

Long-Term Effects of Aspirin on Colorectal Cancer

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The term *evidence-based medicine* was first coined by Sackett and colleagues¹ as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility, and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program titled “Evidence-Based Reviews in Surgery” (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how

to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserv discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence-Based Reviews in Surgery through the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews, which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS website or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in *the Canadian Journal of Surgery*, 4 in the *Journal of the American College of Surgeons*, and 4 in *Diseases of Colon and Rectum* each year.

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SELECTED ARTICLE

Long-Term Effect of Aspirin on Colorectal Cancer Incidence and Mortality: 20-Year Follow-Up of Five Randomized Trials

Rothwell PM, Wilson M, Elwin CE, et al. *Lancet* 2010;376:1741–1750.

Objective: To assess the effects of ASA on the incidence and mortality due to colorectal cancer in relation to dose, duration of treatment and site of tumor.

Data sources: Four randomized controlled trials comparing aspirin to control in the UK and Sweden in the 1980s and early 1990s.

Study selection: Eligible trials had to have recruited at least 1,000 participants and to have had a median scheduled treatment period of at least 2 to 5 years.

Outcomes measures: Incidence and mortality from colorectal cancer.

Results: In the 4 trials (mean duration of scheduled treatment 6.0 years) 391 (2.8%) of 14,033 patients had colorectal cancer during a median follow-up of 18.3 years. Allocation to aspirin reduced the 20-year risk of colon cancer (incidence hazard ratio [HR] 0.76, 95% CI 0.60 to 0.96, $p = 0.02$; mortality HR 0.65, 95% CI 0.48 to 0.88, $p = 0.005$), but not rectal cancer (incidence HR

0.90, 95% CI 0.63 to 1.30, $p = 0.58$; mortality HR 0.80, 95% CI 0.50 to 1.28, $p = 0.35$). Where subsite data were available, aspirin reduced risk of cancer of the proximal colon (incidence HR 0.45, 95% CI 0.28 to 0.74, $p = 0.001$; mortality HR 0.34, 95% CI 0.18 to 0.66, $p = 0.001$), but not the distal colon (incidence HR 1.10, 95% CI 0.73 to 1.64, $p = 0.66$; mortality HR 1.21, 95% CI 0.66 to 2.24, $p = 0.54$; for incidence difference $p = 0.04$, for mortality difference $p = 0.01$). However, benefit increased with scheduled duration of treatment, such that allocation to aspirin of 5 years or longer reduced the risk of proximal colon cancer by about 70% (incidence HR 0.35, 95% CI 0.20 to 0.63; mortality HR 0.24, 95% CI 0.11 to 0.52; both $p < 0.0001$) and also reduced the risk of rectal cancer (incidence HR 0.58, 95% CI 0.36 to 0.92, $p = 0.02$; mortality HR 0.47, 95% CI 0.26 to 0.87, $p = 0.01$). There was no increased benefit at doses of aspirin greater than 75 mg daily, with an absolute reduction of 1.76% (95% CI 0.61 to 2.91; $p = 0.001$) in 20-year risk of any fatal colorectal cancer after 5 years of treatment with 75 to 300 mg daily. However, the risk of fatal colorectal cancer was higher on 30 mg vs 283 mg daily on long-term follow-up of the Dutch TIA trial (odds ratio 2.02, 95% CI 0.70 to 6.05, $p = 0.15$).

Conclusions: Aspirin taken for several years at doses of at least 75 mg daily reduced long-term incidence and mortality due to colorectal cancer. Benefit was greatest for cancers of the proximal colon, which are not otherwise prevented effectively by screening with sigmoidoscopy or colonoscopy.

Commentary: Although secondary prevention of colorectal cancer by endoscopic screening is attractive due to the long window of opportunity inherent in the adenoma-to-carcinoma sequence, screening is expensive, compliance with screening is relatively poor and there is potential morbidity. As a result, there has been long-standing interest and hope that primary prevention or chemoprevention using "simple" pharmacologic strategies may modulate or obviate the need for endoscopic screening to prevent colorectal cancer.

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain one of the oldest and most studied class of agents for chemoprevention of colorectal cancer. The mechanism of prevention of adenoma formation by NSAIDs is cyclooxygenase inhibition. Right-sided colon cancers often develop through the mechanism of DNA promoter methylation, along the serrated pathway to CpG island methylation phenotype (CIMP) cancer.¹ Aspirin might be as or more effective in this pathway and mechanism com-

pared with the more common chromosomal instability-driven, adenoma-carcinoma sequence. The CAPP study² also showed that aspirin is effective in the third major mechanism of colorectal carcinogenesis; the mutator phenotype driven by inactivation of DNA mismatch repair.³ Aspirin should be effective therefore, no matter how colorectal cancer develops. Despite the possibility of side effects and morbidity associated with long-term use of aspirin, this approach remains a potentially promising strategy to prevent deaths from colorectal cancer. This is in addition to the well-demonstrated beneficial effects of aspirin in preventing cardiovascular events in placebo-controlled trials.

The study by Rothwell and colleagues attempts to address 4 areas of uncertainty found in most previous studies of aspirin and colorectal neoplasia chemoprevention: the nature of the endpoint, the duration of follow-up, the dose of the drug, and the location of the neoplasia. In cancer chemoprevention the ultimate endpoint is cancer, but this is not a frequent enough occurrence for most single short-term studies. Such studies use the adenoma as a surrogate for cancer, and lose relevance by doing so. Certainly, some have separated advanced adenomas from "not advanced" adenomas⁴ and that is helpful, but the rate of cancer is the most clinically relevant endpoint and the one of most interest.

For this meta-analysis, the authors chose randomized controlled trials comparing aspirin with placebo for either primary or secondary prevention of cardiovascular events. It would appear that the authors included studies in this meta-analysis primarily based on convenience. They chose trials from the 1980s and 1990s so that follow-up would be adequate to determine long-term cancer outcomes. There was no description of a literature search or any other grey literature search that would facilitate reproduction of their search strategy. The authors declare that they chose trials performed in the United Kingdom and Sweden because these 2 countries have central death registries that were complete from the 1980s forward. However, they subsequently included a Dutch trial because "long term follow-up data on cause of death were also available," suggesting not much rigor in application of the few inclusion and exclusion criteria the authors had described. The only other inclusion criteria described were clinical trials that recruited a minimum of 1,000 patients and demonstrated a median scheduled treatment duration of 2.5 years. These criteria seem arbitrary and designed to match the studies included, rather than guiding a search. The authors indicated that 5 studies met the inclusion criteria, but one of these studies was subsequently excluded because the data had been destroyed.

The methodology of this study is a variant of a meta-analysis called a *pooled analysis*, whereby individual pa-

tient data from multiple studies are combined and analyzed. Individual patient level data are required so it is usually not possible to perform with standard aggregated data available in published trials. Instead, patient level data are requested from the original investigators. Pooled analyses are usually considered more rigorous than meta-analyses. First, the author has the raw data and is not relying on assumptions made by the original investigators. Second, the author can impose common inclusion, exclusion criteria, statistical methods, etc, across all data. Third, the statistic may be more accurate because in a meta-analysis, means are rounded, or sometimes the data have to be approximated by looking at graphs. Fourth, the author can control for publication bias if the data were not chosen based on publications, but rather based on knowledge of existing trials.

Most pooled analyses focus on outcomes that were primary or secondary outcomes of the original studies included. In this study, the primary outcome was colorectal cancer incidence and mortality, which was not the primary outcome in any of the studies included. This adds another layer of complexity, as the authors retrieved this information from national cancer registry data (UK), death registries (UK and Sweden) or primary patient follow up (Dutch).

Initially, the authors used conventional meta-analysis statistics and determined the pooled estimate of the odds ratio for death due to colorectal cancer using a fixed effects model in all included studies and a similar analysis for incidence of colorectal cancer in the 3 UK studies in which this outcome could be determined using registry data. From this analysis, the authors demonstrated a consistent reduction in the risk of death from colorectal cancer across studies (odds ratio [OR] 0.5 to 0.73) with an overall OR of 0.66 (95% CI 0.55 to 0.85). These findings were also consistent across the different dosing ranges (75 to 300 mg or 500 to 1,200 mg daily). It is unclear which test of homogeneity was performed, but the authors reported no statistically significant heterogeneity ($p = 0.84$). Similarly, in the 3 UK studies, the authors reported consistent reduction in the risk of development of colorectal cancer with acetylsalicylic acid treatment (OR 0.75 95% CI 0.61 to 0.92) and reported that the test of heterogeneity was not significant ($p = 0.91$).

Next, the authors presented their pooled analysis results. In the pooled analysis, there were 14,033 patients treated for a median of 6.0 years and followed for a median of 18.3 years. In patients treated with low-dose aspirin (75 to 300 mg), Cox proportional hazards modeling demonstrated a reduction in the incidence of colorectal cancer (HR 0.75, 95% CI 0.56 to 0.97) and cancer-specific mortality (HR 0.61, 95% CI 0.43 to

0.87). The absolute risk reduction for colorectal cancer incidence was 1.2% (95% CI 0.19% to 2.22%). In all patients treated with aspirin, including doses up to 1,500 mg per day, there was a reduction in colorectal cancer incidence (HR 0.76, 95% CI 0.63 to 0.94) and cancer-specific mortality (HR 0.68, 95% CI 0.54 to 0.87).

The authors conducted a subgroup analysis to determine the influence of aspirin prophylaxis on colon vs rectal cancer. They found that most of the effect of aspirin prophylaxis was seen in the reduced incidence of colon cancer (HR 0.76, 95% CI 0.60 to 0.96) and not rectal cancer (HR 0.90, 95% CI 0.63 to 1.30). The authors demonstrated that the risk of fatal colon cancer was reduced with aspirin prophylaxis (HR 0.65, 95% CI 0.48 to 0.88); rectal cancer fatality was unaffected (HR 0.80, 95% CI 0.50 to 1.28).

Finally, the authors demonstrated there was a significant influence of duration of treatment. In every analysis, when the group of patients treated for at least 5 years was isolated, the effect of the chemoprophylaxis decreased both the incidence and improved cancer-specific mortality.

In studies with uncommon events, large patient enrollment is necessary to demonstrate even important differences in the outcome. Because the incidence of colorectal cancer is expected to be very low, the inclusion of more than 14,000 patients in this pooled analysis provided the power to improve the precision. In the Rothwell study, the relative risk reduction (expressed as a hazard ratio) ranged from 25% to 40%. So, the absolute risk reduction for colorectal cancer incidence was approximately 1.2%, with relatively wide 95% CI ranging from 0.19% to 2.22%. Although this is a meaningful result, long-term preventative therapy is required in 83 patients to prevent 1 cancer.

Although the primary objective of this study was to determine the influence of prophylactic aspirin in the prevention of colorectal cancer and cancer-specific mortality, a major criticism is that there was no consideration given to the possible adverse effects of aspirin use. There was no discussion of gastrointestinal bleeds or renal complications, presumably because these data were not readily available. Further, overall mortality would have been helpful. Presumably, if there are important reductions in both vascular and colorectal cancer mortality, there should be an overall reduction in mortality reflecting these benefits. However, if there are significant but adverse effects of this chemoprophylaxis, overall mortality may be unchanged.

The results of this study are not generalizable to patients at average risk of developing colorectal cancer. The majority of the patients were elderly men at high risk of cardio-

vascular events. From a clinical point of view, consideration of the use of chemoprophylaxis for cancer would ideally start well before patients are in their mid- to late 60s. The authors had no data on these patients' baseline risk factors for colorectal cancer or their previous history of screening for colorectal cancer. Further, there are no data on which patients had screening colonoscopy during the follow-up period. Colonoscopy and polypectomy would certainly reduce both the incidence and mortality of colorectal cancer in these patients and confound the results.

The novel aspect of this study is that it shows a site-specific benefit for a reduction in colon cancer incidence and mortality, in favor of the right colon. The magnitude of the reduction of deaths from right-sided colon cancer and the apparent inadequacy of colonoscopy suggests a complementary role for long-term aspirin use for colon cancer chemoprevention.⁵ This makes it a potentially very useful strategy. It is an inexpensive drug and a low dose seems to work as well as a standard dose and its side effects are likely acceptable. However, multiple questions need to be answered before wholesale aspirin use as a chemopreventive is recommended. Are there high risk groups that would benefit more than lower risk groups from aspirin therapy? How does family history play a role in triaging patients to aspirin or no aspirin? How should surveillance intervals be determined in patients whose polyps are suppressed by aspirin? Does aspirin have its biggest effect on serrated polyps or adenomas? Will improvements in the quality of colonoscopy minimize the benefits of aspirin? Why do patients taking aspirin suffer fewer colorectal cancers and die from them less frequently? Is it because cancers are diagnosed at an earlier stage in the aspirin groups, possibly because of bleeding secondary to aspirin use or in some way, is the aspirin inhibiting cancer progression? Even if the gains are derived from identifying cancers earlier, they are gains nonetheless.

Although this study provides the best evidence to date that the long-term use of aspirin may reduce the incidence of colorectal cancer, a randomized controlled trial enrolling men and women with a known risk of developing colorectal cancer would be the best way to determine both the risks and benefits of this preventative strategy. However, starting prospective randomized controlled trials of any chemopreventive agent with cancer as the primary endpoint is difficult because the follow-up would be prohibitively long and the number of patients to be enrolled will be prohibitively

high. The study by Rothwell and colleagues is a reasonable short cut to such a study.

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