

*Primary Care***CHEMOPREVENTION OF COLORECTAL
CANCER**

PASI A. JÄNNE, M.D., PH.D., AND ROBERT J. MAYER, M.D.

COLORECTAL cancer is the second leading cause of cancer-related deaths in the United States. It is estimated that this cancer will develop in 130,000 people in the United States in 2000 and that 56,000 will die from the disease.¹ Surgical resection remains the only curative treatment, and the likelihood of cure is greater when the disease is detected at an earlier pathological stage. Early detection is the goal of screening programs that use periodic examination of stool for occult blood, with or without intermittent endoscopic examination of the bowel. Three randomized studies have shown a reduction in mortality of 15 to 33 percent in those who undergo routine screening.²⁻⁴ Flexible sigmoidoscopy has been shown in case-control studies to decrease the incidence of and mortality associated with colorectal cancer.^{5,6} Nevertheless, the optimal method for early detection remains uncertain, and despite widely published recommendations for such screening programs, compliance remains poor.⁷

An alternative approach to reducing mortality from colorectal cancer involves the long-term use of a variety of oral agents that can prevent neoplasms from developing in the large bowel. Such pharmacologic prevention, known as chemoprevention, is directed at preventing the development of adenomatous polyps and their subsequent progression to colorectal cancers. Colon cancers are thought to arise as the result of a series of histopathologic and molecular changes that transform normal colonic epithelial cells into a colorectal carcinoma, with an adenomatous polyp as an intermediate step in this process (Fig. 1).⁸ Polyps occur universally in those with familial adenomatous polyposis, an autosomal dominant hereditary condition, but this disorder accounts for only 1 percent of cases of colorectal cancer.⁹ Adenomatous polyps are

found in approximately 33 percent of the general population by the age of 50 years and in approximately 50 percent by the age of 70 years.¹⁰

Molecular analyses of colorectal adenomas and carcinomas have led to a genetic model of colon carcinogenesis, in which the development of cancer results not from any single genetic event but from the accumulation of a number of genetic alterations (Fig. 1).⁸ By interfering with these molecular events, chemoprevention could inhibit or reverse the development of adenomas or the progression from adenoma to cancer. Recent studies have suggested the potential of this approach in patients with familial adenomatous polyposis as well as in persons with no known genetic syndrome but with a history of sporadic polyps. As evidence emerges of the efficacy of chemoprevention in persons at high risk for colorectal cancer, it seems appropriate to consider a similar strategy for the general population.

CHEMOPREVENTIVE AGENTS**Aspirin and Other Nonsteroidal Antiinflammatory Drugs***Mechanisms*

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are the most widely studied agents for the chemoprevention of colorectal cancer. These compounds exert their effects by a number of mechanisms (Table 1 and Fig. 2). They inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), catalytic enzymes involved in prostaglandin synthesis, by irreversible acetylation and competitive inhibition, respectively.¹¹ COX-1 is constitutively expressed in many tissues, whereas COX-2 is induced by cytokines, growth factors, and mitogens. Analysis of COX-2 expression shows that it is elevated in up to 90 percent of sporadic colon carcinomas and 40 percent of colonic adenomas but is not elevated in the normal colonic epithelium.^{19,20} Increased levels of COX-2, prostaglandins, or both are found in adenomas in patients with familial adenomatous polyposis²¹ and in experimentally induced colon tumors in rodents.^{22,23} When the rodents are treated with sulindac, an NSAID that inhibits both COX-1 and COX-2, the number of intestinal adenomas is reduced by more than 90 percent²⁴ and the total volume of colon tumors by more than 52 percent.^{16,25}

Moreover, this reduction in polyp formation can be improved by use of a more selective COX-2 inhibitor or by the deletion of the COX-2 gene itself.^{26,27} These findings are of particular therapeutic relevance, since the side effects associated with aspirin and other NSAIDs, such as gastric irritation and platelet dys-

From the Department of Adult Oncology, Dana-Farber Cancer Institute, and Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston. Address reprint requests to Dr. Mayer at the Dana-Farber Cancer Institute, 44 Binney St., Boston, MA 02115.

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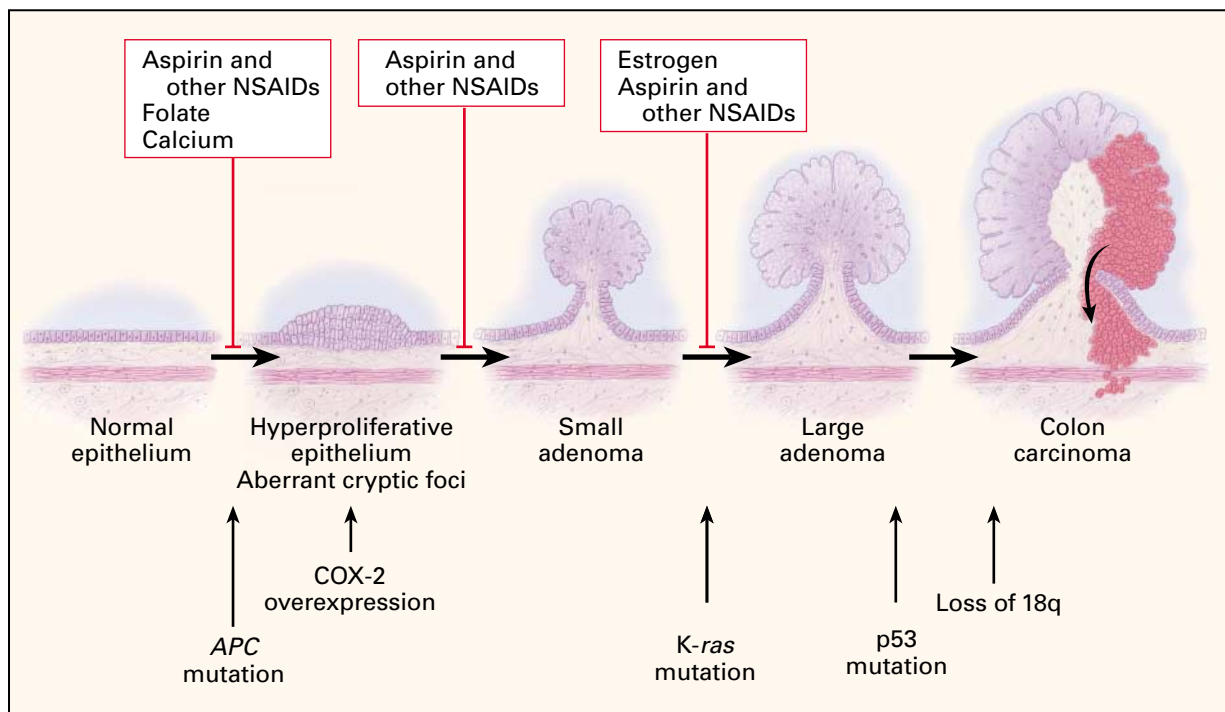


Figure 1. Colon Carcinogenesis and the Effects of Chemopreventive Agents.

Colon cancers result from a series of pathologic changes that transform normal colonic epithelium into invasive carcinoma. Specific genetic events, shown by vertical arrows, accompany this multistep process.⁸ The various chemopreventive agents exert their effects at different steps in this pathway, and this is depicted on the basis of the available epidemiologic evidence, the results of studies in animals, and the known mechanisms of action of the agents. NSAIDs denotes nonsteroidal antiinflammatory drugs, COX-2 cyclooxygenase-2, and APC the adenomatous polyposis coli gene.

TABLE 1. MECHANISMS OF ACTION OF CHEMOPREVENTIVE AGENTS.

AGENT	MECHANISM
Nonsteroidal anti-inflammatory drugs	Inhibition of cyclooxygenase-2 Other mechanisms independent of cyclooxygenase-2 inhibition
Folate	Increased intracellular folate pools
Calcium	Binding of bile and fatty acids Direct inhibition of epithelial-cell proliferation
Estrogens	Decreased synthesis of secondary bile acids Decreased production of insulin-like growth factor I Direct effects on colorectal epithelium

function, are believed to be the result of the inhibition of COX-1. The mechanisms by which the inhibition of COX-2 leads to decreased colon carcinogenesis are not fully understood, but they may involve an increase in apoptosis,^{12,13,28} the regulation of angiogenesis, or both (Fig. 2).¹⁴

Aspirin and other NSAIDs may also act by COX-independent mechanisms, such as inhibition of the activation of nuclear factor- κ B (NF- κ B)¹⁷ or interference with the binding of the peroxisome-proliferator-activated receptor δ (PPAR δ) to DNA (Fig. 2).¹⁸ The relative proportion of COX-dependent to COX-independent mechanisms in the chemoprevention of colorectal carcinogenesis is unknown. On the basis of these observations, it is likely that aspirin and other NSAIDs act as chemopreventive agents at early stages of carcinogenesis (Fig. 1).

Familial Adenomatous Polyposis

Sulindac substantially reduced the size and number of colonic polyps in an initial observational study of four patients with familial adenomatous polyposis.²⁹ This clinical observation was then confirmed in additional observational studies³⁰⁻³² and in three randomized trials involving a total of 45 patients with familial adenomatous polyposis who were given either sulindac or placebo (Table 2).³³⁻³⁵ In addition, a selective COX-2 inhibitor, celecoxib, has been shown in a randomized study to cause regression of polyps in patients with familial adenomatous polyposis (Ta-

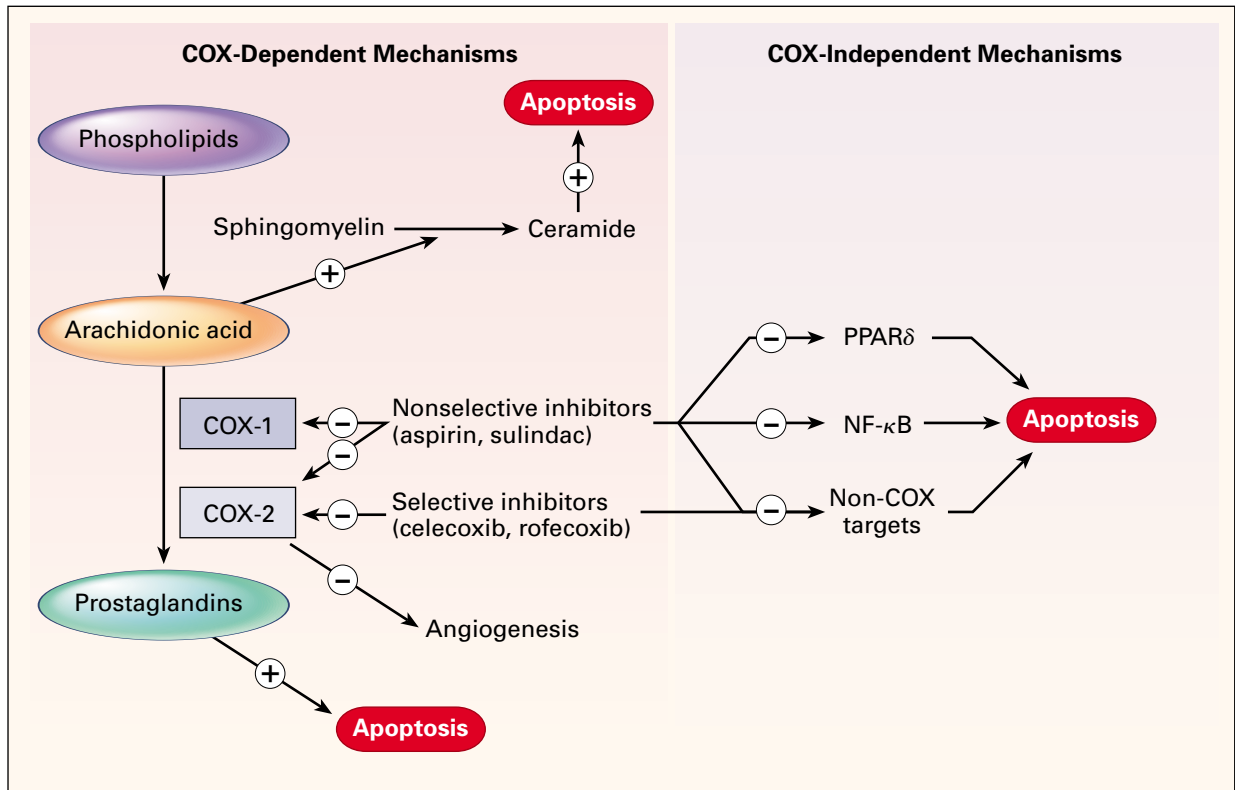


Figure 2. Mechanisms of Action of Aspirin, Other Nonsteroidal Antiinflammatory Drugs, and Selective Cyclooxygenase-2 (COX-2) Inhibitors.

The conversion of arachidonic acid to prostaglandins is catalyzed by the cyclooxygenase (COX) family of enzymes, COX-1 and COX-2.¹¹ Aspirin and sulindac inhibit both COX-1 and COX-2, whereas celecoxib and rofecoxib inhibit only COX-2. These agents induce apoptosis by both COX-dependent and COX-independent mechanisms. The inhibition of COX-2 leads to an increase in arachidonic acid, which, in turn, stimulates the conversion of sphingomyelin to ceramide, a mediator of apoptosis.¹² Inhibition of COX-2 may also lead to apoptosis by altering prostaglandin production and by decreasing angiogenic factors.^{13,14} Aspirin, sulindac, and selective COX-2 inhibitors also exert their effects by COX-independent mechanisms.¹⁵ Sulindac sulfone, a metabolite of sulindac that inhibits neither COX-1 nor COX-2, causes apoptosis of colon-carcinoma cell lines and is chemopreventive in animal models.¹⁶ Some of these effects may be mediated by the ability of aspirin, sulindac, and sulindac metabolites to inhibit the activation of nuclear factor- κ B (NF- κ B)¹⁷ or to interfere with the binding of peroxisome-proliferator-activated receptor δ (PPAR δ) to DNA.¹⁸ Other COX-independent mechanisms are currently not well characterized. Plus signs indicate stimulation or activation, and minus signs inhibition.

ble 2).³⁶ The efficacy and safety of celecoxib and sulindac have not yet been directly compared. Any benefit of these agents is likely to be transient, since an increase in the number and size of polyps has been noted in patients three months after sulindac is discontinued.^{33,35} These treatments should not now replace the standard of care for patients with familial adenomatous polyposis, which is surgical removal of the colon, since there is insufficient information on the long-term benefits of chemoprevention, and since the development of a new colorectal carcinoma in a patient with familial adenomatous polyposis who was receiving sulindac has been reported.³⁷

Clinical Studies

Studies of patients with familial adenomatous polyposis prompted evaluation of the use of aspirin and

other NSAIDs in the general population. A series of case-control studies demonstrated a 40 to 50 percent reduction in the risk of colonic adenomas or colorectal cancer among patients who took aspirin.³⁸ In the Cancer Prevention Study II, questionnaires were circulated to 662,424 people between 1982 and 1989 seeking information about the frequency of aspirin use.³⁹ With infrequent aspirin use (less than once a month), the relative risks of death due to colon cancer were 0.77 for men and 0.73 for women; this risk decreased further to 0.60 for men and 0.58 for women if aspirin was taken more than 16 times per month (Table 3). Because death due to colon cancer was the principal end point of the study, the influence of aspirin on the incidence of colon cancer could not be assessed.

In the Health Professionals Follow-up Study, 47,900

TABLE 2. RANDOMIZED, PLACEBO-CONTROLLED TRIALS OF CHEMOPREVENTION OF COLON CANCER IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS.

STUDY	NO. OF PATIENTS	AGENT	DOSE*	DURATION OF TREATMENT (MO)	EFFECT
Labayle et al. ³³	9	Sulindac	100 mg 3 times daily	4	Decrease in number of polyps†
Nugent et al. ³⁴	14	Sulindac	200 mg twice daily	6	Decrease in number of polyps‡
Giardiello et al. ³⁵	22	Sulindac	150 mg twice daily	9	Decrease in number of polyps by 56% from base line§
Steinbach et al. ³⁶	77	Celecoxib	100 mg twice daily	6	Decrease in number of polyps by 12% from base line¶
		Celecoxib	400 mg twice daily	6	Decrease in number of polyps by 28% from base line

*All doses were oral.

†The actual number of polyps was not available; the difference was significant (P<0.01).

‡The actual number of polyps was not available; the difference was significant (P=0.01).

§The difference was significant (P=0.01).

¶The difference was not significant (P=0.3).

||The difference was significant (P=0.003).

TABLE 3. MAJOR TRIALS OF CHEMOPREVENTION OF COLORECTAL CANCER.*

AGENT AND STUDY	STUDY DESIGN	END POINT	NO. OF PATIENTS	RELATIVE RISK (95% CI)	COMMENT
Aspirin					
Thun et al. ³⁹	Prospective cohort	Death from colon cancer	662,424	0.77 (0.61–0.97) 0.73 (0.56–0.96) for women	Benefit greatest (RR=0.60 for men and 0.58 for women) with more frequent aspirin use
Giovannucci et al. ⁴⁰	Prospective cohort	Colon cancer	47,900	0.68 (0.52–0.92)	Benefit greater (RR=0.35) with continuous aspirin use
Giovannucci et al. ⁴¹	Prospective cohort	Colorectal cancer	89,446	0.56 (0.36–0.90)	Benefit significant after 20 yr of consistent use
Gann et al. ⁴² Stürmer et al. ⁴³	Randomized, placebo-controlled, followed by prospective cohort	Colorectal cancer	22,071	1.15 (0.80–1.65)	
Folate					
Giovannucci et al. ⁴⁴	Prospective cohort	Colorectal adenomas	25,474	0.71 (0.56–0.89)	Benefit greatest in users of folate supplements
Giovannucci et al. ⁴⁵	Prospective cohort	Colon cancer	88,756	0.25 (0.13–0.51)	Benefit seen after 15 yr of use
Calcium					
Baron et al. ⁴⁶	Randomized, placebo-controlled	Colorectal adenomas	913	0.85 (0.74–0.98)	Effect seen as early as 1 yr
Estrogens					
Calle et al. ⁴⁷	Prospective cohort	Death from colon cancer	422,373	0.71 (0.61–0.83)	Benefit greatest for current users (RR=0.55) and continuous users (RR=0.54)
Grodstein et al. ⁴⁸	Prospective cohort	Colorectal cancer Colorectal adenomas	59,002	0.65 (0.50–0.83) 0.74 (0.55–0.99)	Benefit limited to current users For adenomas >1 cm only

*CI denotes confidence interval, and RR relative risk.

men completed biennial questionnaires that included questions about aspirin use; regular use was defined as more than two times per week, and 25 percent of men qualified as regular users.⁴⁰ The relative risk of colorectal cancer was 0.68 when regular aspirin use was reported in a single questionnaire but

declined to 0.35 when such use was reported on three or more successive questionnaires. The benefit of aspirin use in preventing the development of distal colorectal adenomas was also demonstrated (relative risk, 0.72) in a subgroup of patients (22 percent of patients) who underwent screening sigmoidosco-

py, a finding similar to those of other case-control studies.⁴⁹ The influence of the duration of aspirin use or of the dose was not assessed. In a cohort of 89,446 women in the Nurses' Health Study,⁴¹ the regular users of aspirin (two or more times per week) had a relative risk of colon cancer of 0.62. Little or no risk reduction was observed during the first 9 years of aspirin use, whereas the relative risk was 0.56 after 20 or more years of use (Table 3). Although these studies show a protective benefit of aspirin, the minimal effective dose and duration of use have not been defined.

The effect of aspirin on the development of colorectal cancer has been evaluated in only one randomized trial, the Physicians' Health Study, which was designed primarily to assess the effect of aspirin on the risk of coronary artery disease.⁴² This trial, which involved 22,071 male physicians in the United States, was terminated prematurely when a 44 percent reduction in the likelihood of myocardial infarction was noted among aspirin users. When data from the treatment and placebo cohorts were analyzed with respect to colon cancer, there were no significant differences between the cohorts in the incidence of colon cancer, colonic polyps, or in situ cancer, even after 12 years of follow-up.⁴³ However, the aspirin dose used in this study may have been lower than that in the Nurses' Health Study (325 mg every other day, as compared with at least 1300 mg per week), and the periods of continuous use (5 years) and follow-up (12 years) may have been insufficient for the expected effect to be observed.⁵⁰

In the general population, aspirin has been the predominant NSAID evaluated to date; data on the benefits of NSAIDs other than aspirin are limited. Some studies have combined aspirin with another NSAID in the analyses.^{50,51} Although two small case-control studies demonstrated a protective effect of nonaspirin NSAIDs similar to that of aspirin, both lacked the statistical power to analyze the benefits of individual compounds.^{52,53} A recent, larger retrospective study evaluated a cohort of 104,217 persons 65 years of age or older who had received Medicaid prescriptions for nonaspirin NSAIDs.⁵⁴ Although a protective effect against colorectal cancer was demonstrated (relative risk associated with all nonaspirin NSAIDs, 0.61), the study was limited by its retrospective design and inadequate assessment of concurrent aspirin intake.

Folate

Several cohort and case-control studies have suggested that increased consumption of vegetables and fruits reduces the risk of colorectal cancer.^{55,56} Folate is a micronutrient found abundantly in vegetables and fruits. Epidemiologic studies have found a lower incidence of colorectal cancer among those with the highest dietary folate intake,^{57,58} whereas those with

diets low in folate (and often with high alcohol intake) appear to have an increased risk of colorectal adenomas and carcinomas.^{44,59,60} Although large amounts of folate in the diet appear to be protective against the development of colorectal adenomas (relative risk, 0.91 in women and 0.78 in men), the degree of benefit is greater among those who take folate supplements (relative risk, 0.66 for women and 0.63 for men).^{44,60} In the Nurses' Health Study, supplementation with folate (usually as part of multivitamin supplementation) was protective against colorectal cancer, with the greatest risk reduction among women taking high daily doses of folate (more than 400 μg); this reduction (relative risk, 0.25) became statistically significant only after 15 years of use (Table 3).⁴⁵ The long time needed for a clinical benefit to become evident suggests that folate acts early in colon carcinogenesis (Fig. 1).

Folic acid and its metabolites, 5,10-methylenetetrahydrofolate and 5-methyltetrahydrofolate, are critical components of DNA synthesis. 5,10-Methylenetetrahydrofolate undergoes conversion to 5-methyltetrahydrofolate by methylenetetrahydrofolate reductase (MTHFR), which further serves as a methyl donor for methionine synthase, an enzyme that catalyzes the conversion of homocysteine to methionine. The mechanisms through which folic acid acts to inhibit tumorigenesis are unknown, but the role of folate in colon carcinogenesis has been elucidated by studies of patients who are homozygous for the common MTHFR and methionine synthase polymorphisms. Patients with a diet adequate in folate who are homozygous for either the MTHFR or the methionine synthase polymorphism have a decreased risk of colorectal cancer (relative risk, 0.5 for MTHFR and 0.51 for methionine synthase).⁶¹⁻⁶³ However, this protective benefit is lost in those with a diet inadequate in folate. Neither of these genetic polymorphisms provides a benefit against the development of colorectal adenomas.⁶⁴ On the basis of these interactions, the protective effect of folate supplementation appears to be greatest for those who are genetically predisposed to colorectal cancer.

Calcium

Diets rich in red meat and animal fat are associated with an increased risk of colorectal adenomas and cancer.^{65,66} Although the exact mechanism is not known, these diets increase the production of secondary bile acids, which may cause hyperproliferation of the colorectal epithelium and which promote tumor formation in studies in animals.⁶⁷ Calcium may inhibit colon carcinogenesis by binding bile acids and fatty acids in the bowel lumen or by directly inhibiting the proliferation of colonic epithelial cells (Table 1).⁶⁸ In animal models, calcium supplementation reduces colonic epithelial hyperproliferation and reduces the formation of tumors in response to carcin-

ogens and a high-fat diet.⁶⁹ Some, but not all, studies of humans consuming high-calcium diets or receiving calcium supplements have shown decreased proliferation of colorectal epithelial cells, changes in bile-acid composition, or decreased cytotoxicity of fecal water.^{68,70-73} Most of the case-control and cohort studies in humans show an inverse association between high-calcium diets or calcium supplementation and the risk of colon cancer or colorectal adenoma, but the association is statistically significant in only a few studies.^{69,74,75} The chief drawback of all these studies is imprecise assessment of calcium intake and the potential confounding effects of other dietary constituents. In a recent study,⁴⁶ 930 patients with a history of colorectal adenomas were randomly assigned to receive either daily supplementation with 3 g of calcium carbonate (1200 mg of elemental calcium) or placebo. Serial endoscopic examinations performed one and four years after the start of the study showed a moderate but significant reduction (relative risk, 0.85) in the formation of new adenomas in those receiving calcium supplementation (Table 3).⁴⁶ The protective effect of calcium was observed as early as one year after supplementation began. In agreement with its proposed mechanism of action, the data suggest that calcium acts very early in the pathway of colon carcinogenesis (Fig. 1).

Hormone-Replacement Therapy

During the past 20 years, mortality from colorectal cancer has decreased slightly in men but much more in women.¹ A possible explanation for this difference is the increasing use of postmenopausal hormone-replacement therapy.⁷⁶ Estrogens may prevent colorectal cancer by decreasing the production of secondary bile acids, by decreasing the production of insulin-like growth factor I, by exerting direct effects on the colorectal epithelium, or by a combination of these mechanisms (Table 1).⁷⁷⁻⁸⁰ The Cancer Prevention Study II found a significant decrease in mortality from colon cancer with the use of hormone-replacement therapy (relative risk, 0.71); the effect was stronger in women currently receiving therapy (relative risk, 0.55) and in those who had received continuous therapy for more than 11 years (relative risk, 0.54) (Table 3).⁴⁷ The postmenopausal use of hormones also had a protective effect against the development of colorectal cancer in the Nurses' Health Study, but the effect was limited to those currently receiving therapy (relative risk, 0.65) and disappeared within five years after the cessation of therapy.⁴⁸ The use of hormones for more than five years provided no additional reduction in risk. Similar findings have been obtained in case-control studies.^{81,82} Moreover, two recent meta-analyses found an aggregate reduction in the risk of colorectal cancer of 20 percent with hormone-replacement therapy.^{83,84} The effect of hormone-replacement therapy on the development

of colorectal adenomas has been examined in only a few studies. Although some studies found an effect on all adenomas, in the Nurses' Health Study there was a protective effect only with respect to the development of large adenomas (more than 1 cm in diameter), for which the relative risk was 0.74.^{48,84,85} These observations and the mechanism of action of estrogens suggest that estrogens probably act at the later stages of colorectal carcinogenesis (Fig. 1).

Vitamins, Antioxidants, and Fiber

It has been proposed that the protective effects of diets rich in fruits and vegetables against the development of colorectal cancer are due to their content not only of folate, but also of vitamins with antioxidant properties and of fiber.^{56,86} Prospective data, however, do not support this hypothesis. Vitamin supplementation has been evaluated in several cohort and case-control studies. The large prospective cohort studies, including the Nurses' Health Study, the Physicians' Health Study, and the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, all found no protective effect of supplementation with beta carotene or with vitamin A, C, D, or E against colorectal carcinogenesis.^{45,87,88} In the only randomized study evaluating the protective effect of antioxidants, 864 subjects with a history of colorectal adenoma were assigned to receive placebo, beta carotene, vitamins C and E, or a combination of beta carotene and vitamins C and E.⁸⁹ Colonoscopic examination after one and four years showed no difference in the rate of adenoma formation among the four groups.

Meta-analyses of observational epidemiologic and case-control studies have found a protective effect of dietary fiber against colon cancer that increases with intake.^{56,86} However, several large, prospective studies have found only a weak benefit, at best.⁹⁰⁻⁹² Increasing the intake of dietary fiber also does not appear to protect against the development of colorectal adenomas.⁹² Two small, randomized trials, one evaluating a high-fiber, low-fat diet and the other evaluating dietary fiber supplementation, found no effect on the risk of recurrent colorectal polyps.^{93,94} Two larger, randomized trials^{95,96} that were recently completed had results similar to those of the small trials. In the Polyp Prevention Trial, 2079 subjects with a history of colorectal adenomas were randomly assigned to receive counseling together with a low-fat, high-fiber diet rich in fruits and vegetables, or to continue their usual diet with no counseling.⁹⁵ Colonoscopy after one and four years found that the incidence of recurrent adenomas was virtually identical in the two groups. In the randomized study by the Phoenix Colon Cancer Prevention Physicians' Network, conducted in Arizona, 1429 patients with a history of colorectal adenoma were given either 2.0 g or 13.5 g of supplemental wheat bran per day; there was no difference in the incidence of recurrent adenomas between the two

groups.⁹⁶ Thus, there are currently no prospective data to support the hypothesis that vitamins (other than folic acid) or fiber (either dietary or supplemental) is protective against the development of either colorectal adenomas or colorectal carcinomas.

CONCLUSIONS

Although the treatment of advanced colorectal cancer continues to improve, large-bowel cancer remains a major cause of illness and death. Recent observations suggest that aspirin and other NSAIDs, supplemental folate and calcium, and postmenopausal hormone-replacement therapy (estrogen) have a chemopreventive benefit (Table 3). Since the value of such prophylactic strategies has not yet been confirmed in double-blind, placebo-controlled, randomized studies, chemoprevention cannot yet be accepted as standard medical practice. Chemoprevention should not replace periodic fecal occult-blood tests and endoscopic screening, as well as modification in known risk factors for colorectal cancer, such as reduction in the intake of red meat, appropriate exercise, smoking cessation, and weight control.

Any protective benefit must also be balanced against the potential side effects of the long-term ingestion of any putative chemopreventive agent, including the gastric irritation and platelet dysfunction associated with aspirin and other NSAIDs, which are thought to be due to the inhibition of COX-1. More selective COX-2 inhibitors, such as celecoxib and rofecoxib, have already been evaluated in patients with familial adenomatous polyposis and are now being studied in patients with a history of sporadic polyps. In addition, other potential chemopreventive agents, such as ursodiol (a modulator of bile acid composition),⁹⁷ eflornithine (which inhibits cellular proliferation by altering polyamine metabolism),⁹⁸ and oltipraz (an inducer of the mutagen-detoxification enzyme glutathione *S*-transferase),⁹⁹ are undergoing evaluation in studies in animals and clinical studies.

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