

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

The Role of Aspirin in Prevention and Management of Colorectal Cancer

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H&O What are the possible benefits of daily aspirin use?

CF The benefits of aspirin in terms of prevention of cardiovascular disease are well established. The US Preventive Services Task Force recommends regular aspirin use for men 45 years of age and older and for women 55 years of age and older as a preventative for cardiovascular disease. Researchers have since embarked on a number of studies looking at aspirin and its ability to prevent colorectal cancer based, in part, on some early preclinical data and studies in small populations, as well as on the phenomenon that the punitive target of aspirin, cyclooxygenase 2 (COX-2), is expressed in the majority of colorectal adenomas and cancers. We have studied the relationship of aspirin use and colon adenoma and cancer risk in several cohorts, mainly the Nurses' Health Study and the Health Professionals Follow-Up Study; these are large prospective cohorts of over 170,000 patients. From our analysis we found that aspirin use on a regular basis significantly reduces the subsequent risk of developing colorectal adenomas and cancers.

Another noteworthy finding was that there is a dose phenomenon with aspirin. Although for cardiovascular disease, a baby aspirin appears to be adequate in terms of achieving maximum prevention, with respect to colorectal neoplasia, increasing doses of regular aspirin appear to

diminish the risk of adenomas and cancers. For example, in a patient who takes an adult aspirin every other day on average, we generally find an up to 25% reduction in the risk of developing colorectal cancer.

H&O Does duration of aspirin use have any effect on the risk of developing colorectal cancer?

CF Duration of aspirin use does have an effect on the risk of developing colorectal cancer. Indeed, it is possible to see a reduction in polyp risk within 5 years of regular aspirin use. However, to really see a benefit in cancer risk, 10 or more years of aspirin is suggested. This length of time is recommended because it takes 10 years or more for a normal colonic epithelium to evolve into a polyp and then into cancer. This is a relatively slow process, so it would be surprising if short-term aspirin use were to have an effect on it.

H&O How should patients balance the side effects of aspirin with the possible benefits?

CF For each individual patient and physician, one has to weigh the risks and benefits of aspirin, recognizing that there are benefits beyond reduction of colorectal cancer risk, specifically in terms of cardiovascular prevention, and concurrently consider the risks associated with aspirin, principally gastrointestinal bleeding. In a person without any contraindications and for whom not only the reduction of colorectal cancer risk but also prevention of cardiovascular disease is a benefit, I think aspirin is something that physicians should consider.

H&O In which patients is aspirin recommended? In which patients is it contraindicated?

CF For individuals who have risk factors for colorectal cancer—such as a family history of the disease, prior adenomatous polyps, and other standard risk factors such as obesity, sedentary lifestyle, red meat consumption, and cigarette use—aspirin may be beneficial. We know that individuals who have a history of type 2 diabetes are at increased risk of colorectal cancer, and should be considered for aspirin. Moreover, all the risk factors described for colorectal cancer are also risk factors for atherosclerotic vascular disease. So, again, I think that these are individuals in whom aspirin should be considered. In terms of contraindications, someone who has a history of bleeding problems or gastrointestinal bleeding would certainly be someone in whom I would be more reluctant to administer aspirin, and would instead opt for other means of prevention.

With respect to the use of these drugs in the adjuvant setting, we have to wait for the results of the ongoing trials. If those results are positive, I would presume that aspirin use would be something we will need to strongly consider as an addition to our ongoing efforts in adjuvant therapy.

H&O What clinical data are available on the use of aspirin in relation to colorectal cancer?

CF The prospective, observational work done with the Nurses' Health Study and the Health Professionals Follow-Up Study has now been validated by 4 randomized clinical trials in which patients who have had a prior polypectomy were randomly assigned to aspirin or placebo. All 4 studies showed that aspirin use does in fact reduce the risk of recurrent polyps. Moreover, 3 additional studies have shown that the selective COX-2 drugs celecoxib and rofecoxib (now withdrawn from the market) were also associated with a reduced risk of polyp recurrence in similarly designed studies comparing these compounds to placebo. Thus, there are now 7 studies that, in principle, show that drugs of this class significantly reduce the risk of colorectal neoplasia.

In addition to studying the benefits of aspirin and COX-2 inhibitors in terms of prevention, we were also very interested in whether these compounds had any influence on cancer survival, particularly the outcome of patients with established colorectal cancer. We therefore conducted similarly designed prospective, observational studies looking at aspirin use among people diagnosed with colorectal cancer. We found that individuals who regularly use aspirin who had been diagnosed with stage I–III colon cancer had a significant improvement

in cancer survival. Although these were not randomized trials, the reports of aspirin use were collected at the time of study enrollment, and other treatments were carefully controlled, hence the benefit of aspirin in these studies appeared to be independent of any other measure that predicts patient outcome, such as disease stage, treatment, or other characteristics. In a separate effort, we analyzed aspirin and celecoxib use nested within a completed National Cancer Institute trial of adjuvant chemotherapy in stage III colon cancer (CALGB 89803). That study looked at the use of 5-fluorouracil (5-FU), leucovorin, and irinotecan compared to 5-FU and leucovorin alone. Concurrently, we collected data on aspirin, celecoxib, and rofecoxib use on patients enrolled into the trial. Among the individuals who reported aspirin use, there was a significant improvement in disease-free and overall survival; this was independent of treatment because the treatment was prescribed by the clinical trial. To identify consistency in the data, we then analyzed rofecoxib or celecoxib use; those patients that reported use of either drug also experienced an improvement in disease-free and overall survival.

Another interesting area of research has been biomarkers. We wanted to find out whether there were biomarkers within the tumors that predicted patients who would benefit from drugs like aspirin and other COX-2 inhibitors. We therefore examined the influence of aspirin use among healthy people on the subsequent expression of COX-2 in the tumors. We found that aspirin preferentially reduced the risk of COX-2–overexpressing tumors. On the basis of this finding, we evaluated aspirin use in cancer patients and found that the benefit of aspirin was far greater in individuals whose tumors overexpressed COX-2 (between 66–75% of the tumors). This discovery provided insight into the biology of the disease, internal validation of the findings, and information in regard to clinical practice. This being said, the potential benefit of aspirin and related compounds in cancer survival requires further research before we can routinely recommend its use in our patients.

H&O Are there any ongoing studies?

CF There is an ongoing intergroup trial that is led by Dr. Jeffrey Meyerhardt (CALGB 80702). It is looking at adjuvant chemotherapy in patients (estimated 2,500 patients) with stage III colon cancer who are randomly assigned to 3 years of celecoxib once a day or placebo to test the hypothesis that celecoxib can improve outcome in stage III colon cancer patients following a curative resection. A separate randomization is assigning patients to 3 versus 6 months of 5-FU, leucovorin, and oxaliplatin. We expect this study to address whether celecoxib should be used as an adjunct to chemotherapy for stage III colon

cancer and to ascertain tumor and blood biomarkers that predict patients most likely to benefit from celecoxib in the adjuvant setting.

H&O What kind of impact do you think the study findings have on practice?

CF In terms of prevention, I do not think aspirin has played into routine practice mainly because the US Preventive Services Task Force did not recommend it as a routine prevention approach to patients who are at average risk of colorectal cancer, as they did not think the benefits outweighed the risks. In the average risk population, the decision whether or not to use aspirin is probably driven principally by efforts to reduce cardiovascular disease, with the realization that its use will impact the risk of colorectal cancer.

There are multiple trials demonstrating the benefit of aspirin and reduction of recurrent polyps; therefore,

an individual who has a history of polyps is someone in whom I would think about aspirin if there were no contraindications.

Suggested Readings

ClinicalTrials.gov. Oxaliplatin, leucovorin calcium, and fluorouracil with or without celecoxib in treating patients with stage III colon cancer previously treated with surgery. ClinicalTrials.gov Identifier: NCT01150045. <http://clinicaltrials.gov/ct2/show/NCT01150045?term=CALGB+80702&rank=1>.

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