Randomized Trial of Aspirin, Vitamin E Raises Questions for Future Chemoprevention Studies

Randomized trials of aspirin and vitamin E as potential agents for cancer prevention draw support from epidemiologic and observational evidence. They both have a plausible biological mechanism—as an antioxidant, it seems natural that vitamin E may have the ability to protect people from cancer, and the nonsteroidal anti-inflammatory drug (NSAID) aspirin has already proven its ability to protect against heart disease and strokes. Not to mention that they are both widely available and already taken by many people.

“The dream was, wouldn’t it be wonderful if [aspirin] also reduced the risk of cancer at the same time?” said Julie Buring, Sc.D., of Harvard Medical School and Brigham and Women’s Hospital in Boston.

This summer, Buring and colleagues published two papers in the Journal of the American Medical Association that documented the results of a large randomized controlled trial called the Women’s Health Study (WHS), the first of its kind to examine these agents in healthy women. The study included nearly 40,000 women randomly assigned to take aspirin, vitamin E, and/or a placebo for 10 years in hopes of finally clarifying what clinical association existed between taking aspirin and/or vitamin E and cancer risk. However, according the results, there is no association. These findings raise questions about where to go next with cancer prevention trials of vitamin E and aspirin and whether new trials of this magnitude will ever be mounted for these agents.

Some researchers don’t think that the WHS is the final word for aspirin in chemoprevention. Buring’s colleague Nancy R. Cook, Sc.D., also of Brigham and Women’s Hospital and lead author of one of the two JAMA papers, believes that further aspirin studies may still yield positive results for specific types of cancers. For example, the study revealed a statistically significant reduction in mortality from lung cancer among aspirin users.

Aspirin may also prove effective if the dose is increased. “The dose was low and [taken] every other day,” said Cook, explaining that the study examined a low 100-mg dose, an amount recommended for preventing cardiovascular disease, in hopes that a dose that many Americans may already be taking could also prevent cancer.

Cook suggested that future clinical studies should look at the effects of higher doses, as well as...
specific cancers. “There is little evidence that low-dose aspirin can reduce risk of cancer, although observational studies consistently suggest regular-dose aspirin reduces risk of colorectal cancer,” agreed Eric Jacobs, Ph.D., of the American Cancer Society, who wrote an editorial that accompanied Cook’s article in JAMA. To that end, Peter Rothwell, M.D., Ph.D., of the University of Oxford is currently conducting a meta-analysis that will initially focus on high-dose (300 mg or more) aspirin and colon cancer. They hope to have some results within the next few months.

A higher dose could prove to prevent cancer, but the duration that the subjects take the drug may matter more, commented John A. Baron, M.D., of Dartmouth Medical School in Lebanon, N.H. The Nurse’s Health Study, for example, suggested that aspirin use was associated with a reduced risk of colon cancer after 15 years, he pointed out. “It takes cancer a long time to grow up and become real cancer,” he explained, “so the agent needs to be in the body for a long period of time.”

As for the next step for vitamin E chemoprevention studies, the Southwest Oncology Group is coordinating the nationwide Selenium and Vitamin E Cancer Prevention Trial (SELECT), another large randomized controlled trial. The vitamin E results of the WHS, although disappointing, have not affected SELECT, aside from providing safety data on long-term use of vitamin E, says Eric Klein, M.D., the lead coordinator of the SELECT study.

However, Klein and others believe that the WHS results, coupled with other negative results from similar large clinical trials, may affect chemoprevention studies of the future.

Additional trials of this nature raise questions of practicality—they require years or even decades of follow-up of huge numbers of study participants to gather accurate conclusions. Because they use healthy subjects, as opposed to sick or dying patients, chemoprevention trials like the WHS need even longer to achieve their primary endpoints and even larger numbers of patients to see measurable incidence rates than other types of clinical trials, said I-Min Lee, MBBS, Sc.D., also of the Brigham and Women’s Hospital in Boston.

Thus, these types of trials entail vast sums of money, resources, and labor. With a current lack of positive findings, such expenses may discourage future studies of the magnitude of the WHS, said Klein. He said he believes that most future studies will be much smaller in size and scope and will be based on biologic and genetic evidence, as opposed to observational and epidemiologic indications—as were the WHS and SELECT. Such studies examining the biologic and genetic mechanisms of agents will only be “increasing in intensity as negative studies keep rolling out,” agreed Leslie Ford, M.D., associate director for clinical research at the National Cancer Institute.

Perhaps more important than money and resources, trials like the WHS rely on compliant subjects willing to stick to a pill regimen for years and years, said Baron. “It is hard to keep people on drugs for very long periods of time when they are healthy and feeling well,” he said, highlighting an obstacle for chemoprevention trials of healthy people.

“It’s amazing that [Buring and colleagues] were able to keep on going for 10 years,” he said. Although impressed with the aspirin study’s 73% compliance rate after 5 years and 67% after 10 years, Baron added that the dropout rate could still have had an effect on the study’s results. Furthermore, low compliance rates often plague long-term studies. Even if some anticancer benefit does occur, if subjects in clinical trials cannot keep to a long-term regimen, it may be unreasonable to expect that the general population will, he added. Instead of concentrating on pharmaceutical studies to test agents, he suggests creating a greater focus on behavioral studies to find ways of keeping test subjects compliant.

The future of prevention studies may rely not only on these types of behavioral studies but also on a host of studies focusing on a more holistic arsenal of agents, according to Lee, another author of the WHS studies. She believes that studies of single agents, from the beta-carotene trials of the 1990s to this summer’s aspirin and vitamin E study, are beginning to fall out of favor. Instead, chemoprevention studies of the future will examine the entire health and body of a patient, especially body weight and physical activity levels. However, such behavior modifications may prove more difficult and less enticing than merely swallowing a pill, she said. “I do believe we need to be doing good trials of diet and exercise and cancer prevention,” agreed Jacobs.

“We also need trials to discover effective methods for promoting smoking cessation and colorectal cancer screening,” he added. Ultimately, a single “magic bullet” that can protect against cancer could be an unrealistic dream, said Lee.

In the meantime, researchers await the results of the SELECT study, as well as dozens of other ongoing cancer prevention trials involving agents varying from other NSAIDs to green tea to the Mediterranean diet. Lee, Buring, Cook, and colleagues also plan to continue collecting data from their study subjects over the next 5 years.

“It’s not the end of the story for [NSAIDs like aspirin] … and other targeted agents,” said NCI’s Ford.

—Elana Hayasaka