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## A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer

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### ABSTRACT

#### BACKGROUND

Experimental studies in animals and observational studies in humans suggest that regular aspirin use may decrease the risk of colorectal adenomas, the precursors to most colorectal cancers.

#### METHODS

We conducted a randomized, double-blind trial to determine the effect of aspirin on the incidence of colorectal adenomas. We randomly assigned 635 patients with previous colorectal cancer to receive either 325 mg of aspirin per day or placebo. We determined the proportion of patients with adenomas, the number of recurrent adenomas, and the time to the development of adenoma between randomization and subsequent colonoscopic examinations. Relative risks were adjusted for age, sex, cancer stage, the number of colonoscopic examinations, and the time to a first colonoscopy. The study was terminated early by an independent data and safety monitoring board when statistically significant results were reported during a planned interim analysis.

#### RESULTS

A total of 517 randomized patients had at least one colonoscopic examination a median of 12.8 months after randomization. One or more adenomas were found in 17 percent of patients in the aspirin group and 27 percent of patients in the placebo group ( $P=0.004$ ). The mean ( $\pm$ SD) number of adenomas was lower in the aspirin group than the placebo group ( $0.30\pm 0.87$  vs.  $0.49\pm 0.99$ ,  $P=0.003$  by the Wilcoxon test). The adjusted relative risk of any recurrent adenoma in the aspirin group, as compared with the placebo group, was 0.65 (95 percent confidence interval, 0.46 to 0.91). The time to the detection of a first adenoma was longer in the aspirin group than in the placebo group (hazard ratio for the detection of a new polyp, 0.64; 95 percent confidence interval, 0.43 to 0.94;  $P=0.022$ ).

#### CONCLUSIONS

Daily use of aspirin is associated with a significant reduction in the incidence of colorectal adenomas in patients with previous colorectal cancer.

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**T**HERE IS CONSIDERABLE EVIDENCE that aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) may decrease the risk of colorectal neoplasia.<sup>1-3</sup> Experiments in rodents have demonstrated that indomethacin decreases the incidence of carcinogen-induced colonic tumors,<sup>4</sup> and both retrospective and prospective studies found that NSAIDs protect against colorectal cancer in humans.<sup>5-9</sup> Moreover, randomized trials demonstrated a decrease in the number and size of adenomas in patients with familial adenomatous polyposis who received celecoxib or sulindac.<sup>10,11</sup>

It is difficult to show that NSAIDs prevent colorectal cancer because of the long latency period before cancer develops. Because most colorectal cancers arise from benign adenomas, adenomas have been used as surrogate end points in prevention trials. The results of most adenoma-prevention trials have, however, been disappointing. Studies of antioxidant vitamins,<sup>12</sup> fiber,<sup>13</sup> and diet<sup>14</sup> have all been negative, but calcium has been found to protect against adenomas.<sup>15</sup>

Previous prevention trials have been conducted in average-risk populations. We reasoned that persons with a history of colorectal cancer might constitute a group at higher risk for adenomas and thus be particularly suitable for a study of the chemopreventive effects of NSAIDs. We conducted a randomized, double-blind, placebo-controlled trial designed to determine whether the daily use of 325 mg of aspirin decreases the occurrence of new colorectal adenomas among patients with a history of colorectal cancer.

## METHODS

### STUDY PARTICIPANTS

The Colorectal Adenoma Prevention Study originated in the cooperative-trials group Cancer and Leukemia Group B (CALGB), and enrollment was subsequently extended to other groups, including the Eastern Cooperative Oncology Group, the M.D. Anderson Cancer Center, and the North Central Cancer Treatment Group. Between May 15, 1993, and January 10, 2000, a total of 719 participants were enrolled from the member institutions and their affiliates.

We recruited participants between the ages of 30 and 80 years who had histologically documented colon or rectal cancer with a low risk of recurrent disease. Patients with Dukes' stage A or B1 colon or rectal cancer (tumor–node–metastasis [TNM] stage

T1 to T2, N0, M0) who had undergone curative resection of the primary tumor were immediately eligible for enrollment. Patients with Dukes' stage B2 or C (T3 to T4, N0 to N1, M0) colon or rectal cancer who had undergone curative resection of the primary tumor were eligible if they had been free of disease for more than five years after curative surgery.

Eligible participants had to have undergone, after adequate preparation, colonoscopy to the cecum (or small-bowel anastomosis), with removal of all polyps, within four months before study entry. Patients were eligible if they were in good general health, with an expected survival of at least five years; willing to provide and able to understand informed consent and to cooperate with the study procedures; not currently enrolled in a clinical trial of colon-cancer treatment or other chemoprevention trial; and not pregnant or nursing.

Patients were excluded if they had familial polyposis; had had invasive cancer other than nonmelanoma skin cancer within 5 years before the intake appointment; had cardiovascular disease, as defined by a New York Heart Association functional class of III or IV; had received immunosuppressive therapy within the previous 6 months; had clinically obvious narcotic or alcohol dependence during the previous 6 months; had a history of inflammatory bowel disease; had possible contraindications to the administration of aspirin (documented peptic ulcer disease in the past 15 years, aspirin sensitivity, or bleeding diathesis); had a high likelihood of requiring NSAID use; had used NSAIDs including aspirin at any dose on 3 or more days per month during each of the 3 months before enrollment or for a period of 36 days in the previous year; or had a history of stroke, transient ischemic attacks, angina, myocardial infarction, or atherosclerotic peripheral vascular disease.

### RECRUITMENT AND RANDOMIZATION

Staff members at participating sites reviewed pathology logs, endoscopy reports, and surgery schedules to identify patients who might qualify for the study. They then contacted primary physicians for permission to enroll apparently suitable patients in the study. When permission was granted, potential participants were contacted. Eligible participants provided written informed consent, then entered an initial three-month, single-blind, aspirin run-in period during which adherence to therapy and toxicity were assessed. Staff members evaluated the participants' suitability for randomization on the basis of

self-reported adherence, motivation, and toxic effects at 6 weeks and 10 weeks. To be eligible, a participant must have taken an average of at least five tablets per week during the run-in period.

After the run-in period, eligible participants were randomly assigned to receive 325 mg of aspirin per day or identical-appearing placebo. Randomization was stratified according to the stage of cancer (Dukes' A or B1 vs. Dukes' B2 or C) and sex. The assignment was made centrally by the CALGB Statistical Center after eligibility and adherence were confirmed. Aspirin or placebo was shipped to participants from the research pharmacy at the University of North Carolina, thereby concealing the treatment assignment from the investigators. A supply of study drug and acetaminophen was shipped to each participant at enrollment and every 12 months thereafter with instructions to use acetaminophen for pain. The aspirin was enteric-coated to reduce gastric irritation and to help mask the identity of the study agent.

A total of 719 participants were registered for the trial, 635 of whom (88 percent) completed the run-in period and underwent randomization. Of the 84 patients who did not undergo randomization, 12 were not compliant, 22 were unwilling to continue, 25 were judged ineligible by staff members, 18 had unacceptable side effects, and 7 were not enrolled for unknown reasons. Of the 635 patients who underwent randomization, 10 were subsequently found to be ineligible, 8 withdrew consent, and 2 never started treatment.

Human-subjects committees at each participating institution approved the study protocol. The National Cancer Institute funded the study. The Bayer Corporation provided aspirin and placebo.

#### COLONOSCOPY

Each patient's own gastroenterologist or surgeon performed colonoscopic or sigmoidoscopic examinations. Endoscopy was not performed solely for the purposes of this study, but as part of the usual follow-up for patients with colorectal cancer. Endoscopists were instructed to remove all raised lesions (polyps), and biopsy specimens were submitted to local pathologists for review. The study chair reviewed a copy of the colonoscopy and pathology reports to verify the adequacy and extent of the examination and the size, location, and pathological findings of any lesions. The protocol specified a colonoscopy at exit from the study three years after the qualifying colonoscopy (four years in patients

with early-stage disease who had an examination at one year).

#### END POINTS

The primary end point of this study was the detection of adenomas in the large bowel by either colonoscopy or sigmoidoscopy after randomization. Secondary analyses compared the two groups with respect to the proportion of patients who had at least one adenoma after randomization, the size of the largest adenoma among patients who had at least one adenoma, the time to the detection of a first adenoma, and the proportion of patients with advanced adenomas (those that were at least 1 cm in diameter or had villous components). The time to the detection of a first adenoma was defined as the time from randomization to the date of the colonoscopic examination at which an adenoma was detected. Data on patients who did not have any adenomatous polyps were censored as of the date of the last colonoscopic examination.

#### STATISTICAL ANALYSIS

The CALGB data and safety monitoring board oversaw the study. Planned interim analyses used the Lan and DeMets analogue of the O'Brien–Fleming sequential boundary to maintain an overall level of significance of 0.05. The data and safety monitoring board recommended early termination of the study (after accrual had been completed) and release of results at the second interim analysis when the observed P value for the difference in the number of adenomatous polyps between groups ( $P=0.006$ ) exceeded the Lan–DeMets boundary P value ( $P=0.025$  with 79 percent of data obtained).

The analysis was restricted to all randomized patients who underwent at least one colonoscopic examination after randomization. We compared the two groups with respect to the number of colonoscopic examinations, the number of adenomatous polyps detected, and the maximal size of such polyps using the nonparametric Wilcoxon rank-sum test. We used the chi-square test to compare the proportion of patients in each group who had at least one adenomatous polyp. Furthermore, we used the generalized-estimating-equations approach<sup>16</sup> to evaluate whether the two groups had similar proportions of patients who adhered to treatment (defined as taking seven pills per week) during follow-up, as reported on self-administered questionnaires. The Kaplan–Meier method was used to estimate the time to the detection of a first adenoma, and a pro-

portional-hazards model was used to adjust for important base-line covariates in predicting the time to a first adenomatous polyp. Further log-linear models were used to compute unadjusted and adjusted estimates (and 95 percent confidence intervals) of the relative risk of having at least one adenoma.<sup>17</sup> Variables included in the multivariate models were age (in years), sex, cancer stage, treatment group, number of colonoscopic examinations, and time to the first colonoscopic examination (treated as a continuous variable). All tests were performed with use of a two-sided alpha level of 0.05.

RESULTS

The base-line characteristics of the participants are shown in Table 1. Overall, 517 of the 635 randomized patients (81 percent) had at least one colonoscopic examination after randomization (258 in the placebo group and 259 in the aspirin group) (Table 2). The number of colonoscopic examinations was similar in the two groups (P=0.13 by the Wilcoxon test). The median time to a first colonoscopy was 11.3 months (95 percent confidence interval, 9.2 to 15.1) in the placebo group and 15.5 months (95 percent confidence interval, 11.2 to 20.1) in the aspirin group (P=0.25 by the log-rank test). There

was no significant difference between the two groups in adherence rates over time (P=0.41 by the generalized-estimating-equations approach). The median duration of follow-up was 30.9 months in the aspirin group (interquartile range, 20.1 to 35.3) and 31.6 months in the placebo group (interquartile range, 19.9 to 35.3).

Table 3 shows the number of adenomas detected after randomization. The mean (±SD) number was lower in the aspirin group than in the placebo group (0.30±0.87 vs. 0.49±0.99, P=0.003 by the Wilcoxon test). Moreover, the proportion of patients who had at least one adenoma after randomization was lower in the aspirin group than in the placebo group (17 percent vs. 27 percent, P=0.004). The relative risk of a new adenoma was significantly lower in the aspirin group than in the placebo group (relative risk, 0.65; 95 percent confidence interval, 0.46 to 0.91), after adjustment for age, sex, cancer stage, the number of colonoscopic procedures, and the time to a first colonoscopy.

Figure 1 shows the proportion of patients who had at least one polyp detected during the study. After adjustment for the time to a first colonoscopic examination, the number of colonoscopic examinations, cancer stage, age, and sex, the hazard ratio for a new polyp was 0.64 in the aspirin group (95 percent confidence interval, 0.43 to 0.94; P=0.022), indicating that aspirin delayed the development of adenomas.

The median size of the largest polyp was similar in the placebo group and the aspirin group (4.0 and 3.5 mm, respectively; P=0.85 by the Wilcoxon test), and the proportions of patients with advanced adenomas (adenomas that were at least 1 cm in diameter or had villous components) were not significantly different in the two groups.

During the run-in phase there were two grade 4 adverse events (gross upper gastrointestinal bleeding or ulcer, as demonstrated by endoscopy or barium radiograph), three grade 3 adverse events (dyspepsia requiring histamine-H<sub>2</sub>-receptor antagonists, misoprostol, sucralfate, or omeprazole), and one possible transient ischemic attack. After randomization, there were 18 deaths in the aspirin group; 7 were related to cancer (4 recurrent), 7 were due to cardiovascular causes, and 4 were due to various other causes. There were two grade 4 adverse events in the aspirin group, and four grade 3 adverse events. There were 17 deaths in the placebo group: 10 were related to cancer (6 recurrent), 5 were from cardiovascular causes, and 2 were due to miscella-

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

| Characteristic               | Aspirin<br>(N=317)      | Placebo<br>(N=318) | Total<br>(N=635) |
|------------------------------|-------------------------|--------------------|------------------|
|                              | <i>number (percent)</i> |                    |                  |
| Sex                          |                         |                    |                  |
| Male                         | 164 (52)                | 168 (53)           | 332 (52)         |
| Female                       | 153 (48)                | 150 (47)           | 303 (48)         |
| Age                          |                         |                    |                  |
| ≤39 yr                       | 4 (1)                   | 4 (1)              | 8 (1)            |
| 40–49 yr                     | 41 (13)                 | 46 (14)            | 87 (14)          |
| 50–59 yr                     | 77 (24)                 | 75 (24)            | 152 (24)         |
| 60–69 yr                     | 103 (32)                | 105 (33)           | 208 (33)         |
| ≥70 yr                       | 92 (29)                 | 88 (28)            | 180 (28)         |
| Cancer stage                 |                         |                    |                  |
| Dukes' A or B1               | 196 (62)                | 200 (63)           | 396 (62)         |
| Dukes' B2 or C               | 121 (38)                | 118 (37)           | 239 (38)         |
| Type of surgery              |                         |                    |                  |
| Right hemicolectomy          | 94 (30)                 | 82 (26)            | 176 (28)         |
| Left hemicolectomy           | 21 (7)                  | 42 (13)            | 63 (10)          |
| Sigmoid colectomy            | 66 (21)                 | 60 (19)            | 126 (20)         |
| Total abdominal colectomy    | 6 (2)                   | 3 (1)              | 9 (1)            |
| Abdominal perineal resection | 35 (11)                 | 27 (8)             | 62 (10)          |
| Other                        | 95 (30)                 | 104 (33)           | 199 (31)         |

neous causes. There were two grade 4 adverse events and four grade 3 adverse events in the placebo group. There were two strokes, one in each group.

## DISCUSSION

We have shown that, as compared with a placebo, a daily dose of 325 mg of aspirin reduces the risk of adenoma in patients with a history of colorectal cancer. The aspirin treatment decreased the number of adenomas and the time to the development of adenomas. The incidence and types of adverse effects were similar in the two groups.

Support for the hypothesis that aspirin protects against colorectal neoplasia comes from prospective<sup>7-9,18-20</sup> and retrospective<sup>5,6,21-30</sup> studies that have used either colorectal cancer or colorectal adenomas as end points.<sup>31</sup> These studies have had remarkably consistent results, with benefits irrespective of age, race, sex, location of the study centers, and location of the tumor in the colon or the rectum, and have generally shown a 40 to 50 percent reduction in the risk of colorectal neoplasia. The risk estimate in our study is within that range.

Sulindac can decrease the number of adenomas in patients with familial adenomatous polyposis over both the short term<sup>11,32</sup> and the long term.<sup>33</sup> The cyclooxygenase-2-specific inhibitor celecoxib also decreases adenomas in patients with familial adenomatous polyposis.<sup>10</sup> These results, however, cannot be generalized to sporadic colorectal cancer. Our study is important because it demonstrates a protective effect of aspirin in a population at higher risk for sporadic colorectal cancer.<sup>34</sup>

The results of previous trials of other interventions to prevent adenomas have generally been negative.<sup>12-14,35,36</sup> Our study was stopped early by the data and safety monitoring board because of the significant effect of aspirin as compared with that of placebo. It is possible that our selection of patients with a history of cancer permitted us to enroll patients at higher risk for colonic polyps, thereby making it easier to demonstrate an effect of the intervention. Our results are even more striking because all the participants had undergone colon resection, leaving less remaining colon at risk. Our findings cannot be explained by a higher frequency of endoscopy as a result of aspirin-induced bleeding. If there had been intervening endoscopic examinations as a result of aspirin-induced bleeding, the study would have been biased against aspirin because there would have been more opportunities

**Table 2. Number of Colonoscopic Examinations after Randomization.**

| Variable   | Aspirin (N=317) | Placebo (N=318) | Total (N=635) |
|--|-----------------|-----------------|---------------|
| No. of colonoscopic examinations — no. of patients (%) |                 |                 |               |
| 0  | 58 (18)         | 60 (19)         | 118 (19)      |
| 1  | 152 (48)        | 137 (43)        | 289 (46)      |
| 2  | 74 (23)         | 75 (24)         | 149 (23)      |
| 3  | 27 (9)          | 40 (13)         | 67 (11)       |
| ≥4   | 6 (2)           | 6 (2)           | 12 (2)        |
| Median   | 1               | 1               | 1             |
| Interquartile range                                    | 1-2             | 1-2             | 1-2           |
| Mean ±SD   | 1.60±0.86       | 1.68±0.86       | 1.63±0.86     |
| Range  | 1-8             | 1-6             | 1-8           |

**Table 3. Number of Polyps Detected at Follow-up Colonoscopy.**

| Variable   | Aspirin (N=259) | Placebo (N=258) | Total (N=517) |
|--|-----------------|-----------------|---------------|
| No. of polyps — no. of patients (%) <sup>*</sup> |                 |                 |               |
| 0  | 216 (83)        | 188 (73)        | 404 (78)      |
| 1  | 26 (10)         | 37 (14)         | 63 (12)       |
| 2  | 9 (3)           | 19 (7)          | 28 (5)        |
| ≥3   | 8 (3)           | 14 (5)          | 22 (4)        |
| Median   | 0               | 0               | 0             |
| Interquartile range                              | 0-0             | 0-1             | 0-0           |
| Mean ±SD   | 0.30±0.87       | 0.49±0.99       | 0.39±0.94     |
| Range  | 0-6             | 0-6             | 0-6           |

\* P=0.003 by the Wilcoxon test.

to detect an adenoma with each endoscopic examination in the aspirin group.

The goal of chemoprevention is to decrease the risk of colorectal cancer. It is impractical, however, to use colorectal cancer as an end point because of the long interval necessary for the development of cancer. Moreover, because the development of colorectal cancer is a rare event, the sample size necessary for a study with cancer as an end point would be prohibitive. As a consequence, experts have recommended the use of adenomas as surrogate end points for the study of potential preventive agents.<sup>37</sup> Given the strong evidence supporting the adenoma-to-carcinoma sequence, the implications of our study are clear: by reducing the development of adenomas we can reduce the risk of cancer.

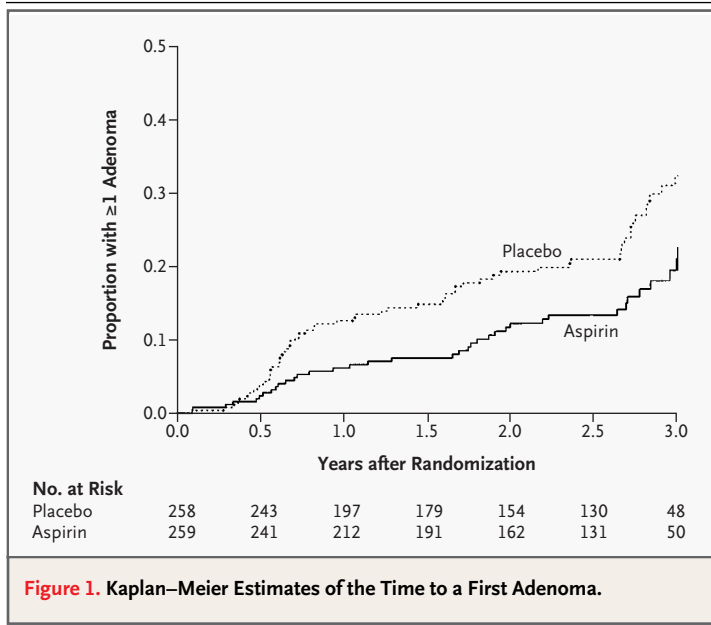


Figure 1. Kaplan–Meier Estimates of the Time to a First Adenoma.

Our study arbitrarily selected a daily dose of aspirin that is widely available — 325 mg. It is not known whether a lower dose would be equally effective or a higher dose would have a stronger effect. A recent dose-finding study of aspirin that used rectal mucosal prostaglandin E<sub>2</sub> levels as a biologic marker found that, as compared with placebo, an 81-mg dose of aspirin significantly suppressed prostaglandin E<sub>2</sub> levels and did so to an extent equivalent to that of higher doses over a four-week treatment period.<sup>38</sup> The companion article by Baron et al.,<sup>39</sup> which appears elsewhere in this issue of the *Journal*, reports a protective effect of the 81-mg dose of aspirin but not of the 325-mg dose. The difference in the two studies could be that we enrolled higher-risk patients, or it could simply be due to chance.

Certain features of our study deserve comment. The study was designed to conform, as much as possible, to customary medical care. For that reason, we relied on the readings of local pathologists for the diagnosis of base-line cancer and subsequent adenomas, rather than using central review of all pathological specimens. We similarly relied on local

gastroenterologists and surgeons for colonoscopic examinations. A large number of endoscopists contributed information to the study. Although our research protocol specified that colonoscopic examinations be conducted at the intervals recommended by experts,<sup>34</sup> unscheduled examinations were common. We believe that these unscheduled examinations were related to the fact that surveillance guidelines are not backed by strong evidence and that there is wide variation in postoperative surveillance.<sup>40,41</sup> Finally, because the study was stopped early, the magnitude of the effect of aspirin may have been exaggerated.<sup>42</sup>

The gastrointestinal toxicity of aspirin is well known, and this adverse effect influences the cost effectiveness of aspirin chemoprevention.<sup>43,44</sup> Drugs with similar mechanisms but better safety profiles might offer superior chemoprevention, but their effectiveness must be established before they can be recommended.

Despite the clear protective effect of aspirin, adenomas developed in some patients in the aspirin group. For that reason, aspirin cannot be viewed as a replacement for surveillance colonoscopy. Before aspirin use can be recommended for patients with colorectal cancer, the risks and benefits of the drug will need to be compared with those of alternative chemopreventive agents. Our results provide proof of the principle that aspirin can prevent colorectal adenomas in patients previously treated for colorectal cancer.

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#### APPENDIX

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Davila; Mount Sinai School of Medicine, New York — J.F. Holland; North Central Cancer Treatment Group, Rochester, Minn. — M.J. O'Connell; North Shore University Hospital, Manhasset, N.Y. — D.R. Budman; Rhode Island Hospital, Providence — L.A. Leone; Roswell Park Cancer Institute, Buffalo, N.Y. — E. Levine; Southeast Cancer Control Consortium CCOP, Goldsboro, N.C. — J.N. Atkins; Southern Nevada Cancer Research Foundation CCOP, Las Vegas — J. Ellerton; SUNY Health Science Center at Syracuse, Syracuse, N.Y. — S.L. Graziano; Ohio State University Medical Center, Columbus — C.D. Bloomfield; University of California at San Diego, San Diego — S.L. Seagren; University of Chicago Medical Center, Chicago — G. Fleming; University of Illinois Minority-Based CCOP, Chicago — J.A. Sosman; University of Iowa Hospitals, Iowa City — G.H. Clamon; University of Maryland Cancer Center, Baltimore — D. Van Echo; University of Massachusetts Medical Center, Worcester — F.M. Stewart; University of Minnesota, Minneapolis — B.A. Peterson; University of Missouri, Ellis Fischel Cancer Center, Columbia — M.C. Perry; University of Nebraska Medical Center, Omaha — A. Kessinger; University of North Carolina at Chapel Hill, Chapel Hill — T.C. Shea; University of Tennessee Memphis, Memphis — H.B. Niell; Vermont Cancer Center, Burlington — H.B. Muss; Virginia Commonwealth University MBCCOP, Richmond — J.D. Roberts; Wake Forest University School of Medicine, Winston-Salem, N.C. — D.D. Hurd; Washington University School of Medicine, St. Louis — N.L. Bartlett; Weill Medical College of Cornell University, New York — M. Schuster; and Research Pharmacy, University of North Carolina General Research Center, Chapel Hill.

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**CORRECTION**

**A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer**

A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer . As a participating institution, the Memorial Sloan-Kettering Cancer Center, New York, should have been included in the Appendix on page 888.