Aspirin for Cancer Chemoprevention: Still a Headache?

Almost 7 million Americans, with the full blessing of their cardiologists, now take daily aspirin to prevent heart attacks, according to the Aspirin Foundation of America. But should we take aspirin to prevent cancer? Answers remain elusive, but the current consensus is: not yet, not even for colorectal cancer, where the strongest evidence exists. “We still have a long way to go to be certain about the [cancer] benefits before we subject people to the risks of low-dose aspirin,” said University of Michigan internist Mark Fendrick, M.D.

Two articles in this issue of the Journal contribute to the debate over aspirin cancer chemoprevention, and a third article, on aspirin and pancreatic cancer, was published in the January 7 issue. One research team (p. 305) reports that regular aspirin use is associated with a reduction in risk of Hodgkin’s lymphoma, based on data from a case–control epidemiologic study in New England. Another group (p. 316) describes a cost-effectiveness model for the use of aspirin to prevent the progression of Barrett’s esophagus to esophageal cancer, concluding that aspirin may be a reasonable choice, assuming that aspirin’s benefits are confirmed by more studies. Finally, last month (see Vol. 96, No. 1, p. 22–28) researchers reported an increased risk of pancreatic cancer with regular aspirin use in the Nurses’ Health Study cohort.

Exploring the Mechanism

Aspirin’s preclinical anticancer effects are well established. Like other nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin blocks the cyclooxygenases, COX-1 and COX-2, which have been implicated in carcinogenesis and tumor growth through the production of prostaglandins. Prostaglandins or their metabolites may initiate and promote cancer by triggering cell proliferation, inhibition of apoptosis, stimulation of angiogenesis, or suppression of the immune response—the exact mechanism remains unknown. But abnormally high levels of cyclooxygenases are found in many cancer cell lines, and aspirin and other NSAIDs have consistently prevented or arrested cancer in rodents.

The cyclooxygenases are not aspirin’s only targets. “There’s a lot of evidence to suggest that the [anticancer] effects may be through some other mechanism,” said Thomas Adrian, Ph.D., director of gastrointestinal oncology at Northwestern University. The Hodgkin’s disease study in this issue suggests one such mechanism. Nuclear factor κB (NFκB), a transcription factor strongly implicated in tumor development, is almost universally present in Hodgkin’s and Reed–Sternberg cells, the transformed lymphocytes that are typical of the disease, and blocking NFκB arrests tumor growth in Hodgkin’s cell lines. Ten years ago, Elizabeth Kopp, Ph.D., and Sankar Gosh, Ph.D., both at Yale University, discovered that aspirin blocks NFκB activation. So when a group at Harvard led by Nancy Mueller, Sc.D., found a 40% risk reduction for Hodgkin’s lymphoma in regular aspirin users, they postulated that aspirin’s anti-NFκB activity was the reason. “We found the protective, the inverse, association with aspirin, and not with other NSAIDs,” said Ellen Chang, Sc.D., the lead author. “And the NFκB pathway is particularly relevant to Hodgkin’s disease.”

But because Hodgkin’s lymphoma is so rare, taking aspirin to prevent it is not worth risking aspirin’s side effects, even if this protective effect were confirmed in large-scale studies. “I can’t imagine that it would be recommended to the general public, or even to people at high risk for Hodgkin’s,” said Chang. “It’s more likely that [aspirin studies] would provide information about what causes the disease.”

Non-Hodgkin’s lymphoma (NHL) is much more common—and deadlier—than Hodgkin’s lymphoma. Unfortunately, aspirin at best has little effect on NHL, and at worst promotes the disease. Recent case–control and cohort studies both showed increased risk for NHL from NSAID use. Reasons for this association, assuming it holds up, remain unknown, but may have something to do with the complex immunomodulatory effects of NSAIDs.

Esophageal Cancer

Although no one is pushing aspirin chemoprevention for lymphoma, the cost-effectiveness model of aspirin and Barrett’s esophagus in this issue may have clinical implications. “Based on current limited data, our model predicts that aspirin can be a cost-effective chemoprevention” for Barrett’s esophagus progression to esophageal cancer, said lead investigator Chin Hur, M.D., a gastroenterologist at Massachusetts General Hospital. Hur added that more clinical trials are necessary to validate the worth of aspirin in preventing esophageal cancer, but said that even for younger Barrett’s patients at low risk for heart attacks, aspirin chemoprevention now for cancer “might be reasonable.”

Barrett’s esophagus is a premalignant condition in which part of the smooth, pink lining of the esophagus is replaced by darker, rougher tissue similar to that of the intestine. About a million Americans have Barrett’s esophagus, and a small percentage of those will go on to develop esophageal cancer, one of the deadliest of all cancers. (It has an overall 5-year survival rate of 12.4%.) Hur and his colleagues built a Markov decision model, calculating that regular
Aspirin use plus endoscopic surveillance yielded 0.27 more quality-adjusted life years (QALYs) than no therapy, with an incremental cost-effectiveness ratio (ICER) of $49,600 per QALY. Therapies with ICERs below $85,000 in these models are often considered worth doing, so aspirin chemoprevention seems to make sense. “If you trust the results of the analysis, then everyone should do that, because it saves money, and it’s better,” said Hur.

But a model is only as good as its assumptions, and reliable data is lacking for aspirin and esophageal cancer. “Barrett’s esophagus—forget about chemoprevention,” said Michigan’s Fendrick in response to the Hur study. “The science of that progression [to cancer] is nowhere near as well-described as what we know about colorectal cancer.” For aspirin’s anticancer effect, Hur relied on a meta-analysis by researchers at the University of California at San Francisco, who concluded that aspirin confers a 50% risk reduction for esophageal cancer, a figure Fendrick said is unreliable. “To think that aspirin might reduce the risk by 50%, given that there’s no well-designed prospective studies, it really leaves me suspect [of the estimate],” he said. Hur admitted that the 50% figure is “probably an overestimate.”

Fendrick and colleague John Inadomi, M.D., recently modeled endoscopic surveillance of patients with Barrett’s esophagus, and concluded that surveillance alone, even without aspirin, was not a cost-effective strategy, although it did make sense for patients who had advanced dysplasia. So a combination aspirin/surveillance strategy, argued Fendrick, is unlikely to tip the balance toward cost-effectiveness for Barrett’s patients, given aspirin’s proven risks and uncertain benefits.

Aspirin’s big drawback as a chemopreventive is the risk of serious side effects, mainly gastrointestinal (GI) bleeding and hemorrhagic stroke. The GI risk alone lies somewhere between 0.1% and 1% a year. “Even the 1 in a 1000 is a lot when you look at the rate of these cancers,” said Fendrick, who pointed out that all NSAIDs together kill between 10,000 and 15,000 people a year in the United States.

Feeding LOX

Aspirin is no panacea for pancreatic cancer, either. Earlier epidemiologic studies had delivered contradictory results, with one study showing reduced risk from regular aspirin use (see Vol. 94, No. 15, p.1168–71), two showing no effect, and two reporting a higher risk from aspirin. The new results, from more than 88,000 women participating in the Nurses’ Health Study, again suggested that regular aspirin use is associated with pancreatic cancer. Women who reported more than 20 years of regular aspirin use had a 58% increased risk of pancreatic cancer compared with women who were never regular users, and the higher the aspirin dose, the higher the observed incidence of cancer.

Why might aspirin cause pancreatic cancer? One possible reason is that the COX pathways are probably less important in pancreatic cancer than the parallel lipoxygenase (LOX) pathways. “We’ve not found a single pancreatic cancer in which those enzymes are not upregulated,” said Northwestern’s Adrian. “Furthermore, we see upregulation even in early lesions … so we think it’s a very early event in [pancreatic] cancer.” Adrian pointed out that blocking the COX pathways with aspirin makes more arachidonic acid substrate available for LOX catalytic pathways. “That would stimulate the growth of the tumors,” he said.

Given the contradictory epidemiologic results to date, it is unclear that aspirin use leads to pancreatic cancer. More studies are needed to confirm the association, study lead author Eva Schernhammer, M.D., of Harvard Medical School, told the New York Times. But one thing’s for sure. “There’s no evidence to really support that aspirin itself is going to be a useful chemopreventive” for pancreatic cancer, said Adrian. “That’s not to say that other nonsteroidal anti-inflammatory agents may not be valuable for chemoprevention, we just don’t know that. It’s too early to say.”

The aspirin chemoprevention story is still developing, but for now, taking aspirin for the sole purpose of preventing cancer—any cancer—doesn’t appear to make sense. That’s not to say there aren’t valid reasons to take aspirin, mainly to prevent heart attacks in people at high risk. “I’m this huge fan of aspirin; I love the drug,” said Fendrick. “If I could take just one drug to a desert island with me, it would be aspirin, at low doses. [But] the bang for the pill in aspirin is what it does for the reduction of the number one killer in the United States.” That, of course, is coronary artery disease—not cancer.

—Ken Garber

Some Recent Articles on Aspirin and Cancer