REVIEW

CME CREDIT

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Chemoprevention of colorectal cancer: Slow, steady progress

ABSTRACT

In population-based observational studies, people had lower rates of colorectal cancer if they were taking various agents, including nonsteroidal anti-inflammatory drugs, calcium, and folate. In placebo-controlled trials in patients with familial adenomatous polyposis and in patients with sporadic colon adenomas, nonsteroidal anti-inflammatory drugs reduced the rates of adenomas, and there is a biologic rationale that they would be effective in reducing colorectal cancer as well. Randomized trials of chemopreventive agents are underway in the general population.

KEY POINTS

Aspirin has shown a modest risk reduction, but is associated with concomitant risks. The decision to use aspirin should not be based solely on its chemopreventive benefits.

Celecoxib, a selective cyclo-oxygenase 2 (COX-2) inhibitor, is approved for adenoma regression as an adjunct to endoscopic surveillance and surgery in patients with familial adenomatous polyposis.

Exisulind, the sulfone metabolite of sulindac, reduces adenomas in patients with familial adenomatous polyposis.

Calcium and folate supplementation have been found to moderately reduce adenoma formation without significant risk.

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LITTLE BY LITTLE, we are learning how to use drugs to prevent colorectal cancer, or at least reduce its incidence.

And none too soon. Although the number of cases has steadily declined over the past 20 years, in large part thanks to widespread screening and removal of colonic adenomas, colorectal cancer still accounts for more than 147,500 new cases and 57,000 deaths each year in the United States.[1]

By the age of 50, one third of the US population has adenomatous polyps, a precursor to colorectal cancer. By age 70, the number increases to one half.

Fortunately, carcinogenesis is thought to take years, involving the accumulation of genetic alterations that transform the normal mucosa to carcinoma through progressive stages of dysplasia (FIGURE 1).[2] Several steps in this process could potentially be modified or inhibited by chemopreventive agents.

The following is a limited review of the best-studied chemopreventive agents to date.

LESSONS FROM FAMILIAL ADENOMATOUS POLYPOSIS

The benefit of chemoprevention of colorectal neoplasia was first identified in patients with familial adenomatous polyposis, an autosomal-dominant condition which, if untreated, leads to colorectal cancer in nearly 100% of patients.

Sulindac, a nonsteroidal anti-inflammatory drug (NSAID) was reported in 1983 to induce regression of colorectal adenomas.[3] Its benefits for familial adenomatous polyposis have been confirmed in many studies since then,[4,5] although it is not officially approved by the US Food and Drug Administration for

this indication.

Patients with familial adenomatous polyposis have a germline mutation in the tumor-suppressor gene APC, which leads to formation of multiple colonic adenomas at a young age. Somatic mutations of this gene are also one of the earliest alterations in sporadic neoplasia,[6] suggesting that carcinogenesis is biologically similar in sporadic colorectal cancer and in familial adenomatous polyposis. Agents that prevent adenomas in patients with familial adenomatous polyposis should therefore also be effective in the general population.

HOW DO NSAIDs PREVENT CANCER?

Exactly how aspirin and other NSAIDs work is not completely understood, but their chemopreventive activity has been attributed to inhibition of cyclo-oxygenase (COX), an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins.

Prostaglandins increase cellular proliferation, decrease programmed cell death (apoptosis), and are found in elevated levels in colorectal neoplasia.[7] By inhibiting COX, NSAIDs also increase levels of arachidonic acid, which has been found to stimulate the activity of neutral sphingomyelinase, resulting in a cascade of reactions that induce apoptosis.[8–11]

COX exists as two isoenzymes, COX-1 and COX-2. COX-1 is constitutively expressed in many tissues, including the gastric mucosa and platelets. COX-2 is not detectable in normal human colonic epithelium but can be induced by cytokines, mitogens, and growth factors.

COX-2 is, however, overexpressed in colonic adenomas and cancers.[12] In rat intestinal epithelial cells, overexpression of COX-2 has many effects that lead to carcinogenesis, including loss of cell-cell adhesion, cell-cycle delay, and resistance to apoptosis.[13,14] Conversely, inhibiting COX-2 in cancer cell lines induces apoptosis, which may be an important mechanism for the chemopreventive effects of NSAIDs.[15]

Other mechanisms must be at work as well. For example, Apc delta 716 knockout mice, like humans with familial adenomatous polyposis, are prone to develop multiple colon polyps. When these mice also have their gene for COX-2 knocked out or receive a COX-2 inhibitor, they develop fewer polyps, but they still develop some,[16] leading investigators to believe that other targets for chemoprevention may also exist.

Evidence is mounting that many biologic activities of NSAIDs are unrelated to COX, including inhibiting activation of nuclear transcription factors, interfering with the binding of other receptors to DNA, and effects on angiogenesis and other mediators of apoptosis.[11,17]

How good cells go bad: Proposed molecular genetic events in the evolution of colon cancer

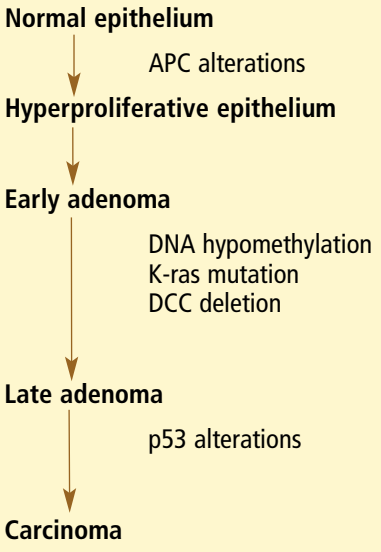

FIGURE 1

Agents that work in familial adenomatous polyposis should also work in the general population

CELECOXIB

Celecoxib (Celebrex), a selective COX-2 inhibitor, is the first agent approved for regression of colonic polyps in patients with familial adenomatous polyposis.

In a 6-month, placebo-controlled trial in 77 patients with familial adenomatous polyposis, the mean number of polyps was reduced by 28% from baseline with celecoxib 400 mg twice a day, 12% with 100 mg twice a day, and 5% with placebo.[18]

Celecoxib must be viewed as an adjunct for the management of colorectal adenomas in familial adenomatous polyposis and does not supplant regular endoscopic surveillance and polypectomies.

The efficacy of the selective COX-2 inhibitors is currently being studied in patients with sporadic adenomas.

ASPIRIN

The largest body of evidence that aspirin prevents cancer in humans comes from epidemiologic studies, although not all of the studies of aspirin use found a reduction in the incidence of colorectal cancer.

In the Health Professionals Follow-up Study,[19] more than 47,000 men age 40 to 75 years were asked about aspirin use. The relative risk of colorectal cancer was 0.68 for those who used aspirin regularly (more than 2 times per week), dropping to 0.35 in those who reported using aspirin on three or more successive questionnaires, which were completed every 2 years. The relative risk of adenomas was 0.77 in the aspirin users, although the incidence of large adenomas (> 1 cm) did not differ between the groups.

Preventive drugs cannot replace screening for colon cancer

In the Nurses' Health Study of more than 89,000 women,[20] the relative risk of colorectal cancer was 0.56 in women who took aspirin 4 to 6 times per week for 20 years. Subjects who took aspirin less often or who did not take it as long did not derive any benefit.

On the other hand, the randomized Physicians Health Study found that aspirin (325 mg every other day) had no effect on the incidence of colorectal cancer after 5 years,[21] nor after 12 years.[22] Possible reasons for the lack of effect: the dose of aspirin may have been too low, the duration of the treatment may have been too short, and the study was not designed to detect an effect of aspirin on colorectal neoplasia.

The Cleveland Clinic Foundation participated in a 3-year, multicenter study that showed aspirin to have a modest effect on preventing recurrent adenomas.[23] The study involved 1,121 patients with a previous adenoma, who were randomized to receive placebo, aspirin 80 mg/day, or aspirin 325 mg/day. Those receiving aspirin 80 mg had a 19% reduction in recurrent adenomas compared with the placebo group (95% confidence interval 4%–32%, number needed to treat = 5). Those receiving aspirin 325 mg had a 4% reduction (95% confidence interval –13%–18%; number needed to treat = 25).

Adenoma recurrence rates were 47% with placebo, 38% with low-dose aspirin, and 45% with high-dose aspirin (P = .04). For cancers or adenomas with tubulovillous or villous histology, the risk reduction was 40% (95% confidence interval –3%–65%) with low-dose aspirin and 19% (95% confidence interval –32%–51%) with high-dose aspirin.[23]

Why a lower dose of aspirin would seem to be more effective than a higher dose is not clear.

Another study[24] comparing asprin 325 mg vs placebo in patients who had previous colorectal cancer found a significant decrease in recurrent adenomas. One or more adenomas were found in 17% of the aspirin group and 27% of the placebo group.

Two studies[25,26] determined that it was not cost-effective to add aspirin therapy to subjects participating in colorectal cancer screening (with either annual fecal occult blood testing and flexible sigmoidoscopy every 5 years or colonoscopy every 10 years), mostly because of complications from aspirin. However, it *was* cost-effective to start screening for colorectal cancer in patients who were already using aspirin for other conditions.

The decision to take aspirin should not be based on its chemopreventive benefit but on other considerations, including cardiovascular disease prevention and compliance with colorectal cancer screening.

EXISULIND

Exisulind (Aptosyn), the sulfone metabolite of sulindac, has also been studied as a chemopreventive agent in patients with familial adenomatous polyposis. It is not a COX-1 or COX-2 inhibitor and therefore is not associated with the gastric and renal toxicities of NSAIDs.

Exisulind induces apoptosis by inhibiting cyclic GMP phosphodiesterase, which is overexpressed in colorectal adenomas and cancer.[27]

In a 1-year trial of exisulind in 73 patients with familial adenomatous polyposis, a 25% reduction in rectal adenomas was seen in the exisulind group.[28] In a 1-year, open-label extension of the trial, polyp formation decreased by 58% in patients continuing on exisulind.[29]

CALCIUM AND VITAMIN D

Calcium may decrease the risk of colorectal adenomas by reacting with ionized fatty acids and secondary bile acids in the colonic lumen, reducing proliferation of the colonic mucosa.[30–33]

Vitamin D inhibits cell proliferation and DNA synthesis, modulates signal transduction pathways, and induces apoptosis. Calcium and vitamin D reduce bile acid-induced epithelial cell proliferation and suppress chemically induced colorectal cancer.[34,35]

Most of the case-control and cohort studies that examined this issue showed that a high-calcium diet is associated with a decreased risk of colonic neoplasia. Two recently published trials support the use of calcium supplementation to moderately reduce the risk of recurrent colorectal adenomas.

In a 4-year, double-blind trial of 930 subjects,[36] the adjusted risk ratio for any recurrence of adenoma with calcium as compared with placebo was 0.85 (95% confidence interval 0.74–0.98, P = .03), and the adjusted ratio of the average number of adenomas in the calcium group to that in the placebo was 0.76 (95% confidence interval 0.60–0.96, P = .02).

In a 3-year trial,[37] the adjusted odds ratio for recurrent adenomas was 0.66 (95% confidence interval 0.38–1.17, P = .16) for patients treated with elemental calcium 2 g/day vs placebo.

FOLATE

Folate is found in vegetables, fruits, most multivitamin supplements, and fortified breakfast cereals. Deficient intake leads to inappropriate activation of proto-oncogenes and the induction of malignant transformation.

Folate is an essential cofactor for DNA methylation. Reduced DNA methylation has been observed in human colorectal cancer and adenomatous polyps, and is one of the earliest events in the adenoma-carcinoma sequence.

Folic acid deficiency may also cause an imbalance in DNA precursors, uracil misincorporation into DNA, and chromosomal breakage.[38]

Efficacy of folate

Case-control and cohort studies have confirmed an inverse relationship between dietary folate intake and colorectal adenomas and cancer.[39–41]

In the Physicians Health Study,[42] low folate intake was strongly associated with an increased risk for colorectal cancer, while high folate consumption was beneficial.

In the Nurses' Health Study,[40] higher energy-adjusted folate intake was related to a lower risk for colon cancer (relative risk 0.69; 95% confidence interval 0.52–0.93) for intake greater than 400 μg/day compared with intake of 200 μg/day or less. After 15 years of use of multivitamin supplements containing 400 μg of folate, the risk reduction in colorectal cancer was marked (relative risk 0.25; 95% confidence interval 0.13–0.51).[43] High dietary folate was associated with a reduction in risk of adenomas of 0.66 in women and 0.63 in men.

Although the chemopreventive effect of folate has not been confirmed in a placebo-controlled trial, the epidemiologic evidence, safety profile, and low cost of folate make it an attractive micronutrient to recommend.

Do not start aspirin to prevent colorectal cancer only

RECOMMENDATIONS

The current standard of care to prevent colorectal cancer is to perform screening in average-risk American men and women beginning at the age of 50. Those without colorectal neoplasia should continue average-risk screening.

If precancerous polyps are found or patients have had a previous colorectal cancer it is reasonable to recommend agents that have been found effective in the prevention of recurrent disease. These include calcium carbonate 1,200 mg daily, folate 400 μg or more daily, and aspirin 81 to 325 mg daily.

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