

Aspirin as Adjuvant Therapy for Colorectal Cancer

A Promising New Twist for an Old Drug

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EVEN BEFORE THE TIME OF HIPPOCRATES, WILLOW EXTRACTS, which contain salicylates, were used in medicine as analgesic, anti-inflammatory, and antipyretic agents. Acetylsalicylic acid was isolated in the mid-19th century, and since 1899 when it was patented, aspirin has enjoyed global popularity. The relatively recent discovery of its antiplatelet activity has also led to the widespread use of aspirin as an antistroke and cardioprotective agent, but the list of its medical applications continues to increase.¹

More than 30 years ago, Sporn et al² coined the term *chemoprevention* to describe and propose the use of oral drugs, chemicals, or supplements to reduce the risk of cancer. In the ensuing decades, chemoprevention research has generated high hopes and enormous increases in funding, although only a few agents have shown efficacy in clinical trials, and of those few, most are too toxic for use by average-risk individuals. In addition to its other effects, aspirin has been shown to be a potentially effective chemopreventive agent for a number of cancers, but most clearly for colorectal neoplasia.³ Numerous observational studies and randomized trials have demonstrated the efficacy of aspirin against the development of colorectal adenomas and cancer through its actions as an inhibitor of the cyclooxygenase 2 (COX-2) pathway, which is overexpressed in 80% to 85% of colorectal cancers.^{4,5} Nonetheless, aspirin is not recommended as a colorectal cancer chemopreventive agent because of its adverse effects— notably gastrointestinal irritation and bleeding.⁶ Specific COX-2 inhibitors, such as rofecoxib or celecoxib, which have less gastrointestinal toxicity than aspirin, also have failed to come into widespread use because of their unexpected cardiovascular toxicity.⁷⁻¹⁰

However, aspirin may now have yet another new role as a cancer treatment agent, at least in the adjuvant setting. In this issue of JAMA, Chan and colleagues¹¹ report that, among patients with colorectal cancer participating in a large cohort study, aspirin users had a 29% lower cancer-specific mortality and a 21% lower overall mortality than nonusers. The reduction in mortality was even

greater among patients who initiated aspirin use after cancer diagnosis than among those who used it before, and the benefit was limited to those with tumors that overexpressed COX-2.

Although these findings are based on an observational study rather than an intervention trial, they meet many of the usual criteria for acceptance as valid and causal. In a previous observational study of stage III colon cancer patients treated in a randomized chemotherapy trial, Fuchs et al¹² found similar survival benefits among consistent aspirin users. The finding that former aspirin users derived less benefit from subsequent aspirin use than former nonusers did is biologically plausible, considering the tumors that developed in former users were not prevented by aspirin use. Furthermore, the results were consistent across a variety of strata such as age, sex, and cancer site (colon vs rectum). Most compelling, the benefits of aspirin use were observed only among patients who had COX-2-expressing tumors, enhancing the biological plausibility of the findings.

In the study by Chan et al,¹¹ the survival benefits of aspirin were similar in patients who received standard adjuvant chemotherapy and those who did not, and in patients with stage I and stage II disease as well as those who had stage III disease at diagnosis. Thus, aspirin may have the potential to be useful as adjuvant therapy not just for locally advanced disease but for early stage patients as well. Further studies are needed to confirm and extend these findings, and should also investigate the use of aspirin as an agent in individuals with metastatic disease. One such study is the Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib (BICC-C) study, which started in 2003 and randomized patients with untreated metastatic colorectal cancer to 1 of 3 chemotherapy regimens, and in addition randomized them to either a COX-2 inhibitor (celecoxib) or placebo.¹³ The COX-2 inhibitor portion of the study was discontinued in 2005 because the cardiovascular toxicity of the agent became apparent¹⁴ and initial results of the trial indicated no survival benefit for the celecoxib-treated group.¹⁵

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A major recent priority in clinical oncology has been to develop biomarkers for prognosis and to predict response to specific interventions. This quest for so-called personalized medicine reflects the serious toxicity of most cancer drugs with the concomitant low response; better definition of who is likely to respond would identify a smaller subgroup that is much more likely to benefit and spare other patients the toxicity. Such biomarkers reflect the longstanding success of hormone receptors and *ERBB2* status in breast cancer to determine use of hormonal therapy and trastuzumab. In colorectal cancer, *KRAS* mutations have recently attained similar status as predictors of response to cetuximab and panitumumab,¹⁶ and *BRAF* mutations are likely to achieve similar status soon.¹⁷ The specificity of the response of colorectal cancers to aspirin for patients in whom tumors overexpressed COX-2¹¹ suggests that this potential future treatment comes with its own ready-made predictive biomarker.

Cardiologists have made post-myocardial infarction patients acutely aware of the need to alter their lifestyle, use aspirin prophylaxis, and stop smoking, even as patients receive the standard cardiac treatments, such as stents and β -blockers. By recommending such behavior changes, cardiologists have empowered patients and their families to participate more actively in their own healing. Similar behavioral and lifestyle changes in cardiology also may be appropriate in oncology¹⁸ as oncology patients and their families often seek similar means of controlling their outcomes. Only the rare cancer patient or next of kin does not ask at some time during the first encounter, after hearing the diagnosis, stage, prognosis, and plans for chemotherapy, "What else should be done doctor? What should be eaten?"

To date, few studies have assessed the effects of such lifestyle factors on survival among colorectal cancer patients. Fuchs, Meyerhardt, and Chan have led the way with a series of elegant observational studies on diet,¹⁹ physical activity,^{20,21} obesity and weight loss,^{22,23} cigarette smoking,²⁴ and now aspirin use.¹¹ Although most of these findings require confirmation in further observational studies or clinical trials, and some of the results may represent confounding—the current study on aspirin use in nonmetastatic colorectal cancer,¹¹ in conjunction with the wealth of data in the precancerous setting, the similar findings in the prior study in the Cancer and Leukemia Group B (CALGB) trial,¹² and the extraordinarily specific COX-2 biomarker findings bring an observational study as close as it can to offering patients a way to help themselves. An ongoing randomized trial sponsored by the National Cancer Center of Singapore will potentially confirm these findings. Moreover, in the near future, COX-2 expression may well join *KRAS* mutation analysis as a standard predictive marker and aspirin may become standard adjuvant therapy in the management of colorectal cancer.

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