"Convincing Evidence" That Aspirin Prevents Colorectal Cancer

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Disclosures

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Learning Objectives
Upon completion of this activity, participants will be able to:

• Describe previous research into the chemoprevention of colorectal cancer.
• Identify the long-term effect of aspirin in the prevention of colorectal cancer.

Authors and Disclosures
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May 14, 2007 — Aspirin (acetylsalicylic acid) can prevent colorectal cancer, concludes an analysis of data from 2 large randomized trials. It found that aspirin at a dosage of 300 mg or more per day for about 5 years reduced the subsequent incidence of colorectal cancer by 37% overall, and by 74% during the period 10 to 15 years after treatment was started.

The results, published in the May 12 issue of The Lancet, taken together with previous studies, "provide convincing evidence that aspirin, at biologically relevant doses, can reduce the incidence of colorectal cancer," comments Andrew T. Chan, MD, from Massachusetts General Hospital in Boston, in an accompanying editorial.

However, "these findings are not sufficient to warrant a recommendation for the general population to use aspirin for cancer prevention," Dr. Chan notes. He cites concern over the potential risks of long-term aspirin use and also the availability of alternative prevention strategies, such as screening.
Peter M. Rothwell, FRCP, from University of Oxford, United Kingdom, and lead author of the study, told Medscape that he agrees with this caution about the general population. Overall from the studies of aspirin use in healthy individuals for the primary prevention of cardiovascular disease, the benefit of aspirin is more or less outweighed by the risk of bleeding (mainly in the gastrointestinal tract, but also in the brain), he noted.

However, Dr. Rothwell would argue for use of aspirin to prevent colorectal cancer in certain high-risk populations, for example in first-degree relatives of patients with colorectal cancer. This group has an increase risk for colorectal cancer — whereas the general population has a lifetime risk for colorectal cancer of about 5%, in first-degree relatives the risk is increased about 2- to 4-fold, so their lifetime risk is 10% to 20%, he said.

Another example would be patients with vascular disease (angina, or previous myocardial infarction or stroke) who are taking aspirin or an antiplatelet agent such as clopidogrel for secondary cardiovascular prophylaxis. In this group, aspirin would have an additional benefit of also offering protection against colorectal cancer (via its inhibition of the cyclooxygenase [COX] enzymes, COX-1 and COX-2), whereas the other antiplatelet agents do not, as they work through a different mechanism. “This new evidence pushes the balance in favor of aspirin over these other drugs,” Dr. Rathwell commented in an interview, and as a result, he would expect to see a shift back towards aspirin and way from the newer agents, which are also more expensive, he noted.

One further point Dr. Rothwell made is that screening for colorectal cancer is very advanced in the United States, with regular colonoscopies and regular removal of polyps offered as a standard of care. However, the United States is almost alone in offering such a service, he commented, and in other countries around the world where there is limited access to these procedures, and so little else offered for prophylaxis against colorectal cancer, the benefit of using aspirin as a chemopreventive would be viewed differently.

New Analysis of Data From Old Studies

The latest results come from a new analysis of data that were collected in 2 large trials carried out some time ago: the British Doctors Aspirin Trial (5139 individuals, two thirds allocated to aspirin [500 mg] for 5 years) and the UK Transient Ischaemic Attack (UK-TIA) Aspirin Trial (2449 individuals, two thirds allocated to aspirin [300 or 1200 mg] for 1 - 7 years). Both trials were conducted in the late 1970s/early 1980s, before the effect of aspirin on cancer was recognized, and so colorectal cancer was not a prespecified endpoint.

The analysis showed a reduction in the incidence of colorectal cancer, but not any other type of cancer, in individuals who had been taking aspirin compared with the control subjects. The effect was seen only after a latency of 10 years, the researchers comment and was greatest at 10 to 14 years after randomization in patients who had taken aspirin for 5 years or more.
"These results are remarkably consistent with several previous observational studies," notes the editorialist. In the current study, Rothwell and colleagues systematically review 19 case-control studies (n = 20,815) and 11 cohort studies (n = 1,136,110) and report that regular use of aspirin or a nonsteroidal anti-inflammatory drugs was consistently associated with a reduced risk for colorectal cancer, especially after use for 10 years or more. "However, a consistent association was only seen with use of 300 mg or more of aspirin a day, with diminished and inconsistent results for lower or less frequent doses," the authors write.

This effect of aspirin dose may explain why no effect on colorectal cancer was seen in 2 large US studies, the Physicians' Health Study (which used 162.5 mg of aspirin) and the Women's Health Study (which used 50 mg of aspirin), the editorialist notes.

More study is needed to determine the optimum dose of aspirin, the editorial suggests, as well as the mechanisms involved. The studies to data "provide proof-of-principle that chemoprevention of colorectal cancer with aspirin is feasible," Dr. Chan concludes. "However, before chemoprevention can be practical, more work is needed to characterize those for whom the potential benefits of aspirin outweigh the hazards."

Dr. Rothwell has disclosed receiving honoraria for talks, advisory boards, and clinical trial committees from several pharmaceutical companies with an interest in antithrombotic agents, including Sanofi-BMS, Servier, Bayer, and AstraZeneca.


Clinical Context

The inhibition of COX-2 might have a particularly prominent role in the prevention of colorectal cancer, and randomized trials have demonstrated that aspirin can reduce the recurrence of adenomas among patients with a previous history of colorectal cancer or adenomas by approximately 40%. However, only about 10% of adenomas progress to become malignant, so preventing adenoma formation is not guaranteed to reduce the risk for colon cancer among all adults. For example, aspirin use was not associated with a protective effect against colorectal cancer after a mean of 10 years of follow-up in the Women's Health Study.

The Women's Health Study had a longer follow-up period than most trials of aspirin, but the dosage of aspirin (100 mg every other day) was low. The current research examines long-term results of 2 previous studies to determine if higher doses of aspirin and a longer duration of surveillance may result in reduced rates of colorectal cancer.

Study Highlights

- Study participants were drawn from the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial, both of which began around 1980.
The British Doctors Aspirin Trial compared treatment with aspirin (300 - 500 mg daily) with no aspirin therapy during a 5- to 6-year treatment period. 5139 male clinicians began the study and were also entered in a cancer registry, and cancer diagnoses were followed for 23 years after the initiation of the study.

The UK-TIA Aspirin Trial recruited 2449 patients with a history of cerebrovascular disease. Participants received aspirin (1200 or 300 mg per day) or placebo and were followed up until the end of the trial in 1986. Cancer data were available for a mean of 23 years after study initiation.

Neither trial featured colorectal cancer as a primary endpoint. Cancer data were obtained from registry records, which were found to be reliable by the study authors. The primary goal of the current study was to determine the long-term relationship between aspirin use and the risk for colorectal cancer.

No benefit of aspirin therapy was noted during the first 10 years of follow-up. However, the hazard ratio of colorectal cancer in pooled data from the 2 trials between years 10 to 19 of follow-up was 0.60 in comparing those who received aspirin vs those who did not. The overall risk reduction during follow-up was significant at 26%.

Aspirin had no significant effect on the risk for cancer other than colorectal cancer.

Subjects who had received aspirin for 5 years or more derived the greatest reduction in the risk for colorectal cancer. The greatest reduction in the rates of colorectal cancer was noted at 10 to 14 years after study initiation, but there were insufficient data to compare different doses of aspirin used in the 2 studies.

The authors included a review of 19 case-control studies and 11 cohort studies of aspirin in the prevention of colorectal cancer. Overall, they found that these observational studies confirmed a protective effect of aspirin as well as other nonsteroidal anti-inflammatory drugs against colorectal cancer, although this protection again appeared to be dose-dependent and apparent only after long-term use. Aspirin was protective regardless of age, sex, race, or family history, and it was effective in preventing both colon and rectal cancer.

Pearls for Practice

- Previous research has demonstrated that aspirin can reduce the risk for recurrent adenomas among high-risk patients, but its efficacy in reducing the risk for colorectal cancer has been questionable.
- The current study demonstrates that aspirin at a daily dose of 300 mg or more may protect individuals against colorectal cancer, but this benefit may not be apparent for 10 years after the initiation of aspirin.

CME/CE Test
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