Chemoprophylaxis with aspirin (81 mg daily) reduced the incidence of colorectal adenomas in persons at risk

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.

QUESTION

In persons at risk (recent history of histologically documented adenomas) is chemoprophylaxis with aspirin more effective than placebo for reducing the incidence of colorectal adenomas?

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians and patients),* placebo-controlled trial with a mean follow-up of 33 months.

SETTING

9 clinical centers in Canada and the United States.

PATIENTS

1121 patients (mean age 57 y, 64% men) who had ≥ 1 of the following: ≥ 1 histologically confirmed colorectal adenoma removed < 3 months before recruitment; ≥ 1 histologically confirmed adenoma removed ≤ 16 months before recruitment and a lifetime history of ≥ 2 confirmed adenomas; or a histologically confirmed adenoma ≥ 1 cm in diameter removed < 16 months before recruitment. Exclusion criteria included a history of a familial colorectal cancer syndrome, invasive colorectal cancer, and malabsorption syndromes. Follow-up was 97%.

INTERVENTION

Patients were allocated to aspirin, 325 mg/d (n = 372) or 81 mg/d (n = 377), or placebo (n = 372).

MAIN OUTCOME MEASURE

Number of patients in whom ≥ 1 colorectal adenoma was detected at ≥ 1 year of follow-up.

MAIN RESULTS

At ≥ 1 year, ≥ 1 colorectal adenoma was detected in fewer patients who received aspirin, 81 mg, than in those who received placebo (Table). The 325-mg aspirin and placebo groups did not differ for incidence of colorectal adenomas.

CONCLUSION

In persons at risk (with a recent history of colorectal adenomas) chemoprophylaxis with aspirin (81 mg daily) was more effective than placebo for reducing the incidence of new colorectal adenomas.

Source of funding: National Institutes of Health. Aspirin and placebo tablets provided by Bayer.

For correspondence: Dr. J.A. Baron, Dartmouth–Hitchcock Medical Center, Lebanon, NH, USA. E-mail john.a.baron@dartmouth.edu. ■

*See Glossary.

†Information provided by author.

Aspirin (81 or 325 mg daily) vs placebo in patients with a recent history of histologically confirmed adenomas at ≥ 1 year‡

Outcome	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
≥ 1 colorectal adenoma detected	Aspirin, 81 mg, vs placebo	38% vs 47%	19% (3.8 to 32)	12 (7 to 60)
	Aspirin, 325 mg, vs placebo	45% vs 47%	4.3% (–12 to 18)	Not significant

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

A series of animal experiments as well as epidemiologic studies dating back to the early 1980s have supported the protective effects of nonsteroidal anti-inflammatory drugs against the development of colorectal adenomas. Over time, these studies have been consistent and positive, and now, with the studies by Baron and colleagues and Sandler and colleagues, we can add 2 well-designed, randomized, placebo-controlled trials to this body of evidence.

In the study by Baron and colleagues, 2 doses of aspirin, 81 mg and 325 mg daily, were compared with placebo. A modest 19% reduction in the relative risk for any adenoma was found in patients who received aspirin, 81 mg/d, but no significant protection was found in those who received aspirin, 325 mg/d, when compared with placebo. In the study by Sandler and colleagues, only 1 dose of aspirin (325 mg/d) was evaluated. A 36% reduction in the relative risk for ≥ 1 polyp was found. The greater benefit observed in the study by Sandler and colleagues may be attributed to differences in the populations of the 2 studies. Both recruited patients at "high risk" for polyps, but Sandler and colleagues selected patients with a history of colorectal cancer, whereas Baron and colleagues selected those with a history of polyps. The side effects from regular use of aspirin were similar to placebo in the study by Sandler and colleagues. However, in the study by Baron and colleagues the incidence of stroke was of concern: There were none among those who received placebo, 2 among those who received aspirin, 81 mg/d, and 5 among those who received aspirin, 325 mg/d (P = 0.06).

The results from these studies raise several important questions: First, how does aspirin protect against adenoma formation? In a separate study, it has been proposed that aspirin might increase the catabolism of carcinogenic polyamines (1). The most commonly proposed mechanism of action is inhibition of cyclooxygenase enzymes and subsequent inhibition of prostaglandin synthesis. Prostaglandin E_2 is the most abundant prostaglandin in colorectal tumors and can block apoptosis (2). It has also been reported that the doses of aspirin from 81 mg to 650 mg daily are equally effective at inhibiting the production of prostaglandin E_2 in the rectal mucosa (3). Similarly, no dose effect is evident for aspirin used in cardiovascular prophylaxis (4). Therefore, if a physician were to recommend aspirin to prevent colorectal polyps, the smaller dose would seem justifiable and may minimize rates of such other adverse events as gastrointestinal bleeding.

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Aspirin prevented new colorectal adenomas in patients with previous colorectal cancer

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.

QUESTION

In patients with previous colorectal cancer, is aspirin effective for preventing the occurrence of new colorectal adenomas?

DESIGN

Randomized (allocation concealed*), blinded (investigators, patients, clinicians, data collectors, and outcome assessors),* placebo-controlled trial with median follow-up of 31 months (The Colorectal Adenoma Prevention Study).

SETTING

39 cancer centers in the United States.

PATIENTS

635 patients who were 30 to 80 years of age (mean age 62 y, 52% men) and previously had curative resection of early-stage colon or rectal cancer and colonoscopy to the cecum with removal of all polyps within 4 months before study entry. Exclusion criteria included recent use of aspirin or nonsteriodal anti-inflammatory drugs, poor general health, expected survival < 5 years, pregnancy or nursing, familial polyposis, invasive cancer, and cardiovascular disease. Follow-up was 81%.

INTERVENTION

After a 3-month run-in period, patients were allocated to enteric-coated aspirin, 325 mg/d (n = 317), or identical placebo (n = 318).

MAIN OUTCOME MEASURES

Primary outcomes were the detection of adenomas after randomization, time to detection of a first adenoma, and proportion with advanced adenomas (≥ 1 cm in diameter or villous components).

MAIN RESULTS

The aspirin and placebo groups had a similar mean number of colonoscopic examinations (1.60 vs 1.68, P = 0.13). The aspirin group was associated with a lower mean number of adenomas detected during the study than the placebo group (0.30 vs 0.49, P = 0.003). Furthermore, fewer patients in the aspirin group had ≥ 1 adenoma detected during the study than did those in the placebo group (Table). The groups did not differ for proportions of patients with advanced adenomas.

CONCLUSION

In patients with previous colorectal cancer, aspirin was effective for preventing the occurrence of new colorectal adenomas.

Source of funding: National Institutes of Health. Aspirin and placebo tablets provided by Bayer.

For correspondence: Dr. R.S. Sandler, University of North Carolina, Chapel Hill, NC, USA. E-mail rsandler@med.unc.edu.

*See Glossary.

Aspirin vs placebo for colorectal adenomas in previous colorectal cancer†

Outcome	Aspirin	Placebo	Adjusted hazard ratio (95% CI)‡	NNT (CI)
≥ 1 colorectal adenoma detected	17%	27%	0.64 (0.43 to 0.94)	9 (6 to 29)

†Abbreviations defined in Glossary; NNT and CI calculated from data in article.
‡Hazard ratio adjusted for time to a first colonoscopic examination, number of colonoscopic examinations, cancer stage, age, and sex.

COMMENTARY *(continued from page 72)*

In the study by Sandler and colleagues, aspirin protected against the development of new adenomas overall but had no effect on larger (> 1 cm) polyps or polyps with villous features. This differs from the Baron study, where the only significant effect was a reduced incidence of advanced adenomas among patients randomized to receive aspirin, 81 mg/d. How can this be? Whether this observation is because of differences in the colonic milieu of persons who have had colon cancer compared with those who have had previous adenomas, other undisclosed factors, or chance is yet undetermined. Other curious findings were noted in the subgroup analyses of the study by Baron and colleagues. Patients who were younger than the median age of 57 years and women seemed to be more likely to benefit. Explanations for these findings are elusive at present and will require further study before our understanding of the association between aspirin and colorectal adenomas is complete.

Aspirin should not replace endoscopic surveillance or be recommended for everyone. However, for persons at high risk for adenomas, low-dose aspirin can be added with assurance that it is reasonably effective and safe.

James E. Shaw, MD, MPH
Virginia Commonwealth University Health System
Richmond, Virginia, USA

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