Aspirin May Improve Survival in PIK3CA-Mutated Colorectal Cancers

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By Anna Azvolinsky [2]

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Patients with the mutation who used aspirin regularly after initial diagnosis of their colorectal cancer had an 82% reduction in death from colorectal cancer and a 40% reduction in death overall compared to patients who had the PIK3CA mutation but did not use aspirin. Patients who had a nonmutated PIK3CA gene did not benefit from aspirin use.

If these results are validated, aspirin may be particularly effective in enhancing survival of the 15% to 20% of colorectal cancer patients whose cancer have a PIK3CA mutation. Although the results need to be verified, a PIK3CA mutation may be the first genetic marker available to predict which colorectal cancer patients can benefit from aspirin use.

“This is certainly a very interesting paper,” said Leonard Saltz, MD, chief of the gastrointestinal oncology service at Memorial Sloan-Kettering Cancer Center in New York. “Given that long-term aspirin can have real toxicities, it would be very nice to be able to select a subpopulation of patients who are most likely to benefit.” Regular aspirin use is not advised for all patients as it can lead to stomach bleeding or gastrointestinal ulcers.

Aspirin may be a viable adjuvant therapy for colorectal cancer patients—previous observational and randomized trials have suggested newly diagnosed colorectal patients can benefit from aspirin. However, as colorectal cancer is a diverse spectrum of diseases, it is not clear which colorectal cancer patients are most likely to benefit. Studies have suggested that the effect of aspirin on colorectal cancer depends on the tumor’s level of PTGS2 expression. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are known to inhibit PTGS2. PTGS2 encodes cyclooxygenase-2 (COX-2), involved in inflammation, and implicated in various cancers.

Andrew T. Chan, MD, of the division of gastroenterology at the Massachusetts General Hospital in Boston and Shuji Ogino, MD, PhD, of the Dana-Farber Cancer Institute in Boston, and colleagues hypothesized that because the phosphatidylinositol 3-kinase (PI3K) pathway, which includes PIK3CA, can upregulate PTGS2 activity and inhibit colon-cancer cell death, and because aspirin can block the PI3K pathway, it may selectively effect the survival of patients with PIK3CA-mutated colorectal cancer.

“So far there has been limited evidence that aspirin affects the PI3K pathway in cancer,” said Chan. “There has been research examining the relationship between the PI3K and COX-2 pathway, so the evidence available is early stage.”
The study analyzed 964 patients from two prospective cohort studies—the Nurses' Health Study and the Health Professionals Follow-up Study, 17% of both the 413 patients who used aspirin regularly (at least twice per week) and those 551 patients who did not, had a tumor that was PIK3CA-positive. Of the 90 patients who had PIK3CA-mutated tumors and did not use aspirin, 23 patients (26%) died within 5 years after diagnosis compared to 2 of the 62 (3%) patients who did use aspirin ($P < .001$).

The authors emphasize that large-scale studies are needed to validate these results. “If such studies do confirm [the effect of aspirin], then routine screening for PIK3CA mutations and selective use of aspirin in patients whose tumors have these mutations would be warranted,” said Saltz.

The regular use of aspirin in parallel with a first diagnosis of colorectal cancer may suggest that aspirin may affect early colorectal cancer development and perhaps stave off tumor growth. This hypothesis needs significant validation, especially before regular aspirin use is recommended as a standard practice, said Saltz.

The research also found the effect of aspirin on those patients with both a PTGS2 and PIK3CA mutation was stronger than for those with a PIK3CA mutation alone. “The patients who benefited the most had both mutations in COX-2 and PIK3CA,” said Chan. Aspirin appeared to have no effect on patients with a PTGS2 mutation but wild-type PIK3CA mutation. NSAID use in general did not have an effect on the survival of the patients in the study.

“It may be that the PI3K pathway may be more specific for the types of cancers that are affected by cancer,” said Chan. “I think that it could imply that there could be more mechanistic specificity for the PI3K pathway.” Aspirin may have different mechanism of action and tumors with a PI3K mutation may be enriched for these mechanisms, according to Chan. Chan emphasized that the effect of aspirin on PI3K-mutated tumors may be multifaceted.

In his editorial that accompanied the study publication, Boris Pasche, MD, PhD, of the University of Alabama at Birmingham wrote that “there is compelling epidemiologic evidence that aspirin use reduces tumor progression, recurrence, or both in patients with a diagnosis of colorectal cancer.” Pasche cited several previous studies, including a United Kingdom meta-analysis of over 17,000 patients from five clinical trials that showed daily aspirin among the colorectal cancer participants reduced the risk of metastasis by 74%. “Aspirin may well become one of the oldest drugs to be used as a 21st-century targeted therapy,” he added.

**Next Steps**

“The first thing is that we should confirm this in randomized trials of aspirin therapy, if possible,” said Ogino. “Also if any animal model of PIK3CA-mutant vs PIK3CA-wild type colorectal cancer is available, we can test the interaction between aspirin and PIK3CA.”

“We are working on additional studies to study this question further,” said Chan. “Certainly there is a lot of effort of basic science laboratories to understand whether there are specific mechanisms by which aspirin confers a benefit that are mediated by the PI3K pathway.”

The authors are working on confirming their results in other patient populations as well as to study the PI3K mutation status among cancer patients on aspirin clinical trials. “Certainly there is an interest in embarking on clinical trials of aspirin in patients that have established cancer,” said Chan. These trials could identify the broad benefit to patients and whether there are other molecular subtypes that also may benefit from aspirin use, both within the PI3K pathway as well as downstream pathways.

“The results will hopefully shed some insights by which aspirin operates, which should lead to a better understanding of how [colorectal cancer] tumors arise and also provide information about how other therapies may be effective,” said Chan.

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