ORIGINAL ARTICLE

Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome

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ABSTRACT

BACKGROUND

Observational and epidemiologic data indicate that the use of aspirin reduces the risk of colorectal neoplasia; however, the effects of aspirin in the Lynch syndrome (hereditary nonpolyposis colon cancer) are not known. Resistant starch has been associated with an antineoplastic effect on the colon.

METHODS

In a randomized, placebo-controlled trial, we used a two-by-two design to investigate the effects of aspirin, at a dose of 600 mg per day, and resistant starch (Novelose), at a dose of 30 g per day, in reducing the risk of adenoma and carcinoma among persons with the Lynch syndrome.

RESULTS

Among 1071 persons in 43 centers, 62 were ineligible to participate in the study, 72 did not enter the study, and 191 withdrew from the study. These three categories were equally distributed across the study groups. Over a mean period of 29 months (range, 7 to 74), colonic adenoma or carcinoma developed in 141 participants. Of 693 participants randomly assigned to receive aspirin or placebo, neoplasia developed in 66 participants receiving aspirin (18.9%), as compared with 65 receiving placebo (19.0%) (relative risk, 1.0; 95% confidence interval [CI], 0.7 to 1.4). There were no significant differences between the two groups with respect to the development of advanced neoplasia (7.4% and 9.9%, respectively; P=0.33). Among the 727 participants receiving resistant starch or placebo, neoplasia developed in 67 participants receiving starch (18.7%), as compared with 68 receiving placebo (18.4%) (relative risk, 1.0; 95% CI, 0.7 to 1.4). Advanced adenomas and colorectal cancers were evenly distributed in the two groups. The prevalence of serious adverse events was low, and the events were evenly distributed.

CONCLUSIONS

The use of aspirin, resistant starch, or both for up to 4 years has no effect on the incidence of colorectal adenoma or carcinoma among carriers of the Lynch syndrome. (Current Controlled Trials number, ISRCTN59521990.)

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The regular use of aspirin or aspirin-like agents is associated with a moderate reduction in the risk of colonic polyps and colorectal cancer.[1-4] Randomized trials of high-fiber diets have not shown a reduction in the risk of adenomas or colorectal cancer,[5] but none have investigated the effects of resistant starch. There is epidemiologic evidence of a negative correlation between colon cancer and starch intake.[6] Resistant starches escape digestion in the upper gut; colonic fermentation yields short-chain fatty acids, including butyrate, which has antineoplastic properties.[7] In carcinogen-treated rats, resistant starch reduces the development of intestinal tumors[8,9] and the production of aberrant crypt foci,[10] lowers mucosal DNA damage,[11] and increases apoptosis of damaged cells.[12] Conversely, excess numbers of polyps in the small bowel develop in strain Apc1638N mice fed a diet containing high amounts of resistant starch (200 g per kilogram).[13]

We conducted a trial of colorectal-cancer prevention that focused on carriers of DNA mismatch-repair gene defects. These abnormalities underlie the Lynch syndrome (hereditary nonpolyposis colon cancer), an autosomal dominant genetic defect that confers a predisposition to colorectal cancer. Up to 5% of colorectal cancers result from the Lynch syndrome, which is characterized by microsatellite instability of tumors. Several organs are susceptible to cancer, including the intestines, endometrium, and ovaries.[14] The Lynch syndrome probably represents a "model system" for one of six sporadic cancers featuring microsatellite instability due to somatic *MLH1* silencing.[15] In patients with the Lynch syndrome, adenomas appear at a mean age of 42.5 years, and the first diagnosis of colorectal cancer occurs at a mean age of about 45 years. The risk of colon cancer among mutation carriers is 10% over a period of 10 years. In one study, colonic neoplasia had developed in 70.3% of carriers by 60 years of age.[16]

We describe a randomized trial of chemoprevention with the use of 600 mg of aspirin, 30 g of resistant starch, or both daily for up to 4 years in patients with the Lynch syndrome.

METHODS

In this two-by-two factorial, randomized, double-blind, placebo-controlled trial, we tested whether the use of enteric-coated aspirin at a dose of 600 mg per day, resistant starch at a dose of 30 g per day, or both prevents the development of colonic adenomas or colorectal cancer in patients with the Lynch syndrome. In this study, we used the collective term "neoplasia" to refer to colonic adenomas and colorectal cancer; although the term was used in the general sense of "new growth," it did not include presumably benign hyperplastic polyps. Initially, participants were enrolled for 2 years. In 2001, an approved protocol amendment allowed participants to be invited, immediately before the 2-year date, to continue in the trial for 2 more years.

The study was designed by members of the international steering committee of the Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2). The data were gathered and analyzed by the CAPP2 investigators. During the trial and before publication, except as noted below, data were kept confidential from the sponsors, institutions, and all study organizers except for two of the authors and the data and safety monitoring committee. Bayer and National Starch and Chemical provided the study agents free of charge, including the cost of packaging, and they made donations to Newcastle University to help cover the cost of administration and distribution. They had no influence on the study design, conduct, or analysis or on preparation of the manuscript. The contracts associated with their donations required that the sponsors be given the right to review the results before submission of the manuscript, with up to 90 days for evaluation.

All relevant research ethics committees approved the study. Approval included the addition of an undeclared inert starch-compliance biomarker, 4-aminobenzoic acid (in Denmark, the addition of this biomarker was revealed). All participants gave written informed consent for participation in the study, including explicit consent for the provision of blood and tissue samples.

PATIENTS

Eligible patients were older than 25 years of age and were proven carriers of a pathologic mismatch-repair mutation ("genetic diagnosis") or members of a family that met the Amsterdam diagnostic criteria and had a personal history of a cured Lynch syndrome neoplasm but an intact colon ("clinical diagnosis"). Colonoscopic exam-

ination and clearance of polyps within 3 months after recruitment were prerequisites. Exclusion criteria were pregnancy, contraindications for the use of aspirin, the use of antiinflammatory agents, and severe intercurrent disease. Patients with recent bowel cancer were excluded for 1 year if the pathological findings were consistent with Dukes' stage A, for 2 years if they were consistent with Dukes' stage B, and for 5 years if they were consistent with Dukes' stage C or D. If a partial colectomy had been performed, a daily bowel movement of three or fewer formed stools was required.

STUDY DESIGN

The protocol specified a colonoscopic examination at study entry and an exit colonoscopic examination after 2 years of the study intervention, along with routine surveillance. Copies of histologic reports plus pathological samples were requested for independent pathological review.

Participants were randomly assigned separately for the two interventions (either assignment to aspirin or placebo or assignment to resistant starch or placebo), and half the participants were randomly assigned to receive either the active agent or placebo for each intervention. This randomization should have resulted in four groups of equal size for assignments to aspirin plus placebo, aspirin plus starch, starch plus placebo, and placebo plus placebo. For some persons, however, randomization to one intervention was precluded by a factor such as sensitivity to aspirin, and in such cases, randomization to the other intervention was permitted; this resulted in four additional (smaller) groups. For the main analysis, the two interventions were analyzed separately (e.g., participants who were randomly assigned to receive aspirin were compared with participants who were randomly assigned to receive aspirin plus placebo, regardless of whether they received resistant starch or placebo starch). Only the interaction analysis excluded participants who were randomly assigned to receive a single agent.

Randomization was computer-generated. The study centers were categorized into six geographic groups — Americas, southern Europe (the Iberian Peninsula and Italy), northern Europe, South Africa, the United Kingdom, and the Pacific Rim (Australia and Hong Kong). Block randomization (in blocks of 16) was performed separately for each group of centers to ensure balance across the four main study groups.

STUDY REGIMENS

The daily regimen consisted of 30 g of resistant starch (Novelose, National Starch and Chemical) or placebo cornstarch (with recommended administration in two separate doses) or two enteric-coated aspirin tablets plus placebo or aspirin plus resistant starch. The test starch was a 1:1 blend of Novelose 240 and Novelose 330. Novelose 240, based on a corn (maize) hybrid containing 70% amylose and 30% amylopectin, is a granular source of resistant starch; Novelose 330 is similar but nongranular. The estimated dose of resistant starch was 13.2 g (habitual intake in Europe was estimated to be 4.1 g per day)[17]; a daily dose of 28 g of resistant starch was found by others to cause considerable bloating. The resistant-starch control was waxy starch (Amioca) containing only amylopectin, a highly branched high-molecular-weight polymer of α1,4-linked glucose with negligible resistant starch. The compliance biomarker used to assess compliance with the starch regimen was 4-aminobenzoic acid at a level of 50 mg per day.

For aspirin, we used an enteric-coated tablet (Bayer) that contained 300 mg of acetylsalicylic acid. The aspirin placebo contained 36 mg of calcium hydrogen phosphate, a trivial dietary dose.

The investigators and patients were unaware of the study-group assignments. Dispensing and related records were managed by the Newcastle Hospitals NHS Foundation Trust Pharmacy. After colonoscopic examination at study entry, packs containing the study drugs were sent directly to the participants or local clinicians and thereafter were sent every 6 months, when compliance data were collected.

STATISTICAL ANALYSIS

Descriptive statistics were used for study variables (including age, sex, eligibility status, and months in the study), with frequency tabulations for categorical variables and summary statistics (mean and range) for continuously distributed variables.

Participants who underwent a follow-up colonoscopic examination were included in the analyses of treatment effects. The primary outcome was detection of at least one adenoma or colorectal carcinoma at follow-up; since intervals be-

tween colonoscopic examinations and the duration of participation in the study varied, the analysis considered time in the study in its entirety. Secondary outcomes were the detection of an adenoma only, colorectal cancer only, adenoma and colorectal cancer, and advanced adenoma or colorectal cancer. A neoplasm was classified as an advanced adenoma on the basis of one or more of the following features: a diameter of 1 cm or more, a villous or tubulovillous component, or high-grade dysplasia. Other secondary outcomes were the neoplastic burden, defined as the sum of the maximum diameters of neoplasms detected by means of endoscopic examination during the study, and other cancers associated with the Lynch syndrome.

The primary analysis compared the occurrence of each outcome involving a neoplasm according to whether the subject received resistant starch or aspirin. Secondary analyses were ad-

Table 1. Characteristics of the Participants.

Variable	Participants Recruited and Given Study Drug (N=937)	Participants Included in Outcome Analysis (N=746)	Participants Not Included in Outcome Analysis (N=191)	P Value*
Age at study entry — yr				0.63
Mean	45	46	46	
Range	25–79	25–79	25–67	
Sex — no. (%)				0.19
Female	525 (56.0)	410 (55.0)	76 (39.8)	
Male	412 (44.0)	336 (45.0)	115 (60.2)	
Geographic region — no. (%)				0.07
Northern Europe	423 (45.1)	334 (44.8)	89 (46.6)	
United Kingdom	277 (29.6)	218 (29.2)	59 (30.9)	
Australia and Hong Kong	133 (14.2)	116 (15.6)	17 (8.9)	
Southern Europe	56 (6.0)	46 (6.2)	10 (5.2)	
South Africa	44 (4.7)	29 (3.9)	15 (7.9)	
Americas	4 (0.4)	3 (0.4)	1 (0.5)	
Eligibility status — no. (%)				0.63
Clinical diagnosis	163 (17.4)	132 (17.7)	31 (16.2)	
Genetic diagnosis	774 (82.6)	614 (82.3)	160 (83.8)	
Mutation — no./total no. (%)				0.18
MLH1	464/774 (60.0)	358/614 (58.3)	106/160 (66.3)	
MSH2	284/774 (36.7)	235/614 (38.3)	49/160 (30.6)	
MSH6	26/774 (3.4)	21/614 (3.4)	5/160 (3.1)	
Time in study — mo				
Mean		29.0		
Range		7–74		
Duration of receipt of study drug — mo				
Mean		26.5		
Range		1–67		
No. of colonoscopic examinations				
Mean		2.6		
Range		2–7		

* The P values are for the comparisons of patients who were included in the analysis with the patients who were not included.

justed for age and sex. Adjustment for the presence or absence of bowel neoplasms before participation in the study, the number of colonoscopic examinations, or both with the use of generalized linear models gave results that were equivalent to those seen after adjustment for age and sex only; these results are not reported. Time-to-event analysis was used in the secondary analysis, with the number of months to detection of any neoplasia or an advanced adenoma or colorectal cancer as end points. Cox proportional-hazards models adjusted for age and sex were used for treatment effects and Kaplan–Meier survival curves.

Pearson's chi-square test was used for analyses of reasons for withdrawal from the study and serious adverse events as defined in the trial (peptic ulcer, cerebrovascular incident, cardiovascular incident, deep venous thrombosis, cancer not associated with the Lynch syndrome, cancer other than colorectal cancer associated with the Lynch syndrome, other major events, and other minor events, including bleeding). Analyses included all events that occurred after study entry.

We anticipated that at least one adenoma would develop over a period of 2 years in 10% of the patients in the placebo group[18]; assuming a 20% dropout rate, we calculated that a sample of 1200 participants followed for 2 years would provide 90% power at a significance level of 0.05, based on a treatment effect of a 40% reduction in risk. The study had 73% power to detect a 50% reduction in the risk of an advanced adenoma or carcinomas.

Since there were fewer eligible gene carriers than predicted, an early approved protocol amendment allowed participants to remain in the study longer; this reduced the target recruitment to 1000 persons, assuming that 20% of participants would withdraw from the study and that 20% would continue for 2 more years. This amendment also stated that all participants would be included in the analysis, provided that there was a colonoscopic examination at both study entry and study exit and regardless of the time in the study.

RESULTS

CHARACTERISTICS OF THE PATIENTS

We recruited 1009 eligible patients. The analysis excluded 263 participants (26%); 72 withdrew before the colonoscopic examination at study entry, and 191 withdrew before the follow-up colonoscopic examination. The remaining 746 participants were included in the analysis. There were no notable differences between the patients who were recruited and those who completed the study.

Table 1 and Table 1 in the Supplementary Appendix (available with the full text of this article at www.nejm.org) show the characteristics of the participants; at recruitment, 83% had a genetic diagnosis, and 17% had a clinical diagnosis. Subsequently, a mismatch-repair mutation was discovered in 49 of 163 patients who had a clinical diagnosis, but the original status was retained for the analysis. A total of 464 participants with a genetic diagnosis had a pathologic mutation in *MLH1*, 284 had a mutation in *MSH2*, and 26 had a mutation in *MSH6*. A total of 152 Finnish participants had an *MLH1* exon 16 deletion, and 35 South African participants had a C1528T *MLH1* mutation. For at least 80% of the time, 81% of participants complied with the use of aspirin and 77% of the participants complied with the use of resistant starch. A subgroup of 100 participants from the United Kingdom completed a 4-day dietary assessment and provided a urine sample; the compliance biomarker 4-aminobenzoic acid was detected in 93% of these participants.

The average duration of participation in the study was 29 months (range, 7 to 74); they received the study drugs for 27 months (Table 1) and underwent an average of 3 colonoscopic examinations (range, 2 to 7, including the examination at study entry). There was even distribution among study groups (Table 2) with regard to total years of follow-up, the mean age of the participants, and the number of colonoscopic examinations. Table 2 includes data on participants who were randomly assigned to receive one agent only. A central histologic review of all of the available tumor tissue obtained from 132 of 197 persons (67.0%) was performed. There was 93% agreement between local and central reviews of detected neoplasia and 79% agreement for classification of nonadvanced and advanced neoplasia. Discordant opinions were reviewed by the study team, and the opinion of the reviewers at the central site was preferred if it was clear that both pathologists had examined the same tissue.

Table 2. Distribution of Characteristics According to Study Group.

Variable	All Participants Recruited (N=937)	Participants Assigned to Both Interventions			
		Aspirin plus Resistant Starch (N=214)	Aspirin plus Placebo (N=204)	Resistant Starch plus Placebo (N=208)	Placebo plus Placebo (N=216)
Withdrawal from study — no. (%)	191 (20.4)	39 (18.2)	38 (18.6)	51 (24.5)	40 (18.5)
Inclusion in analysis — no. (%)	746 (79.6)	175 (81.8)	166 (81.4)	157 (75.5)	176 (81.5)
Age — yr					
Mean		44	43	43	44
Range		24–8	21–68	24–75	25–77
Sex — no./total no. (%)					
Female	410/746 (55.0)	94/175 (53.7)	103/166 (62.0)	80/157 (51.0)	96/176 (54.5)
Male	336/746 (45.0)	81/175 (46.3)	63/166 (38.0)	77/157 (49.0)	80/176 (45.4)
Diagnosis — no./total no. (%)					
Clinical	132/746 (17.7)	21/175 (12.0)	29/166 (17.5)	33/157 (21.0)	31/176 (17.6)
Genetic	614/746 (82.3)	154/175 (88.0)	137/166 (82.5)	124/157 (79.0)	145/176 (82.4)
Neoplasia before study entry — no./total no. with full, available medical records (%)					
No	231/525 (44.0)	57/128 (44.5)	55/108 (50.9)	48/114 (42.1)	57/123 (46.3)
Yes	294/525 (56.0)	71/128 (55.5)	53/109 (49.1)	66/114 (57.9)	66/123 (53.7)
Neoplasia at colonoscopic examination at study entry — no./total no. (%)					
No	641/746 (85.9)	155/175 (88.6)	140/166 (84.3)	134/157 (85.4)	154/176 (87.5)
Yes	105/746 (14.1)	20/175 (11.4)	26/166 (15.7)	23/157 (14.6)	22/176 (12.5)
Advanced adenoma at colonoscopic examination at study entry — no./total no. (%)	35/746 (4.7)	9/175 (5.1)	6/166 (3.6)	9/157 (5.7)	8/176 (4.5)
No. of adenomas — no./total no. (%)					
1	88/105 (83.8)	16	23	18	18
2	13/105 (12.4)	4	2	3	3
3	3/105 (2.9)	0	0	2	1
4	0/105	0	0	0	0
5	1/105 (0.9)	0	1	0	0
Total	105/105 (100)	20	26	23	22
No. of colonoscopic examinations					
Mean		2.6	2.6	2.7	2.7
Range		2–7	2–6	2–6	2–5
Follow-up — yr					
Total person-years of follow-up		415	393	390	434
Mean		2.4	2.4	2.5	2.5
Range		0.8–4.7	0.7–4.5	0.9–6.2	0.9–4.9
Compliance					
Mean proportion of unused aspirin tablets		0.11	0.09	0.11	0.13
Mean proportion of unused starch sachets		0.14	0.10	0.16	0.14

Participants Assigned to a Single Intervention			
Aspirin Only (N=9)	Placebo Only (N=10)	Resistant Starch Only (N=41)	Placebo Only (N=35)
0	0	15 (36.6)	8 (22.9)
9 (100)	10 (100)	26 (63.4)	27 (77.1)
59	47	54	57
36–71	32–56	27–78	40–74
4/9 (44.4)	4/10 (40.0)	14/26 (53.8)	15/27 (55.6)
5/9 (55.6)	6/10 (60.0)	12/26 (46.1)	12/27 (44.4)
2/9 (22.2)	1/10 (10.0)	9/26 (34.6)	6/27 (22.2)
7/9 (77.8)	9/10 (90.0)	17/26 (65.4)	21/27 (77.8)
3/7 (42.9)	2/7 (28.6)	3/19 (15.8)	6/19 (31.6)
4/7 (57.1)	5/7 (71.4)	16/19 (84.2)	13/19 (68.4)
7/9 (77.8)	8/10 (80.0)	21/26 (80.8)	22/27 (81.5)
2/9 (22.2)	2/10 (20.0)	5/26 (19.2)	5/27 (18.5)
0/9	0/10	2/26 (7.7)	1/27 (3.7)
2	2	4	5
0	0	1	0
0	0	0	0
0	0	0	0
0	0	0	0
2	2	5	5
2	2.7	2.7	2.8
2–2	2–5	2–5	2–5
17	27	63	65
1.9	2.7	2.4	2.4
1.6–2.1	1.9–4.6	0.6–4.3	1.0–4.8
—	—	—	—

OUTCOMES

A bowel neoplasm was identified in 141 participants (18.9%), reflecting 90% power to detect a 40% difference in risk, as anticipated. Isolated colorectal cancer occurred in 13 participants, a combination of colorectal cancer and adenomas in 10, and adenomas only in the remaining 118. Numbers and mean diameters of the neoplasms are listed in Table 3. Table 4 shows the comparison for the two study agents separately; of 693 participants who were randomly assigned to receive aspirin or placebo, 66 of 349 (18.9%) had one or more neoplastic lesions while receiving aspirin, as compared with 65 of 342 in the placebo group (19.0%). Overall, the crude relative risk for the development of neoplasms in the aspirin group was 1.0 (95% confidence interval [CI], 0.7 to 1.4). After adjustment for age at enrollment, sex, and the number of colonoscopic examinations, there was no statistical evidence of a difference between the active-treatment and placebo groups. The analyses of adenomas only, colorectal cancer only, and adenomas and colorectal cancer showed no significant differences among the study groups. There was no evidence of an interaction between study agents (P=0.98).

The incidence of advanced adenoma or colorectal cancer, a measure of overt cancer plus adenomas thought to have the highest malignant potential, was 8.4% in the aspirin group and 10.9% in the placebo group (P=0.3). Of the 727 participants who were randomly assigned to receive resistant starch or placebo, 67 of those in the resistant-starch group (18.7%) were found to have neoplasia, as compared with 68 in the placebo group (18.4%), corresponding to a crude odds ratio of 1.0 (95% CI, 0.7 to 1.4). Adenomas and colorectal cancers were distributed evenly between the two groups (Table 4).

Colorectal cancer developed in equal numbers of patients (10) in the aspirin and placebo groups (Table 2 in the Supplementary Appendix). In the aspirin group, colorectal cancer with or without additional adenomas developed in 20 participants, 10 of whom were receiving active treatment and 10 of whom were receiving placebo. In the resistant-starch group, colorectal cancer with or without additional adenomas developed in 22 participants, 10 of whom were receiving active treatment and 12 of whom were receiving placebo. A Lynch syndrome cancer (excluding colorectal cancer) developed in 7 participants who re-

Table 3. Outcomes According to Study Group.

Variable	All Participants	Participants Assigned to Both Interventions				Participants Assigned to a Single Intervention			
	No. (%)	Aspirin plus Resistant Starch	Aspirin plus Placebo	Resistant Starch plus Placebo	Placebo plus Placebo	Aspirin Only	Placebo Only	Resistant Starch Only	Placebo Only
No neoplasia — no./total no. (%)	605/746 (81.1)	142	137	127	143	5	8	22	21
Neoplasia — no./total no. (%)	141/746 (18.9)	33	29	30	33	4	2	4	6
Adenoma only	118/746 (15.8)	29	24	24	29	3	2	4	3
Colorectal cancer only	13/746 (1.7)	2	2	4	3	1	0	0	1
Adenoma and colorectal cancer	10/746 (1.3)	2	3	2	1	0	0	0	2
Advanced adenoma or colorectal cancer	68/746 (9.1)	10	15	18	15	1	1	3	5
Largest dimension of neoplasm — mm									
Mean	137	8.0	10.3	10.8	8.3	2.9	8	11.5	13.0
Range		1–68	2–39	1–70	1–40	1–5	8–8	3–23	2–55
No. of adenomas — no/total no. (%)									
1	97/128 (75.8)	24	21	19	23	3	1	3	3
2	20/128 (15.6)	5	4	3	5	0	1	0	2
3	6/128 (4.7)	1	1	3	1	0	0	0	0
4	2/128 (1.6)	1	0	0	1	0	0	0	0
5	3/128 (2.3)	0	1	1	0	0	0	1	0
Total	128/128 (100)	31	27	26	30	3	2	4	5

ceived resistant starch, as compared with 17 who received placebo (P=0.05).

To test the influence of treatment duration on outcomes,[19] we examined the incidence of neoplasia according to the number of years in the study. Hazard ratios (and 95% confidence intervals) for all bowel neoplasms and advanced neoplasms revealed no evidence of a greater benefit with a longer duration of treatment (Fig. 1A through 1D). The analysis of all pathology reports in each of four 12-month periods, commencing at 6 months, showed no trend for a benefit of resistant starch over time but showed a possible adverse trend for aspirin, with the relative risk of neoplasia increasing from 0.6 to 1.9. Small numbers meant that for each group the confidence interval included 1 (Table 5 in the Supplementary Appendix).

ADVERSE EVENTS

Table 3 in the Supplementary Appendix lists reasons for withdrawal from the study. Serious adverse events (Table 4 in the Supplementary Appendix) were infrequent and did not differ significantly between groups. A total of 11 patients who received aspirin had gastric ulcers or bleeding versus 9 patients receiving placebo, 2 receiving aspirin had cerebrovascular events versus 3 receiving placebo, and 1 receiving aspirin had a cardiovascular event versus 5 among those receiving placebo.

DISCUSSION

We found that neither aspirin (at a dose of 600 mg per day) nor resistant starch (Novelose) (at a dose of 30 g per day), alone or in combination, given for up to 4 years has any detectable effect on the incidence of intestinal neoplasms among adults with the Lynch syndrome. Furthermore, the 40% reduction in neoplasms postulated for aspirin lies at the extreme limit of possible effects, as evidenced by the confidence interval. The lack of effect of aspirin, despite evidence of a

Table 4. Comparison of Outcomes According to Study Agent.*

Variable	Aspirin (N=350)	Placebo (N=343)	P Value	Resistant Starch (N=358)	Placebo (N=369)	P Value
Development of neoplasia — no. of patients (%)						
No neoplasia	284	278		291	301	
Neoplasia	66 (18.9)	65 (19.0)	0.96	67 (18.7)	68 (18.4)	0.99
Adenoma only	56 (16.0)	55 (16.0)	0.96	57 (15.9)	56 (15.2)	0.86
Colorectal cancer only	5 (1.4)	7 (2.0)	0.54	6 (1.7)	6 (1.6)	0.90
Adenoma and colorectal cancer	5 (1.4)	3 (0.9)	0.45	4 (1.1)	6 (1.6)	0.43
Advanced adenoma or colorectal cancer	26 (7.4)	34 (9.9)	0.33	31 (8.7)	35 (9.5)	0.61
Neoplastic burden — mm†						
Mean	8.7	9.4	0.7	9.4	9.5	1.0‡
Range	0.4–68	1–70		1–70	1–55	
No. of adenomas — no. of patients (%)						
1	48 (13.7)	43 (12.5)		46 (12.8)	47 (12.7)	
2	9 (2.6)	9 (2.6)		8 (2.2)	11 (3.0)	
3	2 (0.6)	4 (1.2)		4 (1.1)	2 (0.5)	
4	1 (0.3)	1 (0.3)		1 (0.3)	1 (0.3)	
5	1 (0.3)	1 (0.3)		2 (0.6)	1 (0.3)	

* P values were adjusted for age and sex.
† The neoplastic burden was estimated as the sum of the maximum diameters of lesions.
‡ The P value was calculated on the basis of the two-sided t-test.

benefit in sporadic colorectal cancer,[1-3] may indicate a distinct mismatch-repair–dependent neoplastic pathway that is less susceptible to protection by aspirin. An analysis of expression of cyclooxygenase-2 by Lynch syndrome tumors is under way to test the reported association with aspirin as a chemopreventive agent.[20] In our trial, aspirin was administered at a dose of 600 mg daily. Baron et al.[2] suggested that a daily dose of 325 mg of aspirin is less effective than a daily dose of 81 mg, although epidemiologic studies provide support for a positive dose–response relationship.

The lack of an effect suggests that a larger study is unlikely to result in a different conclusion; more modest protective effects than the postulated 40% reduction in neoplasms are still consistent with our data but would require much larger samples to detect. The results of analyses restricted to proven mutation carriers were indistinguishable from the results presented here (data not shown). Polyps that were present but not detected at study entry could have weakened any effect, but a miss rate equivalent to that reported by Pickhardt et al.[21] would not have changed the results. Furthermore, the frequency of such omissions would probably have been similar among the study groups.

The U.S. Preventive Services Task Force[22] recommended that aspirin not be used routinely for the prevention of primary colorectal cancer. Subsequently, Flossmann and Rothwell[19] reported longer-term effects of aspirin on the risk of death from cancer among British men in two early trials of the benefits of aspirin in cardiovascular and cerebrovascular disease. There were significantly fewer deaths from colorectal cancer among persons who received aspirin; however, this did not become apparent until 10 years after the trial commenced, even though the aspirin was given for only 4 years during the trial. Such an effect — through a later influence on the development of adenomas, the precursors of colorectal cancer — cannot be ruled out in the CAPP2

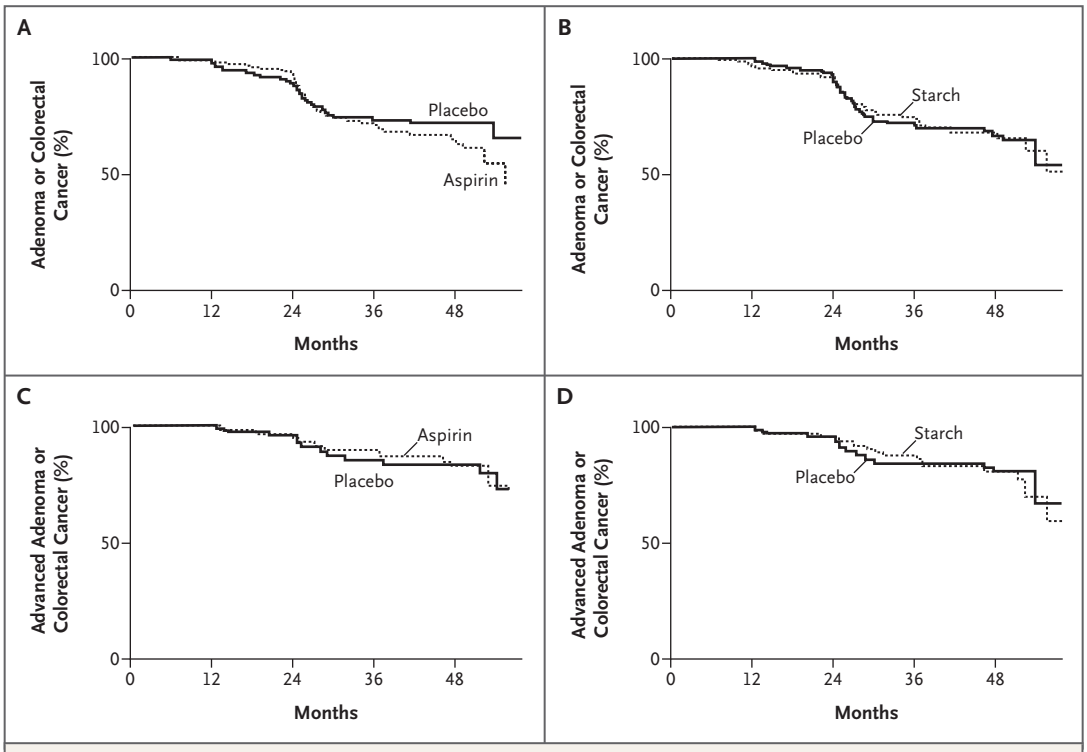

Figure 1. Time to the Development of Neoplasia, According to Study Group.

Panel A shows the time to the development of an adenoma or colorectal cancer among patients who received aspirin as compared with those who received placebo; the unadjusted hazard ratio was 1.1 (95% CI, 0.8 to 1.5; P=0.69). When the data were adjusted for the number of colonoscopic examinations, the hazard ratio was 1.0 (95% CI, 0.7 to 1.5; P=0.79). Panel B shows these outcomes among patients who received resistant starch as compared with those who received placebo; the unadjusted hazard ratio was 1.0 (95% CI, 0.7 to 1.4; P=0.94). When the data were adjusted for the number of colonoscopic examinations, the hazard ratio was 1.0 (95% CI, 0.7 to 1.4; P=0.98). Panel C shows the time to the development of advanced adenoma or colorectal cancer in the aspirin group as compared with the placebo group; the unadjusted hazard ratio was 0.9 (95% CI, 0.5 to 1.5; P=0.71). When the data were adjusted for the number of colonoscopic examinations, the hazard ratio was 0.9 (95% CI, 0.5 to1.5; P=0.67). Panel D shows these outcomes for the resistant-starch group as compared with the placebo group; the unadjusted hazard ratio was 0.8 (95% CI, 0.5 to 1.4; P=0.50).

cohort and is supported by the reduced incidence of cancer among carriers of the Lynch syndrome gene who undergo removal of polyps at regular colonoscopic examinations.[19]

The limited preliminary evidence concerning resistant starch is insufficient to define the optimum dose, and the dose used in our study was based on earlier studies of biomarkers[18] and tolerability. The dose we used was tolerable, but it was three times as high as the typical intake of resistant starch in Europe. The lack of effect may reflect an insufficient dose, a less-than-ideal compliance rate (77%), or the fact that a benefit in laboratory animals does not always translate into a benefit for humans.

Our trial has shown the feasibility of performing chemoprevention trials in a population of people with a genetic susceptibility. The results, however, do not show a clinical benefit among carriers of a mutation for the Lynch syndrome who receive aspirin or resistant starch for up to 4 years. Longer-term effects remain to be evaluated.

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APPENDIX

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CORRECTION

Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome (December 11, 2008;359:2567-78). In Table 2 (pages 2572–2573), the third variable should be "Age at recruitment — yr," and the age ranges should read as follows: Aspirin plus Resistant Starch, 25–70; Aspirin plus Placebo, 25–75; Resistant Starch plus Placebo, 25–75; Placebo plus Placebo, 25–78; Aspirin Only, 37–67; Placebo Only, 33–57; Resistant Starch Only, 28–78; and Placebo Only, 36–75. In the first paragraph under Outcomes (page 2573), the data given in the fourth sentence should read, "66 of 350 (18.9%) had one or more neoplastic lesions while receiving aspirin, as compared with 65 of 343 in the placebo group (19.0%)." The article has been corrected at NEJM.org.

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