Daily Aspirin Reduces Colorectal Cancer Incidence in Patients With Lynch Syndrome

Recent data from the Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) study shows that daily aspirin use in people with Lynch syndrome reduces the incidence of colorectal cancer (Lancet. 2011;378:2081-2087). The authors state that the results are in line with prior observational data that show the risk of colorectal cancer to be decreased in regular long-term aspirin users (Lancet Oncol. 2009;10:501-507). According to the authors, this is the first large-scale, genetically targeted chemoprevention trial.

“The current study provides strong evidence that aspirin for chemoprevention should be discussed with and considered for our patients with Lynch syndrome,” says first author John Burn, MD, professor at the Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom.

CAPP2 investigators reported outcomes that initially showed no evidence that aspirin use affected the development of adenomas or colorectal cancers in 937 patients with Lynch syndrome (N Engl J Med. 2008;359:2567-2578). This original report also included treatment arms investigating the use of resistant starch or resistant starch placebo as chemoprevention. Because prior observational studies suggested that the chemopreventive effect of aspirin takes many years to emerge, the design of CAPP2 included a double-blind, postintervention follow-up for at least 10 years. The current report analyzed only the baseline population of 861 participants randomly assigned to receive daily aspirin (600 mg) or aspirin placebo; this included some individuals with Lynch syndrome cancers that were included in the initial report as well as those that occurred after longer follow-up and cancers that occurred in participants who had not undergone an exit colonoscopy, which had excluded them from the earlier analysis. The primary outcome of CAPP2 was the development of colorectal cancer and the secondary outcomes were the development of adenomas or other Lynch syndrome-associated cancers (endometrial, ovarian, pancreatic, brain, small bowel, gallbladder, ureter, stomach, or kidney cancer) or both.

Results

The mean observation period was 55.7 months. Of the 861 participants in the analysis, 190 had only on-intervention data available and 671 also had longer term follow-up data available. Of those 671 participants with longer term follow-up data, 40 developed colorectal cancer (13 of 342 receiving aspirin and 27 of 329 receiving placebo). Of the 190 participants for whom only on-intervention data were available, 8 developed colorectal cancer (5 of 85 receiving aspirin and 3 of 105 receiving placebo). The hazard ratio (HR) for colorectal cancer in the whole group (regardless of patient adherence to the protocol) over the entire postrandomization period was 0.63 (P = .12), favoring protection from aspirin.

When examining the outcomes in participants who took aspirin or placebo for at least 2 years (about 60% of both groups), the HR was 0.41 (P = .02) and the incidence rate ratio was 0.37 (P = .008), strongly favoring aspirin protection against colorectal cancer.

Participants who took aspirin for 2 or more years had a colorectal cancer incidence rate of 0.06 cases per 100 person-years versus 0.13 cases per 100 person-years in those taking aspirin for fewer than 2 years. A similar analysis showed no difference in the rates of colorectal cancer in those taking placebo for over 2 years versus fewer than 2 years.

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The secondary endpoint analysis of the development of other Lynch syndrome cancers showed HRs that favored aspirin use, but these did not reach statistical significance. However, the combined incidence of all Lynch syndrome-associated cancers, including colorectal cancer, showed a statistically significant HR of 0.65 ($P = .05$) favoring aspirin use on the intention-to-treat analysis, and an HR of 0.45 ($P = .005$) on the per-protocol analysis.

No apparent effect on the development of adenomas could be detected, although the authors note this information was particularly hard to gather and may be incomplete. No difference in the stage or location of colorectal tumors was detected between groups. Furthermore, no differences in adverse events were seen during the treatment period, although data for adverse events after the intervention period are not available.

The authors state that a limitation of this study is that tumor blocks were not analyzed to determine if the noncolonic cancers observed were secondary to the germline mismatch repair mutation seen in Lynch syndrome.

“CAPP2 was hampered by being turned down for continued funding to complete the long-term follow-up and investigate the tumor pathology. Efforts are underway to address this,” Dr. Burn says.

**Implications**

According to the investigators, this study, along with earlier data, supports the use of aspirin in the chemoprevention treatment of patients with Lynch syndrome, although the dose and timing of use have not been established. A CAPP3 study is planned that will investigate optimizing the dose and duration. (More information can be found at www.CAPP3.org.)

“This study provides strong evidence that aspirin use reduces [the] risk of developing colorectal cancer in people with Lynch syndrome, and there is good evidence from previous studies showing that long-term regular aspirin use can also modestly reduce risk of colorectal cancer in people who do not have Lynch syndrome,” says Eric Jacobs, PhD, strategic director of pharmacoepidemiology in the department of epidemiology at the American Cancer Society in Atlanta, Georgia. “However, aspirin use is not currently recommended in the general population specifically for cancer prevention because even low-dose aspirin can increase risk of serious stomach bleeding.”

Authors of an accompanying editorial (Lancet. 2011;378: 2051-2052) say these results help define the use of aspirin for the prevention of colorectal cancer in patients without Lynch syndrome. This, along with previous data, makes the case for the more general use of aspirin for colorectal cancer prevention in the context of an individualized risk-benefit assessment, they say.

“The difficulty of designing studies for people other than those who carry a mismatch repair gene defect is that it will take at least 10 years to achieve a result and would be extremely expensive due to the large number of patients and long follow-up needed,” Dr. Burn says. A meta-analysis following 4 randomized studies evaluating aspirin use for the prevention of vascular events found that a divergence between aspirin and placebo groups with regard to the development of colorectal cancer starts at around 7 years (Lancet. 2010;376:1741-1750). Dr. Burn says anyone with a family history-based increased risk should give serious consideration to the use of regular aspirin.

“Some have noted that the randomized trials in the meta-analysis did not designate colorectal cancer ahead of time as a ‘primary outcome’; however, in my opinion this does not mean they should not be counted as randomized trials given that participants were still randomly assigned to take or not take aspirin, and there is strong consistent evidence from other sources that aspirin lowers risks of colorectal cancer,” Dr. Jacobs says.

He adds that patients should also be aware of other ways to help prevent colorectal cancer. “All people at average risk for colorectal cancer 50 years or older should get screened for colorectal cancer, so that precancerous polyps can be found and removed before they ever turn into cancer,” he says. “In addition, maintaining a healthy weight, being physically active, not smoking, and eating less red meat can help lower risk of colorectal cancer.”

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