NSAIDs (including aspirin): Role in prevention of colorectal cancer

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INTRODUCTION

Colorectal cancer ranks among the most common malignancies in the United States and other economically developed countries. At current rates, approximately 6 percent of individuals will develop this malignancy in their lifetime. Approximately one-half of individuals diagnosed with colorectal cancer will die from it. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors".)

The risk of colorectal cancer can be reduced by screening, recommendations for which have been issued by several major medical organizations. (See "Screening for colorectal cancer: Strategies in patients at average risk".)

In addition, several protective factors have been identified, stimulating interest in primary prevention. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors".)

Among the protective agents are aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). A large and compelling body of research has shown that NSAIDs inhibit colorectal carcinogenesis. The evidence is diverse and is based upon animal models, epidemiologic data, intervention trials of NSAIDs in patients with familial polyposis, and, more recently, randomized controlled trials of aspirin and selective COX-2 inhibitors in humans.

This topic review will summarize the data supporting the potentially beneficial role of aspirin and other NSAIDs for colorectal cancer, and discuss the potential clinical implications. The potential benefits of aspirin for the incidence and mortality of other cancers is discussed separately. (See "Aspirin in the primary prevention of cardiovascular disease and cancer".)

COLORECTAL CANCER

The initial human evidence of a potential role of aspirin as a chemopreventive agent was somewhat serendipitous. A large case-control study of colorectal cancer published in 1988 explored numerous potential associations between various medications [1]. One of the unexpected findings was an inverse association between aspirin use and risk of colorectal cancer. The association persisted even when the investigators controlled for potential confounding factors, leading the authors to speculate that this inverse association could be causal.

A large number of subsequent studies of varying designs confirmed this association with both aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) [2,3]. These data have demonstrated a reduction in the risk of colonic adenomas and colorectal cancer in the range of 20 to 40 percent, depending in part upon the dose and duration of therapy and study design.

Systematic reviews — Meta-analyses and systematic reviews suggest that aspirin use is associated with a decreased incidence of colonic adenomas, colorectal cancer, metastatic colorectal cancer, and death due to colorectal cancer.

One meta-analysis of controlled and observational studies reached the following conclusions regarding aspirin [2]:

- Regular use of aspirin reduced the incidence of colonic adenomas in randomized controlled trials (relative risk [RR] 0.82, 95% CI 0.7-0.95), in case-control studies (RR 0.87, 95% CI 0.77-0.98), and in cohort studies (RR 0.72, 95% CI 0.61-0.85).

- In cohort studies, regular use of aspirin was associated with a 22 percent reduction in the incidence of colorectal cancer. By contrast, two randomized controlled trials of low-dose aspirin did not show a protective effect during initial follow-up. (See 'Aspirin trials' below.) This difference may be related to the dose and duration of aspirin therapy. Benefits of aspirin in observational studies were more apparent when used in high doses and for periods longer than 10 years.

Similar estimates were made in a later meta-analysis of four placebo-controlled trials of aspirin [4]. The risk of recurrent adenomas was reduced by approximately 17 percent (RR 0.83, 95% CI 0.72-0.96), corresponding to an absolute risk reduction of 6.7 percent (95% CI 3.2-10.2).

A separate systematic review, examining the evidence related to non-aspirin NSAIDs and colorectal cancer prevention, reached the following conclusions [3]:

- NSAIDs were associated with a reduced incidence of colorectal adenomas in cohort studies (RR 0.64, 95% CI 0.48-0.85) and case-control studies (RR 0.54, 95% CI 0.40-0.74). COX-2 inhibitors were also associated with a reduced incidence of colorectal adenomas in randomized controlled trials (RR 0.72, 95% CI 0.68-0.77).

- NSAIDs were associated with a reduction in colorectal cancer in cohort studies (RR 0.61, 95% CI 0.48-0.77) and in case-control studies (RR 0.70, 95% CI 0.63-0.78).

Two additional systematic reviews of observational studies also concluded that aspirin and NSAIDs were associated with a lower risk of colorectal cancer, with stronger associations noted with increasing dose and duration of use [5,6].

Finally, randomized trials and observational studies have suggested that long-term daily aspirin use reduces the risk of developing metastatic colorectal cancer or dying from colorectal cancer [6-10]. In a meta-analysis of five randomized trials, patients who were cancer-free at study entry and received aspirin were less likely than controls to subsequently be diagnosed with metastatic colorectal cancer (odds ratio [OR] 0.36, 95% CI 0.18-0.74) [11]. A reduction in the number of patients with distant metastases at the time of diagnosis was also noted in a meta-analysis of 195 observational studies (OR 0.69, 95% CI 0.57-0.83) [6]. Cohort studies of aspirin use among patients with established colorectal cancer have also observed a survival benefit, particularly among those with COX-2 positive or PIK3CA mutant tumors [12,13].

Mortality due to cancer was examined in a meta-analysis of 51 randomized trials that compared aspirin with placebo [10]. It found that aspirin use was associated with a decrease in death from all cancers starting three years after the initiation of aspirin (OR 0.85, 95% CI 0.76-0.96), including a decrease in deaths due to colorectal cancer (OR 0.58, 95% CI 0.38-0.89). The meta-analysis of observational studies also showed a decrease in 20-year mortality due to colorectal cancer (OR 0.58, 95% CI 0.44-0.78) [6]. However, these analyses excluded two large randomized trials that used alternate day dosing of aspirin (the Women's Health Study [14] and the Physicians' Health Study [15]). Neither of these trials observed a reduced risk of colorectal cancer after 10 to 12 years of follow-up [16]. However, extended follow-up of the Women's Health Study did observe a benefit [17]. (See 'Aspirin trials' below.)

Aspirin trials — Several intervention trials have evaluated the potential benefit of aspirin in prevention of colorectal neoplasia, which together support a modest benefit in preventing recurrent colorectal adenomas [18]. Of note, many of the controlled trials were carried out in patients with a history of colorectal neoplasia (either adenomas or cancer) and not in patients at average risk for adenoma development. At least two meta-analyses have been published which suggest that the risk of recurrent adenomas is reduced by about 13 to 18 percent [2,4].

The following summarizes the major, controlled human trials looking at the effect of aspirin use on adenoma development:

- A randomized intervention trial supported a benefit of aspirin, especially at low doses (81 mg/day), on recurrent adenoma risk [19]. The study included 1121 patients with a history of adenomas who were randomly assigned to aspirin (81 or 325 mg daily) or placebo. A follow-up colonoscopy was performed at least one year after study entry in 1084 patients (97 percent). The risk of recurrent adenomas was significantly lower in the 81 mg group compared with placebo (38 versus 47 percent, RR 0.81, 95% CI 0.69-0.96). The risk reduction was even greater for the development of advanced neoplasms (RR 0.59, 95% CI 0.38-0.92). For unclear reasons, the 325 mg dose was not associated with a significantly reduced risk of adenoma recurrence.

- A second trial focused on 517 patients with a history of colorectal cancer who were randomly assigned to aspirin (325 mg/day) or placebo [20]. Recurrent adenomas were observed significantly less often in the aspirin group (17 versus 25 percent, RR 0.65, 95% CI 0.46-0.91) during a colonoscopy performed at a median of 13 months after randomization.

- A third study included 272 patients with a history of colorectal adenomas who were randomly assigned to two doses of lysine acetylsalicylate (160 or 300 mg daily) or placebo for four years [21]. After one year, the risk of recurrent adenomas at the planned study colonoscopy was significantly reduced in both active treatment groups (RR 0.63, 95% CI 0.46-0.84 for the 300 mg dose; RR 0.66, 95% CI 0.46-0.95 for the 160 mg dose). By contrast, after four years, neither aspirin treatment group had a reduced risk of recurrent adenoma compared with the placebo group [22]. The authors suggest that this may reflect a stronger influence of aspirin on missed polyps that are more likely to be seen at one year than de novo growth of new polyps that may become apparent at year four. Alternatively, the findings at year four may be due to methodological issues. Overall, protocol adherence was poor, with only 55 percent of the initial patients undergoing a year four protocol colonoscopy. Moreover, there was a disproportionately high drop-out rate in the placebo arm. This form of aspirin is not used in the United States.

- A fourth trial included 945 patients with a history of an adenoma who were randomly assigned to aspirin (300 mg daily), folic acid supplementation (0.5 mg daily), or placebo [23]. Aspirin supplementation but not folic acid was associated with a significantly reduced risk of recurrent adenomas.

- A fifth trial enrolled 311 Japanese patients with a history of an adenoma and randomly assigned them to enteric-coated aspirin (100 mg daily) or placebo. Aspirin reduced the risk of recurrent adenoma (OR 0.60, 95% CI 0.36-0.98) [24].

- A sixth trial enrolled 1107 patients with a history of an adenoma in the United States, Europe, or Russia to a combination of 0.5 ug calcitriol, 75 mg acetylsalicylic acid, and 1250 mg calcium carbonate versus placebo for three years [25]. The trial was stopped early for futility, finding no difference in the rate of recurrence. However, there was a possible interaction with smoking history with a non-significant benefit observed among non-smokers (OR 0.65; 95% CI, 0.26-1.22).

- A seventh trial enrolled 709 patients with a history of an adenoma and randomly assigned them to either aspirin (100 mg daily) or omega-3 fatty acids [26]. Neither aspirin or omega-3 fatty acids was associated with a reduction in risk of recurrent adenoma. However, there was a reduction in adenoma burden.

A meta-analysis of the first five trials found that aspirin users had a pooled risk ratio of 0.83 (95% CI 0.72-0.96) for any adenoma and 0.72 (95% CI 0.57-0.90) for advanced adenomas [4]. However, the results of the four-year follow-up trial that showed no difference in adenoma recurrence rate had not yet been published at the time of the meta-analysis. Although many of these trials offer compelling evidence of causality, they have provided only limited and conflicting data regarding the optimal dose of aspirin for colorectal neoplasia prevention. One trial demonstrated that both 160 mg and 300 mg of daily soluble aspirin were effective [21]; a second trial, which examined only one dose, showed that standard-dose aspirin (325 mg daily) reduced risk [20]; and a third trial did not detect a reduction in adenoma recurrence in a group randomized to standard-dose aspirin, but did observe a moderate benefit in a group randomized to low-dose aspirin [19].

Among 133 evaluable patients with familial adenomatous polyposis in a randomized trial (CAPP1), 600 mg/day of aspirin showed a trend toward a reduced polyp count (RR 0.77; 95% CI 0.54-1.10) at a follow-up sigmoidoscopy or colonoscopy [27,28]. For patients treated for more than one year, aspirin was associated with a significant reduction in polyp size (p = .02).

Additional data on a range of aspirin doses are available from observational cohort studies. The Nurses' Health Study, for example, suggests that the benefit of aspirin on adenoma risk is

highly dose-dependent, with the greatest benefit among participants who used the highest doses of aspirin (RR 0.49, 95% CI 0.36-0.65 in those who used more than 14 tablets per week) [29]. Similar conclusions were reached in the Health Professionals Follow-up Study, which included 47,363 male health professionals observed for 18 years [30]. Regular, long-term aspirin use was associated with a reduced incidence of colorectal cancer with maximal risk reduction also observed at doses greater than 14 tablets per week [30]. A dose relationship has been supported by other human studies [31-34].

Trials focusing on aspirin in the prevention of colorectal cancer have not been entirely consistent with those focusing on adenoma recurrence. The Physicians' Health Study, an intervention trial of aspirin at a dose of 325 mg every other day, failed to find a protective benefit of aspirin during five years of randomized follow-up and up to 18 years of non-randomized, observational follow-up [14,35,36].

Although the results seem at odds with some of the epidemiologic studies and the adenoma recurrence trials, they do not necessarily negate them. The duration of randomized treatment in the Physicians' Health Study was for only five years, while the results of studies that considered duration of aspirin intake suggest that longer observation is required to detect a significant reduction in colorectal cancer incidence [37-41]. This observation is consistent with the long latency underlying progression of normal tissue to adenoma to cancer.

The Women's Health Study, a large, placebo-controlled trial of aspirin at a dose of 100 mg every other day, reported no reduction in colorectal cancer incidence after 10 years of treatment; however, after a median follow-up of 18 years, the risk of colorectal cancer was reduced in women taking aspirin (HR 0.80, 95% CI 0.67-0.97). The reduced risk was primarily for proximal colon cancers (HR 0.73, 95% CI 0.55-0.95) [15,17].

Further support of this hypothesis is a pooled secondary analysis of data from two large randomized trials (British Doctors Aspirin Trial [BDAT] and UK-TIA Trial) of higher doses of aspirin originally designed to examine aspirin for the prevention of vascular disease. After long-term post-trial follow-up, use of between 300 and 1200 mg of aspirin was associated with a reduced incidence of colorectal cancer (RR 0.74, 95% CI 0.56-0.97). However, this benefit was observed only after evaluating patients 10 years after randomization and was greatest 10 to 14 years after randomization among patients who had treatment for at least five years (RR 0.37, 0.20-0.70) [5]. Similarly, a lower risk of colorectal cancer was evident only after 10 years of use in the Nurses' Health Study and six years of use in the Health Professionals Follow-up Study [29,30]. In the latter study, the benefit was no longer evident within four years of discontinuing aspirin [30].

The pooled secondary analysis of the BDAT and UK-TIA trials was expanded with inclusion of two additional randomized trials of aspirin (Swedish Aspirin Low Dose Trial and Dutch TIA Aspirin Trial) that were designed to assess the effect of aspirin use on vascular events [7]. In total, the four trials included 14,033 patients with a median of 18 years follow-up. The 20-year risk of colon cancer was significantly reduced in patients who received aspirin (incidence HR 0.76, mortality HR 0.65) with benefit increasing with longer duration of treatment. Patients allocated to receive aspirin for five years or longer had an absolute risk reduction for colon cancer of approximately 70 percent. Doses of 75 mg daily appeared to be as effective as higher doses, although there were no individual trials that directly compared 75 mg with higher doses; very low doses of aspirin (30 mg daily) were ineffective. Contrary to most observational studies, the risk reduction with aspirin appeared to be confined to cancer of the proximal colon.

Finally, in the ASPREE randomized placebo-controlled trial (of 19,114 apparently healthy older adults [without known active cancer]) suspended treatment due to a lack of an effect of aspirin (100 mg per day) on the primary endpoint of disability-free or dementia-free survival over a mean treatment of 4.6 years. Surprisingly, low dose aspirin was associated with significantly increased all-cause mortality driven by cancer deaths, including deaths from colorectal cancer, that was not accompanied by an increase in cancer incidence [42].

In subsequent analyses, the use of aspirin actually conferred a significantly **increased** risk of incident cancers that had metastasized (HR 1.19, 95% CI 1.00-1.43) or were stage 4 at diagnosis (HR 1.22, 95% CI 1.02-1.45) and had a higher risk of death from all cancers (HR 1.35, 95% CI 1.13-1.61), both localized and metastatic [43]. The explanation for these unanticipated results, which contrast with the aspirin trials conducted in younger adults, is unclear but may be related to a differential biological effect of initiating aspirin in older adults and differences in the biology and behavior of tumors in older adults [44]. Moreover, because prior randomized controlled trials show that the benefit of low dose aspirin for colorectal cancer does not emerge for at least five years, ASPREE follow-up to date has been insufficient to capture a legacy effect of aspirin in reducing risk of incident cancers.

The only randomized placebo-controlled trial of aspirin (CAPP2) in which colorectal cancer was a primary endpoint found no benefit from aspirin (600 mg per day) in 937 patients with Lynch syndrome (hereditary nonpolyposis colon cancer) [45]. The reason for the negative results may be related to a distinct pathway of carcinogenesis in Lynch patients. Another possible explanation is that the study follow-up was only two to four years (median 29 months), which may have been too brief to detect a benefit of aspirin. In support of this explanation, a planned double-blinded, post-intervention follow-up of patients enrolled in CAPP2 (median 56 months) found a marginal nonsignificant reduction in colorectal cancer incidence in an intent-to-treat

analysis. However, in a per protocol analysis of patients treated with 600 mg aspirin per day for at least two years, there was a significant reduction in colorectal cancer incidence. Moreover, in a secondary analysis, there was a decreased rate of overall Lynch cancers in the group treated with aspirin for at least two years [46]. However, further studies are needed to validate this potentially important result and the minimum effective dose needed to balance potential benefits for Lynch-related cancer prevention with potential risks such as bleeding. (See "Molecular genetics of colorectal cancer", section on 'The mutator phenotype/mismatch repair pathway' and "Molecular genetics of colorectal cancer", section on 'Mismatch repair genes' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'Chemoprevention'.)

Non-aspirin NSAID trials — Non-aspirin NSAIDs may also have a role in preventing colorectal cancer.

Sulindac — The NSAID sulindac has been associated with regression of colorectal adenomas in familial adenomatous polyposis (FAP) [47,48]. However, regression of polyps is incomplete, and the degree of protection from the development of colorectal cancer is unknown. In addition, sulindac (75 or 150 mg twice daily) was ineffective in delaying the time of initial development of adenomas in a controlled trial involving 41 proven FAP gene carriers [49]. (See "Familial adenomatous polyposis: Screening and management of patients and families".)

Sulindac has also been studied in combination with the ornithine decarboxylase inhibitor difluoromethylornithine (DFMO) for the prevention of sporadic adenomas. This combination was selected because of the ability of these agents to synergistically reduce levels of colonic polyamines (eg, putrescine, spermidine, and spermine), which are believed to be procarcinogenic. DFMO inhibits polyamine synthesis, whereas sulindac is believed to increase polyamine acetylation and export.

A randomized trial of 375 patients with a history of adenomas assigned patients to receive either a combination of sulindac and DFMO or placebo [50]. Patients who received combination therapy had a significantly lower recurrence rate of adenomas (12 versus 41 percent), were less likely to have advanced adenomas (1 versus 9 percent), and were less likely to have multiple adenomas (1 versus 13 percent). Although there were concerns about potential adverse effects of DFMO on hearing [51], there was no significant difference reported in hearing changes or audiogram results from patients given DFMO compared to those given placebo. However, as observed in patients given COX-2-selective NSAIDs [52], there appeared to be a higher incidence of cardiovascular toxicity among patients with a high baseline risk of cardiovascular events that were given sulindac. Because the trial was not designed to examine sulindac and DFMO separately, it is uncertain if either agent used alone is an effective chemopreventive.

Cyclooxygenase-2 inhibitors — A controlled trial involving 77 patients with familial adenomatous polyposis (FAP) suggested that celecoxib, a cyclooxygenase-2 (COX-2) selective NSAID, was associated with a 28 percent reduction in rectal polyps [53], while another trial of 21 patients with FAP observed a nearly 10 percent reduction with rofecoxib [54]. These data led the FDA to approve the use of celecoxib in patients with phenotypic expression of FAP. However, the manufacturer of celecoxib in February 2011 voluntarily withdrew the FAP indication due to a delay in completing the follow-up trial required under its accelerated initial approval.

There have been several placebo-controlled trials on the use of COX-2 inhibitors in the prevention of adenoma recurrence in non-FAP patients with a prior history of adenoma.

- In one trial, the Adenoma Prevention with Celecoxib (APC) trial, patients who were at high risk for adenoma recurrence (a history of multiple adenomas or a single adenoma more than 5 mm in diameter) were randomly assigned to 200 mg of celecoxib twice daily, 400 mg of celecoxib twice daily, or placebo for three years [55]. Compared with placebo, patients randomized to the higher dose had a 45 percent lower risk of recurrent adenoma, while patients randomized to the lower dose had a 33 percent lower risk. The effect was particularly pronounced for recurrent advanced adenomas. However, patients randomized to celecoxib had a significantly higher risk of cardiovascular events (2.6-fold higher risk for the lower dose and 3.4-fold higher risk for the higher dose).

- In another trial, a single 400-mg daily dose of celecoxib was associated with a 36 percent lower risk of recurrent adenomas [56]. More serious cardiovascular events occurred in patients assigned to celecoxib compared with placebo (2.5 versus 1.9 percent), although the difference was not statistically significant. A similar benefit was noted in a trial using rofecoxib, which is no longer available [57] because patients randomized to rofecoxib also experienced a higher incidence of cardiovascular events [58] and bleeding from peptic ulcers [59].

These data support a consistent benefit from COX-2 inhibitors in prevention of adenoma recurrence, but the benefit of celecoxib appears to be outweighed by an increase in risk of cardiovascular events [55]. However, a pooled analysis of six randomized controlled trials of celecoxib in patients with non-arthritis indications found that celecoxib (400 mg twice daily) was not associated with increased cardiovascular risk among patients with low baseline risk of cardiovascular disease [60]. In a planned five-year efficacy analysis of the APC trial, a previous history of atherosclerotic heart disease was the only risk factor that significantly interacted with celecoxib use in the association with cardiovascular events [61]. Furthermore, among patients in the APC trial with serum hsCRP (>3 mg/L), the relative risk of cardiovascular events compared with placebo was 2.27 (95% CI, 0.72-7.14) for those randomized to celecoxib 200 mg twice daily

and 3.28 (95% CI, 1.09-9.91) for 400 mg twice daily. By contrast, among patients with hsCRP ≤3 mg/L, the corresponding relative risks were 0.99 (95% CI, 0.53-1.83) and 1.11 (95% CI, 0.61-2.02) [62]. Taken together, these data suggest that celecoxib may be relatively safe for individuals who are at low risk for cardiovascular disorders. Unfortunately, many risk factors for colorectal cancer (eg, elevated body mass index, physical inactivity) overlap with those of cardiovascular disease [63]. (See "NSAIDs: Adverse cardiovascular effects".)

CLINICAL IMPLICATIONS

Although the evidence that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may have some anti-carcinogenesis properties in the large bowel is compelling, several important issues remain regarding recommendations for their primary use as chemopreventive agents [64].

Dose and duration — The first important question concerns the dosage required to produce a benefit. While studies have generally not provided precise estimates of the amount of aspirin used, some evidence indicates that moderate doses (such as those used for the prevention of cardiovascular disease) and even alternate day low dose aspirin are sufficient [7,17]. Other data suggest that the optimal chemopreventive benefit may require significantly higher doses than those typically recommended for the prevention of cardiovascular disease [2]. However, given the uncertainty regarding the optimal dose and the increased incidence of adverse effects associated with higher doses, use of such high doses cannot be routinely recommended [39]. (See 'Aspirin trials' above and "Nonselective NSAIDs: Overview of adverse effects".)

Another important consideration is the time required to produce a benefit on cancer risk. Although clinical trials suggest a benefit to aspirin use within three years on adenoma recurrence, an effect on cancer incidence appears to require much longer use. An analysis from the Nurses' Health Study showed that at least 10 years of regular aspirin use may be necessary to achieve substantial reductions in risk of colorectal cancer [38,39]. Other studies support a reduction in colon cancer incidence among individuals using aspirin for 6 to 10 or more years [5,7,30,37,41], and possibly weaker associations following shorter periods of use. Furthermore, it appears that risk reduction requires consistent use. In the Health Professionals Follow-up Study, a benefit from aspirin was no longer evident four years after discontinuing use [30].

Uncertainty remains regarding the duration required to produce a benefit. If a long time lag exists between onset of use and reduction in risk, an individual would have to be exposed to potentially adverse effects of aspirin for a prolonged period before accruing the benefits. (See "Nonselective NSAIDs: Overview of adverse effects".)

In addition to protection against colorectal cancer, aspirin use has other benefits, particularly on cardiovascular disease risk and perhaps on other cancers [8]. From a clinical perspective, all potential risks and benefits of prolonged aspirin use must be carefully weighed before recommending aspirin use for disease prevention. (See "Aspirin in the primary prevention of cardiovascular disease and cancer".)

High-risk populations — Although routine aspirin therapy may not be warranted in the general population, an international consensus panel advocated that additional research be conducted into the use of aspirin in high-risk populations for whom the benefits might outweigh the harms [65]. Such a subgroup would likely include individuals with established colorectal cancer that have undergone a resection for curative intent. Although such patients generally enjoy a favorable prognosis compared with patients diagnosed with unresectable disease, they remain at high risk of recurrence and death from the disease. In an observational study of 1279 patients with established Stage I, II, and III colorectal cancers, use of aspirin after the diagnosis of colorectal cancer was associated with improved survival from the disease. Compared with non-users, participants who regularly used aspirin after diagnosis had a 29 percent reduction in colorectal cancer-specific mortality and a 21 percent reduction in overall mortality. Regular aspirin use after diagnosis was associated with a particularly low risk of colorectal cancer-specific mortality among participants whose primary tumors overexpressed COX-2 [12]. An expanded analysis of this cohort also found markedly improved colorectal cancer-specific survival among regular aspirin users with colorectal cancer with a PIK3CA mutation. These results were corroborated in an analysis of a clinical trial cohort [66]. Additional studies with colorectal cancer also support an effect of aspirin and NSAIDs on survival [67-71]. Randomized trials are needed to confirm these results before routine clinical recommendations can be implemented.

Alternative protective measures — There are alternatives or complementary approaches to NSAID therapy for colorectal cancer prevention. Most notable among these is screening through colonoscopy or sigmoidoscopy. Two independent cost-effectiveness analyses indicate that adherence to colonoscopic screening is far superior to aspirin use as a cost-effective strategy to prevent colorectal cancer [72,73]. Thus, aspirin use alone is unlikely to be an adequate alternative to colonoscopic screening.

However, some authorities have proposed that aspirin or NSAID treatment may be a reasonable strategy for patients at particularly high risk for colorectal cancer who cannot undergo adequate screening [74]. Aspirin or NSAID treatment may also have a future role in multi-agent chemoprevention [75]. Our approach to the decision to prescribe aspirin and recommendations from societal guideline organizations are discussed in detail separately [76]. (See "Aspirin in the

primary prevention of cardiovascular disease and cancer", section on 'Our approach' and "Aspirin in the primary prevention of cardiovascular disease and cancer", section on 'Recommendations of others'.)

COX-2 inhibitors — The hope of a lower incidence of gastrointestinal side effects and a superior therapeutic index for selective COX-2 inhibitors led to studies assessing their efficacy for the prevention of adenomatous polyps in patients who had undergone endoscopic polypectomy. Although COX-2 inhibitors are effective for colorectal neoplasia prevention [55-57], they are associated with increased cardiovascular risk. (See "NSAIDs: Adverse cardiovascular effects".)

Thus, it seems unlikely that selective COX-2 inhibitors will find widespread use in cancer prevention. The traditional NSAIDs that lack COX-2 selectivity also may increase cardiovascular risk. (See "NSAIDs: Adverse cardiovascular effects".)

BIOLOGIC BASIS

The findings in the human studies confirm observations in animal models, which show that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the occurrence of intestinal neoplasia. However, the protective effect of aspirin and NSAIDs may vary by genotype. In a case-control study that included 8634 cases and 8553 controls pooled from 10 observational studies, regular use of aspirin, NSAIDs, or both was associated with a reduced risk of colorectal cancer (odds ratio [OR] 0.69 [95% CI 0.64-0.74]) [77]. Among individuals with the single-nucleotide polymorphism (SNP) rs2965667-TT genotype, regular use of aspirin, NSAIDs, or both also was associated with lower risk of colorectal cancer (prevalence 28 versus 38 percent; OR 0.66 [95% CI 0.61-0.70]). However, among individuals with a TA or AA genotype, which constituted 4 percent of the study population, the use of aspirin, NSAIDs, or both was associated with an increased risk of colorectal cancer (prevalence 35 versus 29 percent; OR 1.89 [95% CI 1.27-2.81]). As compared with nonregular aspirin/NSAID use, regular use in individuals with rs16973225-AA genotype, but not the AC or CC genotypes, was associated with a lower risk of colorectal cancer (prevalence in rs16973225-AA genotype 28 versus 38 percent; OR 0.66 [95% CI 0.62-0.71]). Additional studies are needed to validate this gene-environment interaction.

Animal models — A benefit from NSAIDs is supported from laboratory studies examining the effects of NSAIDS on tumorigenesis. More than 90 percent of 110 published animal studies reported an anti-neoplastic effect of NSAIDs in one review [78].The first group of animal models was based upon induction of cancer using high doses of carcinogens. Anti-inflammatory agents including indomethacin [79-82], piroxicam [83,84], and sulindac [85] reduced the number of animals bearing tumors and the number of tumors per animal. Following the early

epidemiologic studies that showed the potential benefit of aspirin, the chemopreventive influence of aspirin was evaluated in rodent models [86,87]. As for other anti-inflammatory agents, animal data indicated that aspirin inhibited intestinal carcinogenesis, and some studies [86,88], though not all [87], found that the influence was limited to early stages.

A second relevant animal model was based upon the APCMin/+ (Min) mouse, in which an autosomal, dominant heterozygous mutation of the mouse APC gene leads to spontaneous intestinal neoplasia. This model resembles human familial adenomatous polyposis, but an important difference is that tumors are predominantly located in the small rather than in the large intestine as in humans. One study in Min mice showed that aspirin (at high doses, with a human equivalence of 10 and 20 325 mg aspirin tablets per day) significantly reduced tumor multiplicity and total tumor load [89]. The efficacy of lower doses of aspirin was not evaluated.

Effect on a cellular level — The biologic plausibility would be further enhanced by a better understanding of the underlying mechanisms. Some potential mechanisms whereby NSAIDs may inhibit colorectal carcinogenesis have been proposed, but none have been firmly established.

Two general observations provide a basis for understanding their effect:

- NSAIDs induce apoptosis
- Cyclooxygenase is involved in colonic tumorigenesis

Induction of apoptosis — The two prerequisites for the development of cancer are cell proliferation and the inhibition of apoptosis. One study found that sulindac decreased the size of adenomatous polyps in familial adenomatous polyposis by increasing apoptosis rather than diminishing proliferation [90].

NSAIDs may increase the rate of apoptosis in colon cancer cells in part via a dramatic increase in arachidonic acid, a prostaglandin precursor [91]. Arachidonic acid promotes the conversion of sphingomyelin to ceramide, a known mediator of apoptosis. Other pathways may also contribute to this process. NSAIDs increase 15-LOX enzymatic activity, the main enzyme for metabolizing colonic linoleic acid to 13-S-dydroxyoctadecadioic acid (13-S-HODE) [92]. 13-S-HODE inhibits cellular growth and induces apoptosis. In addition, sulindac induced p21 expression, which is associated with cell-cycle arrest and apoptosis [93].

Inhibition of cyclooxygenase — Another possible mechanism by which NSAIDs might prevent colon cancer is inhibition of cyclooxygenase enzymes, which catalyze prostaglandin production [94,95]. Early studies observed higher levels of prostaglandins in colorectal tumors compared with normal tissue. Subsequent reports demonstrated that prostaglandins were associated with

tumor angiogenesis, cell proliferation, and inhibition of immune surveillance and apoptosis [96]. Human studies also support a role for aspirin in suppressing levels of systemic prostaglandins a possible mechanism for its antineoplastic effects [97]. The ASPirin Intervention for the REDuction of colorectal cancer risk (ASPIRED) trial, a double-blind, placebo-controlled trial, showed that aspirin at 81 or 325 mg/day significantly reduced elevated urinary prostaglandin metabolites in individuals with a recent episode of colorectal adenoma [98].

In addition, studies in human colon cancer showed increased COX-2 expression when compared to the adjacent colonic mucosa; similar observations have been made in experimental models of colon cancer [99-101]. In two large prospective cohorts, the protective effect of aspirin appeared to be confined to colorectal cancers that overexpressed COX-2 [12,102]. These data support the hypothesis that aspirin exerts its effect on the formation of adenomas and cancers by inhibiting COX-2 or its downstream effectors.

COX-2 expression may also increase the metastatic potential of colon cancer cells and possibly influence patient survival [103-105]. In one study, for example, COX-2 expression was determined in 76 patients with a variety of stages of colorectal cancer [104]. Ten-year survival was significantly higher in patients with the lowest levels of COX-2 staining (68 versus 35 percent). These findings suggest that COX-2 activation may promote tumor growth. Consistent with this hypothesis is a study in which human colon cancer cells that expressed high levels of COX-2 were implanted into nude mice; treatment with a selective COX-2 inhibitor reduced tumor formation by 85 to 90 percent and inhibited colony formation of cultured cells [100]. This benefit was not seen with tumor cells that lacked COX-2.

There may also be an interaction between COX-2 inhibition and the induction of apoptosis. In one report, the ras mutation (found in 50 percent of colorectal carcinomas) made rat intestinal epithelial cells more resistant to spontaneous apoptosis [106]. The ras-transformed cells also had increased expression of COX-2. Administration of a COX-2 selective antagonist inhibited the growth of these cells by both inhibition of cell proliferation and the induction of apoptosis. However, in another study, a different COX-2 selective antagonist induced apoptosis in a colorectal cancer cell line that lacked detectable COX-2 expression, suggesting that COX-2 selective NSAIDs may induce apoptosis via mechanisms that do not involve COX-2 [107].

There is also growing evidence that COX-2 inhibition may influence epidermal growth factor receptor expression (EGFR). COX-2-derived prostaglandins activate EGFR signaling [108,109]. Animal models have demonstrated an association between the EGFR pathway and the development of intestinal cancer [110,111].

Cyclooxygenase inhibition may also exert its effect via a pathway mediated by prostaglandin E2. Prostaglandin E2 is a potent stimulator of cultured colon cancer cells via a G-protein-coupled receptor leading to accumulation of beta-catenin (which stimulates cell proliferation) in the nucleus. Thus, NSAIDs may exert a beneficial effect by decreasing production of prostaglandin E2 and leading to increased degradation CTNNB1 (beta-catenin) [9,112,113]. Through COX-independent pathways, aspirin also induces phosphorylation, ubiquitination, and degradation of CTNNB1 [114,115]. In support of a potential effect of aspirin in cancer that is mediated by disruption of the CTNNB1 and *Wnt* signaling pathway is a study demonstrating that the association of aspirin with lower risk of colorectal cancer is not evident among individuals who do not have at least one allele of the SNP rs6983267 [116]. This SNP, which has been shown in genome-wide association studies to be associated with lower risk of colorectal cancer, functionally appears to be associated with weaker binding of CTNNB1 to transcription factors associated with expression of the *MYC* oncogene [117].

Much of the focus of experimental evidence on the mechanism of aspirin and NSAIDs on carcinogenesis has focused on blockade of COX-2, which generally requires higher doses of aspirin and NSAIDs. However, the finding that relatively low doses of daily aspirin typically used for prevention of atherothrombosis may also be associated with lower risk of death from cancers has supported a hypothesis that aspirin may mediate additional anti-cancer mechanisms through inhibition of COX-1 present in platelets [118]. Platelet COX-1 activity may generate lipid mediators, such as thromboxane A2 and prostaglandin E2, and the release of stored proteins, such as growth and angiogenic factors.

Other mechanisms — Other mechanisms of aspirin/NSAIDs relevant to carcinogenesis continue to be uncovered. As an example, sulindac decreases the number of aberrant crypt foci in the colon (which may be precursors of adenomas and cancer), possibly by inhibition of pathways that activate nuclear factor kappa B (NF-kappa B) [119,120]. In addition, accumulating evidence has demonstrated that NSAIDs inhibit angiogenesis [121-124], and may modulate insulin-related neoplastic pathways [124]. Finally, mutations in the *BRAF* oncogene are observed in 10 to 15 percent of colorectal cancers, which constitutively activate the RAF/MAPK signaling. In human studies, aspirin use has been associated with a lower risk of *BRAF*-wild-type colorectal cancers but not *BRAF*-mutated cancers, suggesting that aspirin/NSAIDs may also have specific effects on the RAF-MAPK pathway [125]. In a population based case control study that included 2444 cases with a first diagnosis of CRC and 3130 healthy controls, regular use of aspirin or NSAIDs was associated with a reduction in CRC risk (OR 0.69, 95% CI 0.60 to 0.79) [126]. Regular NSAID use was associated with a lower risk of microsatellite stable (OR 0.66, 95% CI 0.57 to 0.77), *BRAF* wildtype (OR 0.67, 95% CI 0.58 to 0.78), and *KRAS* wildtype (OR 0.68, 95% CI 0.58 to 0.80) CRCs. However, regular NSAID use was not significantly associated with CRC risk reduction

for MSI-high, *BRAF*-mutated, or *KRAS*-mutated CRCs. In subgroup analyses of MSI-high CRCs, regular use of NSAIDs was associated with a significant CRC risk reduction in the absence of *BRAF* or *KRAS* mutations (OR 0.34, 95% CI 0.18 to 0.65). However, in MSI-high CRC with *KRAS*- or *BRAF* mutations, regular NSAIDs use was not associated with a reduction in CRC risk. Results for aspirin use were similar.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer".)

SUMMARY AND RECOMMENDATIONS

The preceding observations provide the basis for the following recommendations:

- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a 20 to 40 percent reduction in the risk of colonic adenomas and colorectal cancer in individuals at average risk. (See 'Colorectal cancer' above.)
- These potential benefits of long-term therapy must be weighed against the potential adverse effects (gastroduodenal toxicity and, with non-aspirin NSAIDs, increased cardiovascular risk) given the availability of other options for colorectal cancer screening. (See 'Clinical implications' above.)
- Based upon the long-term results of a single clinical trial, high doses of aspirin (600 mg/day) appear to provide a benefit for patients with hereditary nonpolyposis colorectal cancer. Further studies are needed to understand if such high doses are needed and the net benefits and risks in other high-risk groups such as those with a personal history of colorectal cancer or adenoma. (See 'Aspirin trials' above.)
- In making recommendations regarding aspirin, its benefits for the prevention of coronary heart disease in those at increased risk also need to be considered. (See 'Colorectal cancer' above.)

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Topic 2600 Version 35.0

Contributor Disclosures

Andrew T Chan, MD, MPH Consultant/Advisory Boards: Bayer Pharma AG [Chronic disease prevention]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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