidal antiinflammatory drugs (NSAIDs) reduce the incidence of colorectal adenomas, colorectal cancer, and deaths from colorectal cancer.<sup>3</sup> The effects of NSAIDs have been confirmed in randomized trials showing that aspirin has a modest chemopreventive effect on sporadic colorectal adenomas.<sup>4-6</sup> A leading hypothesis explaining this result is based on the presence of tumorigenic cyclooxygenase-2 (COX-2) within adenomas but not in normal intestinal tissue. COX-2 mediates the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in epithelial tissues, resulting in activation of signaling pathways that promote cell proliferation and inhibit cell death.<sup>7,8</sup> Selective COX-2 inhibitors, such as celecoxib, were originally developed for the treatment of pain and inflammation. In patients with familial adenomatous polyposis, celecoxib (Celebrex) also showed antitumor activity.<sup>9</sup> We conducted a randomized trial to determine whether celecoxib also prevents sporadic colorectal adenomas.

## METHODS

### STUDY DESIGN

The Adenoma Prevention with Celecoxib (APC) trial was a randomized, placebo-controlled trial to test whether celecoxib reduces the occurrence of endoscopically detected colorectal adenomas. We tested the safety and antitumor efficacy of 200 mg of celecoxib twice daily, 400 mg of celecoxib twice daily, and placebo. The randomization was stratified on the basis of the use or nonuse of low-dose aspirin (325 mg or less every other day or 162.5 mg

or less every day) and clinical site. The trial involved 91 clinical sites (72 in the United States, 8 in Australia, 10 in Canada, and 1 in the United Kingdom). The study protocol was approved by the human-subjects committee at each site. All patients provided written informed consent before enrollment. An independent data and safety monitoring board reviewed safety data monthly and efficacy data twice a year. All study colonoscopies were performed by gastroenterologists associated with the APC trial. The APC trial was funded by the National Cancer Institute and by Pfizer, through a clinical trials agreement with the National Cancer Institute. The APC trial was a cooperative effort led by a study steering committee composed of the lead principal investigator, the National Cancer Institute project officer, and a representative from Pfizer. The steering committee of the APC trial directed all aspects of the study, including its design, data gathering, data analysis, and manuscript preparation. The authors vouch for the completeness and veracity of the data and data analysis.

### RECRUITMENT AND RANDOMIZATION

Staff at the clinical sites identified eligible study participants by reviewing colonoscopy records during a recruitment period from November 1999 to March 2002. Participants ranged from 31 to 88 years of age at enrollment and had recently undergone colonoscopic removal of colorectal adenomas and had a high risk of recurrent adenomas on the basis of a history of either multiple adenomas or removal of a single adenoma more than 5 mm in diameter. Within six months before enrollment, eligible patients underwent complete colonoscopy with removal of all polyps, one or more of which was a histologically confirmed adenoma.

Patients were willing to abstain from long-term use of NSAIDs (defined as more than 21 days of use per year) or COX-2 inhibitors, excluding low-dose aspirin, for the duration of the study. Patients not taking aspirin at baseline were required to abstain from taking it during the trial.

Exclusion criteria included a history of familial adenomatous polyposis, hereditary nonpolyposis colon cancer, inflammatory bowel disease, or large-bowel resection other than appendectomy. Other exclusion criteria included a history of a renal or hepatic disorder, a clinically significant bleeding disorder, or treatment for a gastrointestinal ulcer in the month before study entry. Pa-

tients were ineligible if they had used NSAIDs or aspirin at doses of more than 325 mg every other day at least three times a week during the two months before randomization or if they had received treatment with oral or intravenous corticosteroids for more than two weeks during the six months before randomization.

A total of 2457 potential participants entered a 30-day placebo run-in period during which they were required to have at least 80 percent adherence to medication use, as measured by pill counts, in order to proceed to randomization (Fig. 1). During this time, a central study pathologist reviewed baseline adenomas to confirm study eligibility; subsequently, 2035 patients were stratified according to clinical site and the use or nonuse of low-dose aspirin and were randomly assigned to treatment by means of an interactive voice-response system.

#### STUDY TREATMENT

Study medication was distributed in capsules containing 100 mg of celecoxib for the 685 patients assigned to 200 mg twice daily, 200 mg of celecoxib for the 671 patients assigned to 400 mg twice daily, or placebo for the remaining 679 patients. Each capsule was identical in appearance. Patients were provided medication at six-month intervals and were instructed to take two capsules with food in the morning and in the evening each day. Open-label low-dose aspirin was supplied for patients already taking aspirin, and acetaminophen was supplied for the treatment of minor pain and febrile illnesses. In compliance with a recommendation by the data and safety monitoring board, which was based on an analysis revealing that patients taking celecoxib were at increased risk for cardiovascular events, study treatment was discontinued on December 17, 2004, before all patients had completed three years of treatment.<sup>10</sup>

#### ASSESSMENT OF END POINTS AND FOLLOW-UP

All primary efficacy analyses were performed on an intention-to-treat basis, with primary end points determined for all patients by means of follow-up colonoscopies, regardless of whether the patient adhered to the treatment regimen. The primary efficacy end point was the detection of an adenoma during a post-randomization colonoscopy. One secondary end point was the detection of advanced adenomas, defined as adenomas having any of the following characteristics: a diameter of at least

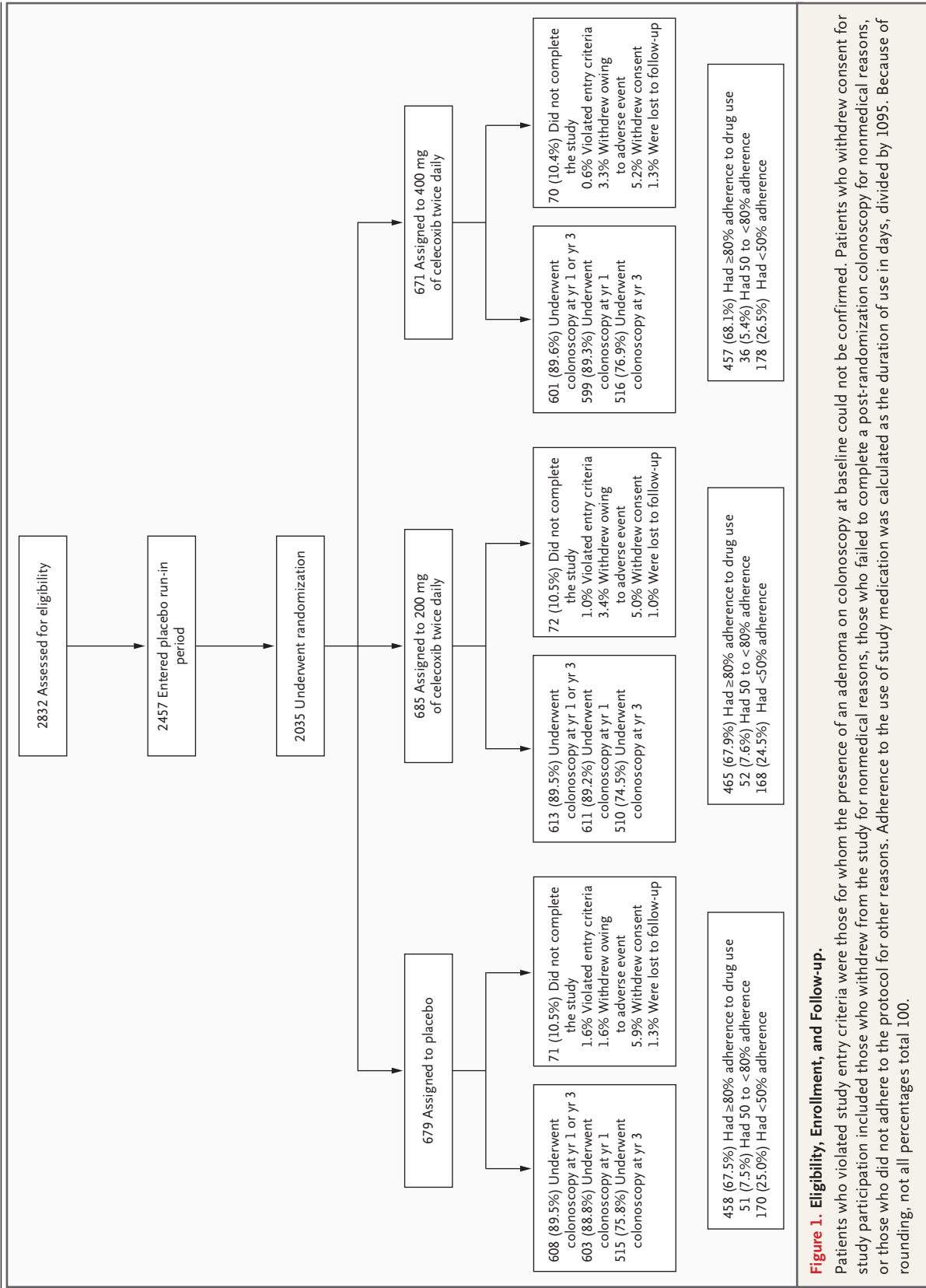
1 cm according to endoscopic measurement, villous or tubulovillous histologic appearance, high-grade dysplasia, intramucosal carcinoma, or invasive cancer. Other secondary end points included the number of adenomas, the size of the largest adenoma, and the adenoma burden (the sum of the diameter of all adenomas).

A complete physical examination, including clinical laboratory tests (i.e., complete blood count, serum chemical analysis, and urinalysis) and determination of vital signs, was performed at baseline and one and three years after randomization. Patients were contacted every two months to report use of concomitant medication and adverse events. During these discussions, patients were also counseled to avoid nonprotocol use of aspirin and NSAIDs.

A study investigator performed a complete colonoscopy with visualization of the cecum and endoscopic removal of all polyps one and three years after randomization. In cases of inadequate bowel preparation or failure to reach the cecum, year 1 colonoscopies were repeated at the discretion of the investigator, and year 3 colonoscopies were repeated within six weeks after the incomplete examination. A central study pathologist examined in a blinded fashion all polyps removed during these colonoscopies. If the central study pathologist and the institutional pathologist disagreed, polyps were examined by an independent, adjudicating pathologist who was unaware of the previous histologic diagnosis and whose opinion resolved the discrepancy. Adverse events reported by investigators were classified according to criteria from the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1. Serious adverse events were reported to a study monitor within 24 hours after identification by personnel at the clinical site.

#### STATISTICAL ANALYSIS

The trial was designed with a statistical power of 96 percent to detect a 35 percent reduction in the relative risk from a placebo incidence of 40 percent<sup>11</sup> in the proportion of patients in whom adenomas were detected during a three-year follow-up period at the 0.025 (two-sided) level of significance for each celecoxib group as compared with the placebo group. Power calculations assumed a dropout rate of up to 40 percent and were adjusted for use or nonuse of aspirin. The primary end point of the detection of an adenoma and the



**Figure 1. Eligibility, Enrollment, and Follow-up.**

Patients who violated study entry criteria were those for whom the presence of an adenoma on colonoscopy at baseline could not be confirmed. Patients who withdrew consent for study participation included those who withdrew from the study for nonmedical reasons, those who failed to complete a post-randomization colonoscopy for nonmedical reasons, or those who did not adhere to the protocol for other reasons. Adherence to the use of study medication was calculated as the duration of use in days, divided by 1095. Because of rounding, not all percentages total 100.

secondary end point of the detection of advanced adenomas were compared for each treatment group with the use of the Mantel–Cox test, which is a life-table extension of the Mantel–Haenszel statistic with stratification for aspirin use or nonuse at baseline.<sup>12–14</sup> The Mantel–Cox procedure also provides a summary risk ratio, which is the weighted average of the relative risk over the two intervals and two aspirin strata.<sup>13,14</sup> Patients with no follow-up colonoscopy were excluded from both intervals. A patient with a colonoscopy at year 3 but with no colonoscopy at year 1 was included in the analysis through year 1, with the assumption that the patient had no adenoma by year 1, and was then included in the analysis through year 3 according to the findings of the colonoscopy at year 3. The analyses at year 3 excluded patients with an adenoma at the year 1 colonoscopy and patients with no adenoma at year 1 and no colonoscopy at year 3.

Investigator-reported adverse events were analyzed in total and according to prespecified categories to describe renal and hypertensive disorders, gastrointestinal ulceration and hemorrhage, and cardiovascular disorders. The analyses included all events occurring after the first dose of study medication. Patients with the end point of an adverse event were defined as those who had at least one of the adverse events during the course of the study, and the risk ratio was estimated on the basis of the relative risk (adjusted for aspirin use).

An additional analysis separately examined serious cardiovascular events, since these events were considered to be of the greatest clinical importance. These serious adverse events were then adjudicated and analyzed by an independent cardiovascular safety team, as reported previously, and updated for the current report with the use of final study data.<sup>10</sup> The outcome of a serious adverse event was based on a time-to-event analysis, and the Cox proportional hazards model was used to assess the risk ratio. There were no formal interim analyses of efficacy. All reported P values for safety analyses are two-sided and not adjusted for multiple testing. All analyses were performed with SAS software, version 8 or higher.

## RESULTS

Baseline variables were similar across all treatment groups (Table 1). Risk factors for adverse events, such as a history of cardiovascular disease,

smoking, or diabetes, were also balanced among treatment groups. Colonoscopic end points were assessed in 1822 of 2035 patients who had undergone randomization (89.5 percent); 1541 patients (75.7 percent) completed the examination at year 3 (Fig. 1). Before assessment of the end points, 10.5 percent of the patients withdrew from the study. This includes 1.2 percent of patients who had undergone randomization but were lost to follow-up before a study colonoscopy was performed. Patients who did not complete the study were relatively evenly distributed among the treatment groups (Fig. 1).

Patients who did not adhere to the use of the study drug for any reason remained in the study until the scheduled completion time for the determination of the end points, in keeping with the intention-to-treat principle. Approximately two thirds of participants adhered to the treatment regimen at least 80 percent of the time, with no significant difference among the treatment groups (Fig. 1). Because of an increased incidence of cardiovascular events in the two groups treated with celecoxib, use of the study medication by patients who had undergone randomization was discontinued on December 17, 2004, in compliance with the recommendations of the data and safety monitoring board. At that time, 1762 patients (86.6 percent) had completed three years of treatment. Of the 273 patients who still had one to three months remaining of planned use of the study drug, 199 (72.9 percent) underwent study colonoscopy at year 3, and these data were used in the primary efficacy analyses.

The primary efficacy analysis considered adenomas detected at any time after randomization (Table 2). A small percentage of polyps removed (1.4 percent) were not retrieved and could not be examined. In the placebo group, 354 patients had at least one adenoma, as did 252 patients in the group receiving 200 mg of celecoxib twice daily, and 213 patients in the group receiving 400 mg of celecoxib twice daily. The estimated cumulative incidence of the detection of one or more adenomas was 60.7 percent in the placebo group, 43.2 percent in the group receiving 200 mg of celecoxib twice daily, and 37.5 percent in the group receiving 400 mg of celecoxib twice daily. This corresponds to a risk ratio of 0.67 (95 percent confidence interval, 0.59 to 0.77) in the 200-mg group and 0.55 (95 percent confidence interval, 0.48 to 0.64) in the 400-mg group.

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Placebo (N=679)	Celecoxib, 200 mg Twice Daily (N=685)	Celecoxib, 400 mg Twice Daily (N=671)
Age — yr			
Median	59	59	59
Range	31–88	35–83	34–87
Male sex — no. (%)	473 (69.7)	460 (67.2)	454 (67.7)
Race or ethnic group — no. (%)†			
Non-Hispanic white	624 (91.9)	632 (92.3)	607 (90.5)
Non-Hispanic black	37 (5.4)	30 (4.4)	45 (6.7)
Hispanic	11 (1.6)	16 (2.3)	10 (1.5)
Asian, Pacific Islander, or other	7 (1.0)	7 (1.0)	9 (1.3)
Body-mass index‡			
Men	28.8±0.2	28.9±0.2	28.6±0.2
Women	29.3±0.4	28.5±0.4	29.0±0.4
Colorectal cancer in a parent — no. (%)	140 (20.6)	147 (21.5)	142 (21.2)
No. of reported adenomas	2.0±0.1	2.1±0.1	2.1±0.1
At least one adenoma ≥1 cm — no. (%)	288 (42.4)	303 (44.2)	291 (43.4)
Multiple adenomas — no. of patients (%)	374 (55.1)	375 (54.7)	363 (54.1)
Adenoma burden — cm§	1.48±0.05	1.50±0.05	1.47±0.04
Use of low-dose aspirin — no. (%)¶	212 (31.2)	211 (30.8)	204 (30.4)
History of cardiovascular events — no. (%)	99 (14.6)	94 (13.7)	99 (14.8)
History of hypertension — no. (%)	280 (41.2)	290 (42.3)	264 (39.3)
History of diabetes — no. (%)	61 (9.0)	67 (9.8)	66 (9.8)
Current cigarette smoker — no. (%)	122 (18.0)	119 (17.4)	96 (14.3)

\* Plus-minus values are means ±SE.

† Race or ethnic group was determined by the investigator.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The adenoma burden was defined as the sum of the diameter of all adenomas reported during colonoscopy at baseline.

¶ Low-dose aspirin was defined as 325 mg or less every other day or 162.5 mg or less every day.

|| Cardiovascular events were defined as myocardial infarction, cerebrovascular disease, congestive heart failure, and angina.

Celecoxib therapy was associated with a reduced number of advanced adenomas; 99 patients in the placebo group had at least one advanced adenoma during the three-year period, as compared with 44 patients in the group receiving 200 mg of celecoxib twice daily and 35 patients in the group receiving 400 mg of celecoxib twice daily. The estimated cumulative incidence of advanced adenomas was 17.2 percent for patients receiving placebo, 7.8 percent for those treated with 200 mg of celecoxib twice daily, and 6.3 percent for those treated with 400 mg of celecoxib twice daily, corresponding to a risk ratio of 0.43 (95 percent confidence interval, 0.31 to 0.61) in the 200-mg group and 0.34 (95 percent confidence

interval, 0.24 to 0.50) in the 400-mg group. Subgroup analyses according to the use or nonuse of low-dose aspirin yielded similar results (Table 2).

During the three-year study, the adenoma burden was smaller among patients given celecoxib than among those given placebo. Patients receiving placebo had a mean (±SE) adenoma burden of 1.3±0.1 cm, as compared with 1.0±0.1 cm among patients receiving 200 mg of celecoxib twice daily (P=0.004) and 0.9±0.1 cm among those receiving 400 mg of celecoxib twice daily (P=0.002) (Fig. 2).

Clinical variables measured during physical examinations during the study showed increased blood pressure among patients in the celecoxib groups, with a change from baseline to year 3 in

**Table 2. Risk of Adenomas.\***

Variable	Placebo (N = 679)	Celecoxib, 200 mg Twice Daily (N = 685)	Celecoxib, 400 mg Twice Daily (N = 671)
<b>Detection of any adenoma†</b>			
All patients			
Year 1 colonoscopy — no. with adenoma/total no. at risk (%)	271/608 (44.6)	186/613 (30.3)	137/601 (22.8)
Year 3 colonoscopy — no. with adenoma/total no. at risk (%)	83/286 (29.0)	66/357 (18.5)	76/400 (19.0)
Cumulative incidence of adenomas detected through year 3 — %	60.7±2.1	43.2±2.1	37.5±2.1
Risk ratio (95% CI)	—	0.67 (0.59–0.77)	0.55 (0.48–0.64)
P value‡	—	<0.001	<0.001
Patients taking aspirin			
Cumulative incidence of adenomas detected through year 3 — %	59.9±3.7	45.7±3.8	38.2±3.8
Risk ratio (95% CI)	—	0.71 (0.57–0.90)	0.55 (0.43–0.72)
P value‡	—	0.004	<0.001
Patients not taking aspirin			
Cumulative incidence of adenomas detected through year 3 — %	60.9±2.5	42.1±2.5	37.2±2.4
Risk ratio (95% CI)	—	0.65 (0.55–0.77)	0.55 (0.46–0.65)
P value‡	—	<0.001	<0.001
<b>Sensitivity analysis imputing adenoma for patients without an end-point determination§</b>			
Cumulative incidence of adenomas detected through year 3 — %	70.1±1.8	57.5±1.9	51.7±1.0
Risk ratio (95% CI)	—	0.76 (0.69–0.85)	0.66 (0.59–0.73)
P value‡	—	<0.001	<0.001
<b>Analysis of patients who adhered to protocol¶</b>			
Cumulative incidence of adenomas detected through year 3 — %	60.7±2.8	38.8±2.8	35.4±2.7
Risk ratio (95% CI)	—	0.59 (0.48–0.73)	0.51 (0.41–0.64)
P value‡	—	<0.001	<0.001
<b>Detection of advanced adenomas  </b>			
All patients			
Year 1 colonoscopy — no. with advanced adenoma/total no. at risk (%)	67/608 (11.0)	26/613 (4.2)	17/601 (2.8)
Year 3 colonoscopy — no. with advanced adenoma/total no. at risk (%)	32/459 (7.0)	18/487 (3.7)	18/503 (3.6)
Cumulative incidence of advanced adenomas detected through year 3 — %	17.2±1.6	7.8±1.1	6.3±1.0
Risk ratio (95% CI)	—	0.43 (0.31–0.61)	0.34 (0.24–0.50)
P value‡	—	<0.001	<0.001

\* Plus–minus values are means ±SE. CI denotes confidence interval, and dashes not applicable.

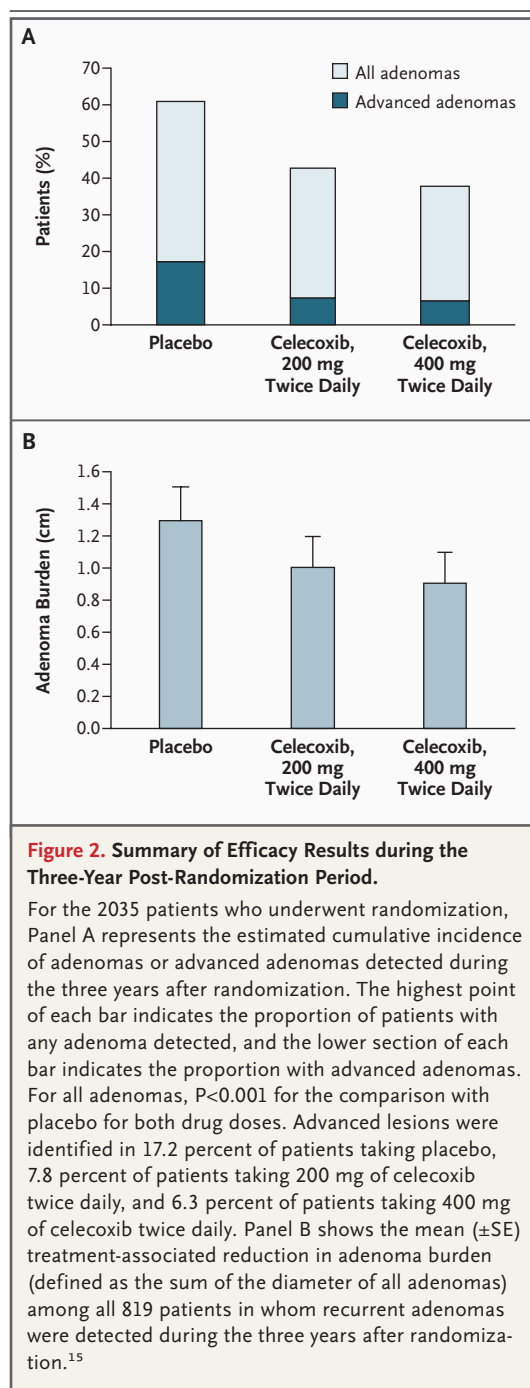
† Patients considered at risk during year 1 included those who underwent colonoscopy at year 1, as well as those who did not undergo colonoscopy at year 1 but did do so at year 3. Patients who underwent colonoscopy at year 3 alone were assumed to have had no adenomas detected at year 1. Patients considered at risk at year 3 included all patients who underwent a colonoscopy at year 3 and who had no adenomas at year 1 or who did not undergo colonoscopy at year 1 and were therefore assumed to have no adenomas at year 1.

‡ The P value is for the comparison with the placebo group.

§ Sensitivity analysis imputing adenoma for patients without an end-point determination assumes that any patient who underwent randomization and did not have an end-point determination (either at year 1 or at year 3) had an adenoma detected at year 1 and that any patient who underwent randomization and had an end-point determination only at year 3 had the same findings present at year 1.

¶ Population compliant with protocol consists of 754 patients who used study medication at a compliance level of ≥80 percent for the period from randomization up to one month before colonoscopy at year 3 and who had no adenoma detected at the colonoscopy at year 1.

|| Advanced adenomas were defined as adenomas that were at least 1 cm in diameter or that had villous or tubulovillous histologic features, high-grade dysplasia, intramucosal carcinoma, or invasive carcinoma. Seven invasive cancers were diagnosed during the trial. Colorectal cancer was diagnosed in three patients in the placebo group, six months after randomization for one patient and three years after randomization for two patients. Four invasive carcinomas were identified in patients treated with 400 mg of celecoxib twice daily; one was diagnosed at the scheduled year 1 study, and three were diagnosed at the scheduled year 3 study.



mean blood pressure of  $-1.6/-3.0$  mm Hg in the placebo group,  $+1.0/-1.2$  mm Hg in patients assigned to 200 mg of celecoxib twice daily, and  $+3.6/-1.0$  mm Hg in patients assigned to 400 mg of celecoxib twice daily ( $P < 0.001$  and  $P = 0.01$  for the comparison of the combined celecoxib groups with the placebo group for systolic and diastolic

blood pressure, respectively). No drug-associated change was observed in serum levels of creatinine, alanine aminotransferase, or hemoglobin.

At least one adverse event was reported in 617 patients in the placebo group (91.3 percent), 645 of those receiving 200 mg of celecoxib twice daily (94.4 percent), and 635 of those receiving 400 mg of celecoxib twice daily (94.9 percent) (Table 3). At least one serious adverse event was reported in 18.8 percent of the patients in the placebo group, as compared with 20.4 percent of those receiving 200 mg of celecoxib twice daily (risk ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3;  $P = 0.5$ ), and 23.0 percent of those receiving 400 mg of celecoxib twice daily (risk ratio, 1.2; 95 percent confidence interval, 1.0 to 1.5;  $P = 0.06$ ) (Table 3 and Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). One patient in the placebo group had grade 3 bleeding after the polypectomy — a serious complication resulting from a study colonoscopy.

Nonadjudicated investigator-reported renal and hypertensive disorders, gastrointestinal ulceration and hemorrhage, and cardiovascular disorders were analyzed separately. No consistent dose-related trend toward an increased incidence of renal and hypertensive disorders or gastrointestinal ulceration and hemorrhage was observed, although aspirin users assigned to receive celecoxib showed a trend toward increased gastrointestinal ulceration and hemorrhage.

Cardiovascular adverse events among participants in the APC trial have been reported previously, according to a prespecified analysis of adjudicated serious adverse events,<sup>10</sup> and were updated with the final study data (Table 3). This analysis indicated an increased risk of serious cardiovascular complications (i.e., death from cardiovascular causes, nonfatal myocardial infarction, stroke, or heart failure) among those receiving celecoxib, with risk ratios of 2.6 (95 percent confidence interval, 1.1 to 6.1) and 3.4 (95 percent confidence interval, 1.5 to 7.9) for the low-dose and high-dose cohorts, respectively. The absolute magnitude of risk was greatest for patients with a history of cardiovascular events at baseline, although no relation between cardiovascular events at baseline and during the study was observed in patients receiving celecoxib. Patients who entered the study with a history of myocardial infarction, stroke, congestive heart failure, or angina had a 3.0 percent incidence of serious cardiovascular

**Table 3. Incidence of Adverse Events after Randomization.\***

Adverse Event†	Placebo (N=676)	Celecoxib, 200 mg Twice Daily (N=683)	Celecoxib, 400 mg Twice Daily (N=669)
<b>All serious adverse events — no. of patients (%)</b>	127 (18.8)	139 (20.4)	154 (23.0)
Risk ratio (95% CI)		1.1 (0.9–1.3)	1.2 (1.0–1.5)
Deaths — no. of patients (%)	6 (0.9)	8 (1.2)	10 (1.5)
Risk ratio (95% CI)		1.3 (0.5–3.8)	1.7 (0.6–4.6)
Adjudicated prespecified serious cardiovascular events — no. of patients (%)‡	7 (1.0)	18 (2.6)	23 (3.4)
Risk ratio (95% CI)		2.6 (1.1–6.1)	3.4 (1.5–7.9)
<b>Any adverse event — no. of patients with adverse event/no. in cohort (%)</b>			
All patients	617/676 (91.3)	645/683 (94.4)	635/669 (94.9)
Risk ratio (95% CI)		1.0 (1.0–1.1)	1.0 (1.0–1.1)
Renal and hypertensive disorders§	130/676 (19.2)	164/683 (24.0)	141/669 (21.1)
Risk ratio (95% CI)		1.2 (1.0–1.5)	1.1 (0.9–1.4)
Gastrointestinal ulceration and hemorrhage¶	80/676 (11.8)	78/683 (11.4)	76/669 (11.4)
Risk ratio (95% CI)		1.0 (0.7–1.3)	1.0 (0.7–1.3)
Nonadjudicated investigator-reported cardiovascular disorders	30/676 (4.4)	45/683 (6.6)	54/669 (8.1)
Risk ratio (95% CI)		1.5 (0.9–2.3)	1.8 (1.2–2.8)
Patients taking aspirin	201/219 (91.8)	193/205 (94.1)	197/211 (93.4)
Risk ratio (95% CI)		1.0 (1.0–1.1)	1.0 (1.0–1.1)
Renal and hypertensive disorders§	44/219 (20.1)	57/205 (27.8)	46/211 (21.8)
Risk ratio (95% CI)		1.4 (1.0–2.0)	1.1 (0.8–1.6)
Gastrointestinal ulceration and hemorrhage¶	24/219 (11.0)	28/205 (13.7)	31/211 (14.7)
Risk ratio (95% CI)		1.2 (0.7–2.1)	1.3 (0.8–2.2)
Nonadjudicated investigator-reported cardiovascular disorders	15/219 (6.8)	21/205 (10.2)	21/211 (10.0)
Risk ratio (95% CI)		1.5 (0.8–2.8)	1.5 (0.8–2.7)
Patients not taking aspirin	416/457 (91.0)	452/478 (94.6)	438/458 (95.6)
Risk ratio (95% CI)		1.0 (1.0–1.1)	1.1 (1.0–1.1)
Renal and hypertensive disorders§	86/457 (18.8)	107/478 (22.4)	95/458 (20.7)
Risk ratio (95% CI)		1.2 (0.9–1.5)	1.1 (0.8–1.4)
Gastrointestinal ulceration and hemorrhage¶	56/457 (12.3)	50/478 (10.5)	45/458 (9.8)
Risk ratio (95% CI)		0.9 (0.6–1.2)	0.8 (0.6–1.2)
Nonadjudicated investigator-reported cardiovascular disorders	15/457 (3.3)	24/478 (5.0)	33/458 (7.2)
Risk ratio (95% CI)		1.5 (0.8–2.9)	2.2 (1.2–4.0)

\* CI denotes confidence interval.

† Safety analyses excluded seven patients who underwent randomization but never received the study drug: three patients in the placebo group, two assigned to 200 mg of celecoxib twice daily, and two assigned to 400 mg of celecoxib twice daily. Events recorded are those that occurred during the time after the first dose of study drug until completion of or withdrawal from the study. Other categories of serious adverse events that were similar among all treatment groups are listed in the Supplementary Appendix.

‡ This category includes myocardial infarction, stroke, congestive heart failure, and death due to cardiovascular disease. Data that were available for up to three years after the beginning of treatment were analyzed for all patients who underwent randomization. Additional data concerning nonadjudicated investigator-reported serious adverse events related to the cardiovascular system are provided in the Supplementary Appendix.

§ This category includes reports of elevated serum creatinine levels, fluid retention and edema, hypertension, proteinuria, and renal failure.

¶ This category includes anemia, gastrointestinal bleeding, gastritis or duodenitis, upper or lower gastrointestinal ulceration, and other hemorrhage.

|| These disorders were defined as angina, myocardial infarction or ischemia, cerebrovascular disease, peripheral vascular disease, venous thrombosis or thromboembolism, peripheral vascular therapeutic procedures, cardiovascular therapeutic procedures, and death or circulatory collapse.

events if they took placebo and an 8.8 percent incidence if they took celecoxib at either dose (risk ratio for the comparison with placebo, 3.0; 95 percent confidence interval, 0.9 to 10.4). Among patients without these risk factors at baseline, 0.7 percent of those in the placebo group had a serious cardiovascular event, as compared with 2.1 percent of those in either celecoxib group (risk ratio, 3.0; 95 percent confidence interval, 1.0 to 8.7). The adjudicated analysis of data pertaining to serious adverse events agreed substantially with nonadjudicated investigator reports of serious adverse events related to cardiovascular disorders.

#### DISCUSSION

Previous attempts to modify the risk of sporadic adenomas through dietary interventions have been largely unsuccessful,<sup>16,17</sup> although calcium and vitamin D supplementation demonstrated a slight benefit.<sup>18-20</sup> Randomized trials of aspirin showed a more substantial chemopreventive effect, with reductions of approximately 20 percent among patients in whom recurrent adenomas developed.<sup>4-6</sup> These findings are tempered somewhat by the observation in one study that low-dose, but not high-dose, aspirin had an antitumor effect.<sup>4</sup> We studied a cohort at high risk for colorectal tumors, as evidenced by a 60.7 percent incidence of newly detected adenomas in the placebo group during the three-year period and a 17.2 percent incidence of advanced lesions. Treatment with a 400-mg dose of celecoxib twice daily for three years reduced the incidence of recurrent adenomas of any type by 45 percent and of high-risk lesions by 66 percent. The effect was confirmed by a similarly designed independent study, the PreSAP Trial, described by Arber et al. elsewhere in this issue of the *Journal*.<sup>21</sup> Patients in the APC trial who took aspirin in addition to celecoxib did not show greater chemopreventive benefit than those who took celecoxib alone.

We did not directly assess the effect of celecoxib on colorectal cancer. In the context of a program of surveillance colonoscopy to detect and remove premalignant adenomas, the benefit of celecoxib in the prevention of colorectal cancer is still unknown, and further research is necessary to develop a successful chemopreventive regimen. To optimize the benefit, studies should focus on persons who are at the highest risk for colorectal cancer, since celecoxib was particularly effective in preventing advanced lesions. Colorectal cancer

takes many years to develop, and celecoxib causes regression, in addition to suppression, of established adenomas.<sup>9</sup> Thus, additional investigations should address the value of various dosing schedules, considering the dose-related effects on the prevention of adenomas and on adverse events.

Selective COX-2 inhibitors were developed as a safer alternative to nonselective NSAIDs, with respect to gastrointestinal bleeding. These agents preferentially inhibit COX-2, an inducible enzyme mediating inflammation and tumorigenesis, and not COX-1, the constitutively expressed enzyme responsible for protective mechanisms in the gastric mucosa and renal vasculature. Selective COX-2 inhibitors have fewer effects on gastric mucosa or platelet function than do the nonselective NSAIDs and, as a result, may be associated with fewer ulcers and hemorrhagic complications.<sup>22</sup> In general, our results are consistent with these assertions, although the combination of aspirin and celecoxib may be associated with more gastrointestinal ulceration and hemorrhagic events than is placebo.

Previously, we reported the results of a cardiovascular analysis conducted of the APC trial while the treatment portion of the study was still under way.<sup>10</sup> The data were analyzed on an intention-to-treat basis and included adjudicated serious cardiovascular events, and the analysis revealed an increased risk among patients taking celecoxib of a combined end point including myocardial infarction, stroke, congestive heart failure, or death due to cardiovascular disease. The updated adjudicated analysis reported here, which includes one additional event in the low-dose celecoxib group, also shows a dose-related increased cardiovascular risk associated with celecoxib. Not surprisingly, subgroup analyses suggested that the absolute risk of cardiovascular events was greatest among patients with a history of cardiovascular events at baseline, but the risk ratio did not differ significantly among those with and those without cardiovascular events at baseline. In addition, blood pressure increased with the use of celecoxib, suggesting that changes in vascular tone may predispose patients to cardiovascular events.

In summary, the use of celecoxib by patients at high risk for colorectal neoplasia significantly reduced the proportion of patients with adenomas detected during a three-year study. This trial documented prevention of premalignant adenomas with celecoxib but was not designed to assess effectiveness of the drug for the prevention of colorectal cancer, and no claims about

its use in this regard can be made from our data. Safety analyses confirmed previous reports of an increased incidence of serious cardiovascular events. If future study of celecoxib for the chemoprevention of colorectal cancer is pursued, the potential addition of this drug to an optimal endoscopic surveillance program must be weighed against the known risk of serious cardiovascular events.

Supported by the National Cancer Institute (N01-CN-95015) and Pfizer.

Drs. Bertagnolli and Redston report having received grant support for the APC trial from Pfizer under a clinical trials agreement with Brigham & Women's Hospital. Dr. Macrae reports having received grant support for clinical trials from Pfizer. Drs. Eagle, Rosenstein, Woloj, and Ms. Tang report being employees of Pfizer. Drs. Eagle, Rosenstein, Gordon, and Ms. Tang report owning stock in Pfizer. Dr. Kim reports being a member of a legal-defense team for Merck. No other potential conflict of interest relevant to this article was reported.

#### APPENDIX

The following persons participated in the APC study: **Steering Committee** — M.M. Bertagnolli, E.T. Hawk, C.J. Eagle; **Statistical Team** — A.G. Zauber, K. Kim, D. Corle, R.B. Rosenstein, J. Tang, T. Hess, A. Wilton; **Medical Monitors** — W. Anderson, L. Doody; **Central Pathology Review** — M. Redston; K. Geisinger, C. Compton; **Project Directors** — G.M. Woloj, D. Bagheri, A. Crawford, F. Boissier, M. Schietrum, V. Ladouceur; **Data and Safety Monitoring Board** — S. Rosen (chair), L. Friedman, R. Makuch, R. Phillips, P. Taylor; **Principal Investigators** — **United States:** S. Auerbach (California Professional Research, Newport Beach), C.F. Barish (Wake Research Associates, Raleigh, N.C.), T. Barringer (Carolinas Medical Center, Charlotte, N.C.), R.W. Bennetts (Northwest Gastroenterology Clinic, Portland, Oreg.), M. Blitstein (Associates in Gastroenterology and Liver Disease, Lake Forest, Ill.), J. Bruggen (Wake Forest University Baptist Medical Center, Winston Salem, N.C.), P. Carricaburu (Veterans Affairs Hospital, Sheridan, Wyo.), D. Chung (Massachusetts General Hospital, Boston), F. Colizzo (Pentucket Medical Associates, Haverhill, Mass.), R. Curtis (Newton-Wellesley Hospital, Newton, Mass.), T. Dewar (Harris Methodist Hospital Fort Worth, Fort Worth, Tex.), R. DuBois (Vanderbilt University Medical Center, Nashville), T. Feinstat (Gastroenterology Consultants of Sacramento, Roseville, Calif.), T.R. Foley (Regional Gastroenterology Associates of Lancaster, Lancaster, Pa.), D. Gabbazadeh (Huntington Research Group, Huntington Station, N.Y.), J. Geenen (Wisconsin Center for Advanced Research, Milwaukee), F. Giardiello (Johns Hopkins Hospital, Baltimore), A. Goetsch (nTouch Research, Huntsville, Ala.), M. Goldberg (Regional Gastroenterology Associates of Lancaster, Evanston, Ill.), J.L. Goldstein (University of Illinois at Chicago, Chicago), W. Harlan, III (Asheville Gastroenterology Associates, Asheville, N.C.), R. Hogan (Gastrointestinal Associates, Jackson, Miss.), M. Kamionkowski (Gastroenterology Associates of Cleveland, Mayfield Heights, Ohio), M. Kelfer (Fallon Clinic, West Boylston, Mass.), B. Kerzner (Health Trends Research, Baltimore), K. Kim (University of Chicago Medical Center, Chicago), I. Klimberg (Gastroenterology Associates of Ocala, Ocala, Fla.), G. Koval (West Hills Gastroenterology Associates, Portland, Oreg.), C. Krone (Advanced Clinical Therapeutics, Tucson, Ariz.), S. Krumholz (Waterside Clinical Research, West Palm Beach, Fla.), M.W. Layton (South Puget Sound Clinical Research Center, Olympia, Wash.), C. Lightdale (Columbia-Presbyterian Medical Center, New York), P.J. Limburg (Mayo Clinic, Rochester, Minn.), C. Lind (Vanderbilt University Medical Center, Nashville), D. Lipkis (Institute for Health Care Assessment, San Diego, Calif.), M. Lloyd (Idaho Gastroenterology, Meridian, Idaho), D. Maccini (Spokane Digestive Disease Center, Spokane, Wash.), F. MacMillan, Sr. (Pentucket Medical Associates, Haverhill, Mass.), R. Madoff (University of Minnesota, Minneapolis), A. Malik (Advanced Clinical Research, North Providence, R.I.), A. Markowitz (Memorial Sloan Kettering Cancer Center, New York), R. Marks (Alabama Digestive Research Center, Alabaster), C.J. McDougall (Manhattan Associates, New York), P. Miner (Oklahoma Foundation for Digestive Research, Oklahoma City), M. Murphy (Southern Digestive and Liver Disease Institute, Savannah, Ga.), A. Namais (Gastrointestinal Physicians, Salem, Mass.), N. Nickl (University of Kentucky Medical Center, Lexington), M. Pochapin (Jay Monahan Center for Gastrointestinal Health, New York), R.E. Pruitt (Nashville Medical Research Institute, Nashville), J. Puolos (Cumberland Research Associates, Fayetteville, N.C.), D.S. Riff (AGMG Clinical Research, Anaheim, Calif.), R. Roman (South Denver Gastroenterology, Englewood, Colo.), L. Rubin (New Jersey Physicians, Passaic), D. Ruff (Healthcare Discoveries, San Antonio, Tex.), M. Safdi (Consultants for Clinical Research, Cincinnati), J. Saltzman (Brigham and Women's Hospital, Boston), B. Salzberg (Atlanta Gastroenterology Associates, Atlanta), J.A. Sattler (Western Clinical Research, Torrance, Calif.), P. Schleinitz (Americas Doctors Research, Medford, Oreg.), J. Schwartz (Northwest Gastroenterologists, Arlington Heights, Ill.), M. Schwartz (Jupiter Research Association, Jupiter, Fla.), M. Silpa (Gastroenterology Associates of the East Bay Medical Group, Berkeley, Calif.), D. Silvers (Drug Research Services, Metairie, La.), D. Smoot (Howard University Cancer Center, Washington, D.C.), S. Sontag (Veterans Affairs Medical Center, Hines, Ill.), R.J. Sorrell (Gastroenterology Specialties, Lincoln, Nebr.), D. Stanton (Community Clinical Trials, Orange, Calif.), J. Sturgeon (Americas Doctors Research, Shawnee Mission, Kans.), J.P. Tracey (Hawthorne Medical Associates, North Dartmouth, Mass.), T. Werth (Charlotte Gastroenterology and Hepatology, Charlotte, N.C.), C.M. Wilcox (University of Alabama at Birmingham, Birmingham), R. Wohlman (Northwest Gastroenterology Associates, Bellevue, Wash.), S. Woods (Gastroenterology Associates of Fairfield County, Bridgeport, Conn.); **United Kingdom:** J. Burn, G. Brigham, (South Cleveland Hospital, Middlesbrough); **Australia:** H. Ee (Sir Charles Gairdner Hospital, Nedlands, W.A.), M. Korman (Monash Medical Centre, Clayton, Victoria), A. Lee (Concord Repatriation and General Hospital, Concord, N.S.W.), B. Leggett (Royal Brisbane Hospital, Herston, Queensland), F. Macrae (Royal Melbourne Hospital, Melbourne, Victoria), L. Mollison (Freemantle Hospital, Freemantle, W.A.), N. Yeomans (Western Hospital, Footscray, Victoria), G. Young (Flinders Medical Center, Bedford, S.A.); **Canada:** G. Aumais (Hospital Maisonneuve-Rosemont, Montreal), R. Bailey (Hys Medical Center, Edmonton, Alta.), C. Bernstein (Winnipeg Health Sciences Centre, Winnipeg, Man.), L. Cohen (Sunnybrook and Women's Hospital, Toronto), C. Dallaire, R. Dube (Centre Hospitalier Universitaire de Quebec, Que.), D. Morgan (McMaster University, Hamilton, Ont.), T. Sylwestrowicz (St. Paul's Hospital, Saskatoon, Sask.), G. Van Rosendaal (University of Calgary, Calgary, Alta.), S.J. Van Zantan (Queen Elizabeth II Health Sciences Centre, Halifax, N.S.).

#### REFERENCES

1. Cancer facts and figures 2006. Atlanta: American Cancer Society, 2006. (Accessed August 4, 2006, at <http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf>)
2. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653-7.
3. Hawk ET, Levin B. Colorectal cancer prevention. *J Clin Oncol* 2005;23:378-91.
4. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; 348:891-9.

5. Benamouzig R, Deyra J, Martin A, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* 2003;125:328-36.
6. 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. [Erratum, *N Engl J Med* 2003;348:1939.]
7. Tsujii M, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell* 1995;83:493-501.
8. Pai R, Sorgehan B, Szabo IL, Pavelka M, Baatar D, Tarnawski AS. Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. *Nat Med* 2002;8:289-93.
9. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946-52.
10. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
11. Winawer SJ, Zauber AG, O'Brien JM, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N Engl J Med* 1993;328:901-6.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
13. Stokes ME, Davis CS, Koch GG. Categorical data analysis using the SAS system. 2nd ed. Cary, N.C.: SAS Institute, 2000: 596-9.
14. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, Calif.: Lifetime Learning, 1982:342-59.
15. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst* 1960;37:351-61.
16. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000;342:1149-55.
17. McKeown-Eyssen GE, Bright-See E, Bruce WR, et al. A randomized trial of a low fat high fibre diet in the recurrence of colorectal polyps. *J Clin Epidemiol* 1994;47:525-36. [Erratum, *J Clin Epidemiol* 1995;48:i.]
18. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999;340:101-7.
19. Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003;95:1765-71.
20. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96. [Erratum, *N Engl J Med* 2006;354:1102.]
21. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of sporadic colorectal adenomatous polyps. *N Engl J Med* 2006;355:885-95.
22. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.

Copyright © 2006 Massachusetts Medical Society.

FULL TEXT OF ALL JOURNAL ARTICLES ON THE WORLD WIDE WEB

Access to the complete text of the *Journal* on the Internet is free to all subscribers. To use this Web site, subscribers should go to the *Journal's* home page ([www.nejm.org](http://www.nejm.org)) and register by entering their names and subscriber numbers as they appear on their mailing labels. After this one-time registration, subscribers can use their passwords to log on for electronic access to the entire *Journal* from any computer that is connected to the Internet. Features include a library of all issues since January 1993 and abstracts since January 1975, a full-text search capacity, and a personal archive for saving articles and search results of interest. All articles can be printed in a format that is virtually identical to that of the typeset pages. Beginning six months after publication, the full text of all Original Articles and Special Articles is available free to nonsubscribers who have completed a brief registration.