New Data on Aspirin and Colorectal Cancer Brings Calls for New Guidelines, More Research

By Caroline McNeil

Three large studies in the past 14 months have reopened a longstanding issue in colorectal cancer: Can aspirin prevent it? Or more precisely, is the evidence for preventive benefit in people at average risk strong enough to outweigh the known risks of regular aspirin use?

Up to now, the committees that draw up cancer prevention guidelines have concluded that the evidence for aspirin’s benefits was insufficient when weighed against the risk of gastrointestinal bleeding, a common side effect that can be severe; aspirin can also cause hemorrhagic stroke.

But the new studies, though not perfect, could tip the scales in favor of aspirin, say some experts. The accumulated data now “arguably support more general recommendations to consider aspirin for prevention of colorectal cancer in the context of individualized risk-benefit assessments,” wrote Andrew Chan, M.D. Harvard Medical School, Boston, and Scott Lippman, M.D. at the M.D. Anderson Cancer Center in Houston, in their Lancet editorial on December 17th.

“We’re in a situation where no single study will settle all the questions for everyone,” Chan said in an interview. “But a lot of evidence is in and we’ve reached a point where there is a sufficient body of evidence for us to no longer question if aspirin can prevent colorectal cancer, but to decide what kind of risk stratification we need.”

Others argue that the evidence is still not strong enough, pointing to weaknesses in the new studies. Nevertheless, it seems certain that guideline committees will revisit the issue in 2012 and that ongoing research on aspirin’s risks and benefits in cancer prevention has taken on new visibility.

**Newest Evidence**

All three studies showed a benefit for aspirin after long-term follow-up. Two of them, led by Peter Rothwell, M.D., Ph.D., at Oxford, looked at cancer outcomes of participants in clinical trials of aspirin to prevent cardiovascular disease. The first (The Lancet, November 2010), found that after 20 years’ follow-up of five pooled randomized trials, daily aspirin, including low-dose aspirin, statistically significantly reduced incidence and mortality from colorectal cancer. The benefits did not begin to appear until after 7-8 years’ follow-up.

The second Rothwell study (The Lancet, January 2011), an analysis of individual patient data from randomized cardiovascular trials, found that aspirin reduced the risk of multiple cancers, including colorectal and other gastrointestinal cancers, lung cancer, brain cancer, and others. Again, the benefit was statistically
significant and unrelated to dose. It appeared after 5 years’ follow-up.

The third study (The Lancet, December 2011) was a randomized controlled trial of patients with Lynch syndrome who have a very high risk of colorectal cancer. Known as CAPP2 and led by John Burn, M.D. at Newcastle University, Newcastle on Tyne, U.K., it compared aspirin to a placebo in 861 patients. After 55.7 months’ follow-up, there was not a strong statistically significant difference between the groups in cancer incidence, the trial’s primary endpoint. However, when the researchers conducted a per-protocol analysis of the 508 participants who had taken aspirin for at least two years, they did find a clear statistically significant difference—23 colorectal cancers in the placebo group versus 10 in the aspirin group.

All three studies had weaknesses. The first two were analyses of data from trials in which colorectal cancer was not an endpoint. And the Lynch syndrome trial was negative until the researchers did the subgroup analysis. Nevertheless, the size of the studies and the results, added to the existing evidence about aspirin’s benefits, was enough to cause a rethinking of current guidelines that recommend against taking aspirin to prevent colon cancer, said leaders in the field.

Eric Jacobs, Ph.D., an epidemiologist with the American Cancer Society, wrote in his editorial for the second Rothwell study that future guideline committees should now consider the overall balance of risks and benefits in daily aspirin use. He wrote in an email that “reduced risk of colorectal cancer alone is probably not enough to meaningfully influence clinical guidelines for aspirin use. The critical question now is whether long-term daily aspirin use has additional benefits with respect to cancer, such as the overall reduction in cancer mortality” seen in that study.

Harvard’s Chan also argues that guidelines should be expanded to take in the evidence for aspirin’s benefits in various cancers and in cardiovascular disease. “Ultimately, it’s most useful to patients and clinicians to have concrete evidence regarding risks and benefits for both conditions since in practice we are interested in recommendations to prevent any common disease that may impact longevity and well-being,” he said.

Revisiting Guidelines

By the end of 2011, guideline committees were taking note.

“We’re all aware of this,” said Virginia Moyer, M.D., speaking as chair of the United States Preventive Services Task Force. All USPSTF guidelines undergo regular updates, Moyer added, but when new information appears, a topic can move up on the priority list for review. “It is likely that [this one] will move up,” she said.

The National Comprehensive Cancer Network in the U.S. will also revisit the issue, according Randall Burt, M.D., at the University of Utah’s Huntsman Cancer Institute. Burt chairs the network’s colorectal cancer screening panel, which also considers chemoprevention. That panel “will definitely be talking about the aspirin issue at its next regular meeting, which is soon,” he said.

Likewise, a group from the International Conference on Cancer Prevention in St. Gallen, Switzerland, is reconsidering its 2009 statement that there was not enough evidence to formulate guidelines. The group’s chair Jack Cuzick, Ph.D., at the Wolfson Institute of Preventive Medicine, Queen Mary, University of London, said the group has “already met and we are preparing a new statement to reflect the new results. We should have something ready early in the new year.” Cuzick added that some new trials are likely to be recommended.

Revisiting the issue does not necessarily mean changing guidelines, of course. Speaking not for the panel but voicing his personal opinion, Burt said he had doubts that they should change. The three new studies “are helpful, they are compelling, but they are just not definitive,” he said.

Burt also questions whether revised guidelines would make a difference in clinical practice. “Would taking aspirin change the recommended colonoscopy intervals?” he asked. “I don’t think so.”

Next Steps

Many experts agree that a gold-standard, randomized controlled trial in people at average risk will never be realistic. Such a trial would require long-term follow-up of thousands of participants and cost billions of dollars. Another challenge would be finding enough participants who weren’t already taking aspirin for its cardiovascular benefits.

“We have to accept that decision-making here will be based on less than optimal data,” said Gad Rennert, M.D., director of Israel’s National Cancer Control Center and chair of the Department of Community Medicine and Epidemiology at Carmel Medical Center in Haifa.

More data, however, will be forthcoming. First, there are ongoing efforts to leverage data from past trials of aspirin, including the Physicians Health Study and the Women’s Health Study. Long-term follow-up of those participants could yield new information and will be important, said Chan.

Likewise, epidemiologists at the American Cancer Society are conducting new analyses of observational data from its Cancer Prevention Study II to help clarify the potential role of aspirin, according to Jacobs. (He also noted that the ACS has no guideline on aspirin use and “has no plans at this time to make recommendations about using aspirin for cancer prevention.”)

For Lynch syndrome patients, Burn and his colleagues are planning to launch a CAPP3 randomized trial to compare different doses of aspirin and duration of use in this high-risk group. That team is also planning an open-label study to compare the optimal dose and duration of aspirin. In what may be the first trial to be organized through the Internet rather than physicians, participants will register online and be randomized to one of three aspirin doses. They will be responsible for going to their local pharmacies to buy the aspirin and asking their own doctors to report results.

Burn said that the CAPP3 website (http://www.capp3.org/) had about 1,500 visitors within a few weeks of its launch in November.

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Finally, two large trials now in progress should provide more data on aspirin’s toxicities. One, the AspECT trial, begun in 2005, is testing whether aspirin combined with a proton pump inhibitor, esomeprazole, can prevent Barrett’s esophagus from progressing to cancer. Its hypothesis is that the proton pump inhibitor will prevent upper gastrointestinal bleeding. The second, called ASPREE, begun in 2009, is examining whether the potential benefits of low dose aspirin outweigh the risks in people over age 70.

**Biomarkers**
Other studies are looking for biomarkers to identify people in whom the benefits of aspirin outweigh the risks. Chan said that these biomarkers could include plasma inflammatory markers, such as soluble TNF-R2, as well as genetic markers, such as genes involved in aspirin metabolism. “We are focusing now on studies which explore such strategies, in conjunction with an individual’s risk profile, with the idea that it is unlikely that a single biomarker may be enough to fully predict responsiveness or toxicity to aspirin.”

Rennert and other biomarker researchers are focused on the COX1 and COX2 pathways, among others. Aspirin is known to inhibit expression of COX2 and tumor development. Rennert said he and Stephen Gruber, M.D., at the University of Michigan, Ann Arbor, are exploring various potential biomarkers, including inflammation-related genes in the COX-1 and COX-2 pathways.

Burn is interested in a newer hypothesis suggesting that aspirin prevents colon polyps from becoming cancerous by killing off cancer stem cells. “Aspirin is doing to stem cells in the [polyp] crypts what salicylates do to diseased cells in plants,” he said, referring to the active ingredient in aspirin which is responsible for getting rid of diseased cells in plants. He is now writing a grant to explore this idea.

Burt, though skeptical of the clinical usefulness of current evidence, agreed that having reliable biomarkers could be the answer. “If we can find a subset of people that really benefit [from aspirin], then absolutely they should use it,” he said. “That’s probably the way this will be sorted out.”