Chemoprevention for Colorectal Neoplasia

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ABSTRACT

Colorectal cancer is a major cause of morbidity and mortality in industrialized societies and leads to significant treatment costs. Currently there are screening programs with fecal occult blood testing, radiographic, and endoscopic evaluation. Despite this, mortality from colorectal cancer has not improved dramatically. As such, attention has turned to finding agents to prevent carcinogenesis. The emerging field known as chemoprevention studies agents that target multiple steps in the development of adenomas and their subsequent transformation to colorectal carcinoma. There are multiple case control, cohort, and randomized controlled trials investigating the efficacy of fiber, calcium, vitamin D, folate, and nonsteroidal antiinflammatory drugs as chemopreventive agents against colorectal cancer.

KEYWORDS: Chemoprevention, colorectal cancer, dietary supplements, carcinogenesis

Objectives: On completion of this article, the reader should be able to assess the effect of dietary fiber, calcium, vitamin D, folate, and nonsteroidal antiinflammatory drugs on the incidence or recurrence of colorectal adenomas and colorectal cancer.

BACKGROUND

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in industrialized societies.¹ Early detection and treatment have decreased morbidity and mortality.² Despite improvement in screening practices, surgical techniques, and adjuvant therapy, the mortality rate from colorectal cancer has decreased by only 1.8% per year over the last 15 years.³ This makes primary prevention an important goal. As such, there is an intense effort to develop cancer prevention strategies in addition to surveillance protocols for early diagnosis.

Migration studies provide support for an environmental component to the etiology of colorectal cancers. An increased mortality due to CRC in Japanese Americans and Chinese Americans was noted when compared with the mortality rates in Japan and China in the 1970s.⁴ It has been suggested that diet and other

environmental factors play a role in the etiology of CRC. It has also been observed that fruit and vegetable intake have been inversely associated with CRC.^{5,6} An alternative approach to reducing mortality from colorectal cancer may therefore involve the long-term use of pharmacologic or natural agents to prevent adenomas from developing in the colon.⁷ This area of research is collectively known as chemoprevention⁸ and is directed at preventing the initiation, promotion, and progression of adenomatous polyps to colorectal cancers. Because multiple steps are involved, it is possible that agents acting at different stages in carcinogenesis pathway could be combined for better efficacy.

Colon cancers are thought to result from a culmination of histologic and molecular changes resulting in abnormal regulation of cellular function; this affects growth of cells, differentiation, adhesion properties,

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and migration.⁹ The end point is transformation of normal colonic epithelial cells into invasive colorectal cancers; adenomatous polyps are an intermediate step.¹⁰ Specific genetic events accompany this multistep transforming a small adenoma into cancer. Diet affects the production of colonic metabolic byproducts that may influence carcinogenesis in this process.¹¹ Various chemopreventive agents are likely to exert their effects at different steps in this pathway.

The majority of sporadic colorectal cancers occurs in adenomas secondary to dysregulation of proto-oncogenes, loss of tumor suppressor gene function, and DNA mismatch repair.¹² These defects result in more localized disease despite the widespread exposure of the colon to environmental factors, whereas patients who inherit cancer syndromes tend to develop numerous polyps.¹³ As the varied pathways in colon cancer development are being better defined, better targets for chemoprevention may be developed.

The ideal agent to prevent colorectal neoplasia must target a step in carcinogenesis, have efficacy against colorectal cancer, be cost effective, have easy administration, and be safe with a favorable side-effect profile. Many studies evaluate patients for adenomas as a surrogate for colorectal cancer because of the assumed shorter time to adenoma formation compared with the development of colorectal cancer. It is easier to evaluate existing drugs and natural agents with already proven efficacy and safety for their chemopreventive qualities.¹⁴ In this chapter, we specifically examine the role of fiber, calcium, vitamin D, folate, and nonsteroidal antiinflammatory drugs (NSAIDs) on chemoprevention of colorectal adenomas and carcinomas.

FIBER

Dietary fiber is composed of the remnants of plant cells resistant to hydrolysis by human alimentary enzymes, including all indigestible polysaccharides and lignin. It can further be classified as soluble and insoluble, and evidence suggests that soluble fibers are less likely to protect against cancer than insoluble dietary fibers.¹⁵ In the early 1970s, Burkitt proposed the hypothesis that dietary fiber protects against the development of CRC when it was noted that colorectal cancer was rare in rural Africa when compared with industrialized countries.¹⁶ It has been proposed that dietary fiber is protective against colon carcinogenesis by several mechanisms. These include increasing stool bulk, decreasing colonic transit time—this decreases the contact of carcinogens with the colonic epithelium, binding bile acids and carcinogens, decreasing colonic pH, and increasing the production of short chain fatty acids.¹⁷

A protective effect of increased dietary fiber against CRC has been shown in meta-analyses of observational, epidemiologic, and case-control studies.¹⁸

One meta-analysis in 1990 reviewed epidemiology studies from 1970 to 1988 and reviewed a combination of case-control studies, correlation studies, cohort studies, and time-trend studies.¹⁹ It concluded that there was “equivocal support for protective effect” with a combined odds ratio (OR) of 0.57 and a 95% confidence interval (CI) of 0.5 to 0.64. Howe published a second meta-analysis in 1992, reviewing case-control studies to examine the effects of fiber, vitamin C, and β -carotene on CRC risks.²⁰ This analysis concluded the relative risk (RR) of CRC was 0.53 when comparing the high and low intake of dietary fiber by using a logistic regression analysis. These meta-analyses have inherent weaknesses because they are derived from case-control studies, which are subject to recall and selection bias.

Prospective data does not support the protective benefits of increased dietary fiber. The Cochrane Collaboration reviewed five randomized control trials with 4349 subjects who met the inclusion criteria (randomized/quasirandomized controlled trials comparing fiber supplementation to control in a general population whose colon had been endoscopically evaluated at baseline and at least 2 years later with pathologically documented adenoma or colorectal cancer).¹⁸ Interventions included wheat bran fiber, ispaghula husk, or a comprehensive dietary intervention with high-fiber foods. The study found no difference between the intervention and control groups for the subjects who had only one adenoma as well as for subjects with multiple adenomas (RR = 1.04, 95% CI = 0.95 to 1.13 and RR = 1.02, 95% CI = 0.89 to 1.17). It concluded that there is no current evidence from randomized controlled trials (RCTs) to suggest that increased dietary fiber intake will reduce the incidence or recurrence of colon adenomas within a 2- to 4-year period.

Two other large American cohort studies found no evidence that dietary fiber or the intake of fruits and vegetables reduced the risk of colorectal cancer. The Nurses Health Study (NHS) included 88,757 women with a 16-year follow-up; the Professionals' Follow-up Study included 47,325 men with a 10-year follow-up. The NHS found no association between the intake of dietary fiber and the risk of colorectal cancer or adenoma with a RR of the high-fiber versus low-fiber group was 0.95 (95% CI = 0.73 to 1.25).²¹ The second study investigated the association of fiber with CRC with both the NHS and Health Professionals Follow-Up Study (HPFS).²² The hazard ratio for a 5-g per day increase in fiber was 0.91 (95% CI = 0.87 to 0.95) and was 0.99 (95% CI = 0.95 to 1.04) after adjusting for covariates. Thus, the authors concluded there was not an important association between dietary fiber and CRC.

The Polyp Prevention Trial is a multicenter randomized controlled trial to evaluate whether a high-fiber, low fat, high fruit and vegetable diet reduces the recurrence of adenomatous colon polyps.¹¹ Over

1900 men and women who were previously found to have polyps were randomized into intervention or control arms. The intervention arm received extensive dietary and behavioral counseling with dietary goals of 20% total energy from fat, 18 g per 1000 kCal of dietary fiber, as well as 5 to 8 daily servings of fruits and vegetables; the control arm had no counseling. Review of the 4-day annual food histories showed that patients in the intervention group significantly decreased the fat intake and increased their fiber intake. There was little change in the diets of the control group. Subjects underwent annual colonoscopy for 4 years after randomization. The unadjusted risk ratio was 1.00 (95% CI = 0.9 to 1.12) and the study found that the rate of recurrence of large adenomas and advanced adenomas was not significantly different between the two groups. Similarly, the Phoenix Colon Cancer Prevention Physicians' Network included 1429 patients with a history of colorectal adenoma who were given either 2.0 g or 13.5 g of supplemental wheat bran per day.²³ The multivariate adjusted OR for recurrent adenoma in the high-fiber group was 0.88 (95% CI = 0.7 to 1.11; $p=0.28$) with a RR of recurrence of 0.99 (95% CI = 0.71 to 1.36; $p=0.93$). Again, there was no difference in the incidence of recurrent adenomas between the groups. Thus, there are currently no prospective data to support the hypothesis that fiber is protective against the development of either colorectal adenomas or carcinomas.

CALCIUM

Diets rich in red meat and animal fat are associated with an increased risk of colorectal adenomas and carcinoma.²⁴ It is hypothesized that these diets may increase production of secondary bile acids, leading to hyperproliferation of the colorectal epithelium, which results in promoting tumor formation.²⁵ Calcium is believed to inhibit colon carcinogenesis by binding bile acids and fatty acids in the bowel lumen or by directly inhibiting the proliferation of colonic epithelial cells. This has been demonstrated in animal models where calcium supplementation reduces colonic epithelial hyperproliferation and reduces the formation of tumors in response to carcinogens and a high-fat diet.²⁶ There have been some human studies demonstrating consumption of high-calcium diets or receiving calcium supplements decreases proliferation of colorectal epithelial cells, changes in bile-acid composition, and decreased cytotoxicity of fecal water.²⁷ 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.^{26,28,29} An inherent flaw in these studies is the imprecise assessment of calcium intake and the potential confounding effects of other dietary constituents.

There are multiple studies in this area, however the results are inconsistent. One study included 930 patients with a history of colorectal adenomas that were randomly assigned to receive either daily supplementation with 3 g of calcium carbonate or placebo.³⁰ The study participants underwent serial endoscopic examinations performed at 1 and 4 years after enrollment. This showed a moderate but significant reduction in the formation of new polyps with a RR of 0.8 in the treatment group. The protective effect of calcium was observed as early as one year after supplementation began. This data suggest that calcium acts very early in the pathway of colon carcinogenesis.

The results of another large prospective randomized controlled trial were inconclusive. It involved 36,282 postmenopausal women in the Women's Health Initiative and examined the role of calcium and vitamin D in colorectal cancer.³¹ Half received 500 mg of calcium carbonate combined with 200 IU of vitamin D3 twice daily versus placebo, with a 7-year follow-up. Daily supplementation of calcium and vitamin D had no effect on the incidence of CRC among postmenopausal women (hazard ratio = 1.08, 95% CI = 0.86 to 1.34; $p=0.51$).

The Cochrane Collaboration reviewed randomized controlled trials where the primary outcomes were occurrence of CRC or adenomas as influenced by dietary calcium supplementation.³² Two RCTs with 1346 subjects met the inclusion criteria. Doses of supplementary calcium were 1200 mg daily for 4 years and 2000 mg daily for 3 years. A reduction was found when the results from both trials were combined with an OR of 0.74. The conclusion was that calcium supplementation may contribute to a moderate degree of prevention of colorectal adenomatous polyps, but more evidence is needed.

A multicenter multinational randomized trial in several European countries looked at the effect of calcium supplementation as well.³³ Six hundred sixty-five patients were randomized into three treatment groups: calcium gluconolactate and carbonate, ispaghula husk, and placebo. The OR of adenoma recurrence in the calcium group was 0.66 (95% CI = 0.38 to 1.17; $p=0.16$). Interestingly, the odds ratio associated with the fiber-treatment group was significantly higher in study participants with baseline dietary calcium intake than those with low intake. The conclusion was that calcium supplementation was associated with a modest, but not significant reduction in the risk of adenoma recurrence.

VITAMIN D

In the early 1980s, it was hypothesized that higher levels of vitamin D were associated with a reduced risk of colorectal cancer.³⁴ It is known that sun exposure increases vitamin D levels, and that people who live in higher latitudes have a higher incidence of colorectal

cancer. Further investigation led to the discovery that normal and neoplastic cells express vitamin D receptors and express 1- α -hydroxylase, which creates the active metabolite of vitamin D.³⁵ The activation of vitamin D receptors induces multiple antineoplastic activities, including reduced proliferation, invasiveness, angiogenesis and metastasis, as well as increased differentiation and apoptosis. There has been recent speculation that activation of vitamin D may take place in the colon as well as the kidney.³⁶ As such, there have been multiple epidemiologic studies, which evaluate the risk of colorectal cancer in individuals who increase their intake of vitamin D.

One of the first cohort studies on the effect of vitamin D on colorectal cancer was examined in the NHS and the HPFS.^{36a} In this study, men and women with left-sided colon or rectal adenomas were matched against study participants without adenomas. Patients completed a food survey from which their vitamin D intake was calculated. The results of this study did not suggest an association between vitamin D intake and adenoma risk (RR = 1.29, 95% CI = 0.87 to 1.93; women RR = 0.68, 95% CI = 0.41 to 1.13; $p = 0.09$). A follow-up study that analyzed 4-year data demonstrated no association with vitamin D (RR = 0.54, 95% CI = 0.42 to 0.85).³⁷ These patients have been followed since that time and a recent analysis of the Nurses' Health Study showed that vitamin D intake was moderately associated with a reduced risk of distal colorectal adenomas in women (RR = 0.79, 95% CI = 0.63 to 0.99; $p = 0.07$).³⁸

Another case-control study evaluating the NHS data found a significant inverse linear association between plasma levels of vitamin D and the risk of colorectal cancer ($p = 0.02$).³⁹ This study used plasma concentrations of 25(OH)D because it was felt to be a better marker than vitamin D intake. One hundred ninety-three CRC cases were identified and compared with controls using conditional logistic regression to adjust for multiple other factors. Women in the highest quintile of plasma 25(OH)D had an OR of 0.53 (95% CI = 0.27 to 1.04). This inverse relationship was only noted in women > 60 years old, and was only observed for cancers of the distal colon and rectum. Finally, there was no association noted between 1,25(OH)D and colorectal cancer (OR = 2.52, 95% CI = 1.04 to 6.11).

This finding was reproduced in a more recent case-control study of plasma 25(OH)D concentrations and colorectal cancer using the HPFS.⁴⁰ One hundred seventy-nine men with colorectal cancer were matched to 356 control subjects. Conditional logistic regression was used to analyze the association between CRC and plasma vitamin D levels. Again, a statistically significant inverse association was found for colon cancer with an OR of 0.46 (95% CI = 0.24 to 0.89; $p(\text{trend}) = 0.005$). However, there was a nonstatistically significant inverse association between higher plasma vitamin D levels and

the risk of colorectal cancer. This study then pooled the results from the Nurses' Health Study to gain enough power to show that higher plasma vitamin D levels were statistically significantly associated with both decreased risk of colorectal cancer as well as colorectal cancer itself (OR = 0.66, 95% CI = 0.42 to 1.05, $p = 0.002$). It also demonstrated that inverse associations of vitamin D did not differ by location of the colorectal carcinoma.

However, prospective studies have not found total vitamin D intake to be associated with reduced risk of colorectal cancer. The U.S. Women's Health Study analyzed 223 who developed colorectal cancer in a pool of 39,876 women.⁴¹ It found that intake of calcium and vitamin D was not associated with higher risk of colorectal cancer (RR = 1.34, 95% CI = 0.84 to 2.13; $p(\text{trend}) = 0.08$ for vitamin D). As previously described the Women's Health Initiative examined both the roles of calcium and vitamin D in colorectal cancer, and concluded that daily supplementation of calcium and vitamin D had no effect on the incidence of CRC among postmenopausal females (hazard ratio = 1.08, 95% CI = 0.86 to 1.34; $p = 0.51$).³¹ It has been argued that the daily vitamin D dose was too low to detect an effect on colorectal cancer.⁴² A more recent dose-response analysis estimated a 50% decreased colorectal cancer risk with 1,000 IU oral vitamin D.⁴³

Because epidemiologic observational studies are inconsistent in defining the relationship between colorectal cancer and vitamins, more randomized controlled trials are needed. Currently, The Cochrane Collaboration is conducting a systematic review to assess the effect of vitamins and minerals on colorectal cancer and the incidence of adenomatous polyps.⁴⁴

FOLATE

Folate is a micronutrient found abundantly in fruits and vegetables. Epidemiologic studies have found a lower incidence of colorectal cancer among those with the highest dietary folate intake,⁴⁵ whereas those with diets low in folate have an increased risk of colorectal adenomas and carcinomas.⁴⁶ Although large amounts of folate in the diet appear to be protective against the development of colorectal adenomas (RR = 0.91 in women; RR = 0.78 in men), the degree of benefit is greater among those who take folate supplements (RR = 0.66 for women; RR = 0.63 for men).^{42,47} The prolonged time needed for a clinical benefit to become evident suggests that folate, like calcium, has an early influence on colon carcinogenesis.

DNA synthesis is dependent on folic acid and its metabolites, 5,10-methylenetetrahydrofolate and 5-methyltetrahydrofolate.^{47a} 5,10-Methylenetetrahydrofolate is converted to 5-methyltetrahydrofolate by methyl-enetetrahydrofolate reductase (MTHFR), which further serves as a methyl donor for methionine

synthase. Methionine synthase is an enzyme that catalyzes the conversion of homocysteine to methionine. The mechanisms through which folic acid acts to inhibit tumorigenesis are unknown, but there are several hypotheses.

Studies of patients who are homozygous for MTHFR and methionine synthase polymorphisms have demonstrated the role of folate in colon carcinogenesis.⁴⁸ These patients who are homozygous for the MTHFR or methionine synthase polymorphism and on a folate-rich diet have a decreased risk of colorectal cancer (OR = 0.5 for MTHFR; OR = 0.51 for methionine synthase).⁴⁹ This protective benefit was noted to be lost in those subjects with inadequate folate intake. Upon further investigation, neither of these genetic polymorphisms results in decreased incidence of colorectal adenomas.⁵⁰ The protective effect of folate supplementation appears to be greatest for those who are genetically predisposed to colorectal cancer.

Duthie hypothesized two other mechanisms of how low folate levels are related to an increased risk of malignancy. The first occurs when the demand for methyl groups in normal cellular metabolism exceeds dietary supply.^{50a} This insufficiency is prevented by *de novo* methyl synthesis by the way of a carbon donation from the folate pool. This site-specific DNA methylation controls gene expression when genes methylated at specific locations in the DNA molecule are not transcribed or translated. As such, folate deficiency can cause DNA hypomethylation. This can lead to dysregulation of proto-oncogenes, which are involved in carcinogenesis. Duthie's second hypothesis is that folate deficiency can alter nucleotide precursor pools, causing uracil to be incorporated incorrectly during DNA synthesis. The result is DNA strand breakage and chromosome damage.

This hypothesis can be applied to colon cancer. A case-control study demonstrated that biopsies of normal colonic mucosa in patients with adenomas show significantly greater [³H]-methyl incorporation than do biopsies taken from controls.^{50b} The [³H]-methyl incorporation was 26% higher (95% CI = 8%–56%, $p = 0.009$) in patients with adenomas and 30% higher (95% CI = 3% to 48%, $p = 0.08$) for patients with cancer. The amount of radiolabeled methyl groups incorporated into DNA was inversely proportional to DNA methylation, indicating that adenoma DNA was hypomethylated when compared with controls. Colorectal cancer biopsies similarly had hypomethylated colonic DNA when compared with controls; however, the difference was not statistically significant ($p = 0.09$). Colorectal cancer patients had 26% lower folate levels in their diet and blood when compared with controls, which was statistically significant (95% CI = 6% to 44%, $p = 0.01$). In this study, high folate levels were associated with a significant reduction in risk for colorectal cancer ($p = 0.01$).^{50b}

The Nurses' Health Study Cohort has provided ample data for analysis regarding the association between folate and colorectal cancer. Giovannucci et al noted that women who took a daily multivitamin that included folate for 15 years had a decreased risk in developing colorectal cancer (RR = 0.25, 95% CI = 0.13 to 0.51, $p = 0.0003$).⁵¹ This effect was most pronounced for women taking high daily doses of folate. However, long-term multivitamin use was not protective against rectal cancer (RR = 1.27, 95% CI = 0.52 to 0.93). The interpretation of this study was limited due to the lack of randomization; thus, the results cannot undeniably be attributed to folate. The long time needed for a clinical benefit to become evident suggests that folate acts early in colon carcinogenesis.

Further analysis was performed by Fuchs et al using the same cohort data. The NHS was used to investigate the relationship between folic acid intake and the risk of colon cancer in patients with a positive family history.⁵² Nearly 7000 individuals were noted to have a positive family history in one or more first-degree relatives initially, and this figure increased to 11,808 10 years later. In this population, women who consumed > 400 μg of folate daily were compared with women who had low folate intake. The RR in women without a family history of CRC was 0.81 (95% CI = 0.28 to 0.83; $p(\text{interaction}) = 0.02$) whereas the RR in women with a family history was 0.48 (95% CI = 0.62 to 1.07, $p = 0.02$). The authors concluded that individuals with a first-degree family history of colorectal cancer who use multivitamins for more than 5 years could decrease their colon cancer risk by nearly 50%. They further speculate that these individuals may be more susceptible to dietary methyl deficiency, which may be due to low penetrance aberrations in DNA methylation and repair.

The Canadian National Breast Screening Study compared folate intake in the 295 cases of colorectal cancer⁵³ observed in the 56,837 women who were enrolled between 1980 and 1985. The colorectal cancer subjects were compared with 5334 randomly selected controls. A dietary questionnaire was performed upon entry to the study and daily nutrient intakes calculated. Folate intake was found to be inversely associated with colorectal cancer risk, with a 40% lower risk among women in the highest compared with the lowest quintile of folate intake. This reduced risk, however, was not statistically significant (IRR = 0.6, 95% CI = 0.4 to 1.1, $p = 0.25$).

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

There are many experimental and observational studies demonstrating NSAIDs and aspirin have chemopreventive properties. NSAIDs exert their effects by several mechanisms. One proposed mechanism is inhibition of

cyclooxygenase-1 and 2, which are enzymes involved in prostaglandin synthesis from arachidonic acid.⁵⁴ COX-1 is expressed constitutively in many tissues and produces prostaglandins that mediate normal physiologic functions. Production of COX-2 is induced by cytokines, growth factors, and mitogens. It is undetectable in normal tissues, but has been demonstrated to be elevated in colorectal adenomas and carcinomas.⁵⁵ Multiple studies have analyzed COX-2 expression, showing it is not elevated in normal colon epithelial cells, but the expression is elevated in 90% of sporadic colon carcinomas and 40% of adenomas.^{56,57} Experimental data in animal models show that COX-2 results in development of colorectal cancer by influencing apoptosis, angiogenesis, cell migration, cell attachment, and invasion.⁵³

Aspirin is a commonly used NSAID and is the subject of many investigations on chemoprevention. There are case control studies that demonstrate a 40 to 50% lower mortality in patients that use aspirin.⁵⁸ The Cancer Prevention Study II examined 662,424 adults and their aspirin use.⁵⁹ The RRs of death were 0.77 for men and 0.73 for women who used aspirin less than one time a month. The risks fell to 0.60 for men and 0.58 for women who used aspirin more frequently (at least 16 times a month). This study used colon cancer as the primary end point, so the effect of aspirin use on the incidence of CRC could not be assessed.

The HPFS⁶⁰ is a prospective study of 47,900 men; nearly 25% used aspirin at least twice per week. Regular aspirin use (more than twice a week) was associated with a 30% reduction in CRC and 50% reduction of advanced cases. The NHS followed 82,911 women for 20 years.⁶¹ The RR for colon cancer was 0.77 (95% CI = 0.67 to 0.88) among regular users of aspirin (more than twice weekly of 325 mg dose) when compared with controls. Significant reduction was not noted until more than 10 years of use, and the benefit appeared to be dose dependent. The RR was 0.56 after 20 or more years of use. Although a protective benefit of aspirin was demonstrated, the minimal effective dose and duration of use have not been defined.

The Physician's Health Study randomized 22,000 men to receive 325 mg of aspirin every other day or placebo for 5 years.⁶² There was not a reduction in adenomas or colorectal cancers. A subsequent study performed as follow-up to the Physician's Health Study demonstrated that there was no association between the incidence of colorectal cancer and aspirin use.⁶³ This conclusion was likewise noted in the Women's Health Study.⁶⁴ The short treatment periods and the low dose of aspirin may explain these results.

A recent randomized controlled study examined 635 patients with a history of colorectal cancer treated with 325 mg of daily aspirin; it showed a significantly reduced risk of recurrent adenomas in the treated

group,⁶⁵ with a RR of adenoma development 0.65 in this group (95% CI = 0.46 to 0.91). In addition, the time to recurrent adenoma was noted to be longer. Because adenoma development was still present in the treated group, routine surveillance was suggested. A second randomized trial compared the effects of placebo to 81 mg and 325 mg of daily aspirin in 1,121 individuals with a history of CRC.⁶⁶ The RR was 0.88 (95% CI = 0.81 to 1.13) for recurrent adenomas in the low dose aspirin group and 0.96 (95% CI = 0.81 to 1.13) for the high-dose aspirin group. Finally, a third controlled study investigated 238 patients with a history of CRC with the treatment of lysine acetylsalicylate against placebo.⁶⁷ The RR of recurrent adenoma was 0.73 (95% CI = 0.52 to 1.04) and the RR for larger adenomas (> 5 mm) was 0.44 in the treatment group (95% CI = 0.24 to 0.82; $p = 0.01$). The study lacked power to distinguish a dose-dependent protective effect.

The side-effect profile of aspirin is notable for gastrointestinal upset, bleeding, and even hemorrhagic stroke. This can make aspirin a less-attractive chemopreventive drug. Over 1250 patients with no history of colorectal carcinoma would need to be treated with aspirin for 10 to 20 years to prevent one CRC death. In a population of 800 individuals taking aspirin over a time frame of 4 to 6 years, at least one patient would have a major gastrointestinal bleed and another would have a hemorrhagic stroke.⁶⁸ Therefore, other drugs with better risk profiles are being targeted as chemopreventive agents. One class of drugs uses synthetically created nitric oxide donating agents to prevent the bleeding side effects of NSAIDs.⁶⁹ There are no human studies evaluating these drugs. COX-2 inhibitors may cause fewer serious side effects than aspirin and can be useful for chemoprevention studies.

The Prevention of Colorectal Sporadic Adenomatous Polyps Study is a randomized, double-blinded controlled study of 1561 subjects who had previous polypectomy.⁷⁰ This study compared celecoxib to placebo, and looked at the rate of adenoma development within the first 3 years of treatment. Thirty-three percent developed adenomas in the treatment group, compared with 49% in the control group (RR = 0.64; 95% CI = 0.56 to 0.75, $p = 0.001$). The difference between the rates of advanced adenoma development was also significant (RR = 0.49, 95% CI = 0.33 to 0.73; $p < 0.001$). The rate of serious cardiovascular events was not statistically significant. Similar results were demonstrated in the Adenoma Prevention with Celecoxib study.⁷¹ Patients were assigned to one of three groups: placebo, 200 mg and 400 mg of celecoxib twice daily. There was a significant difference in the recurrence of adenomas by 3 years in the groups dosed twice daily with celecoxib, 200 mg and 400 mg (RR = 0.67, 95% CI = 0.59 to 0.77, $p = 0.001$ and RR = 0.55, 95% CI = 0.48 to 0.64, $p < 0.001$, respectively). Serious

adverse events were not statistically different; however, celecoxib was associated with an increased risk of cardiovascular events.

The Cochrane Collaboration conducted a systematic review to determine the effects of NSAIDs for the prevention or regression of colorectal adenomas and carcinomas.⁷² The interventions included sulindac (a nonspecific NSAID), celecoxib (COX-2 inhibitor), and aspirin. The study found that subjects taking low-dose aspirin group developed significantly fewer recurrent adenomas after 1 to 3 years (RR = 0.77, 95% CI = 0.61 to 0.96). The treatment groups for sulindac or celecoxib had a greater proportional reduction in the number of recurrent adenomas as compared with control group. There was a moderate increase risk of cardiovascular events, but no significant difference in the recurrence of CRC.

There is evidence in other randomized trials and meta-analyses that demonstrates a moderate increase in cardiovascular events with the use of COX-2 inhibitors. Celecoxib and rofecoxib administration have been associated with death from a cardiovascular cause.^{72a,72b} Along with this increased risk, COX-2 inhibitors do not have a favorable cost-effectiveness ratio for chemoprevention of CRC. A recent analysis showed that chemoprevention as an adjunct to screening programs costs \$400,000 U.S. dollars per year of life saved, even in high-risk individuals.⁷³ This study concluded that COX-2 inhibitors are more costly and less effective than current CRC screening modalities.

CONCLUSIONS

Multiple investigators have attempted to identify the ideal chemopreventive agent for colorectal neoplasia. These studies are difficult for many reasons: the long lead time for the development of cancer, defining true dietary intake of micronutrients, dose effect variability, and the multifactorial nature of carcinogenesis. The well-described adenoma to carcinoma sequence is complex. This complexity allows for many potential targets for chemopreventive agents. Although none of the evidence for any specific agent is clear, it appears unlikely that any have significant adverse affects, with the exception of NSAIDs. The lack of significant differences among groups in many of the studies may be related to inadequate supplementation. Many of the studied agents may have other benefits, such as the prevention of osteoporosis, diverticulosis, or coronary artery disease that might justify their use independent of colorectal cancer prevention. The generally long lead time from adenoma degeneration to carcinoma that makes chemoprevention difficult to study is also the reason that screening and surveillance is effective. For patients at risk for sporadic colon cancers, the available data for chemoprevention with

calcium, vitamin D, folate, and fiber is difficult to interpret, the risks of supplementation appear to be small, and additional benefits may exist. The risk of NSAID use may outweigh the benefits for some patients, but there is good data to support their utility in colorectal cancer prevention. All patients should be encouraged to seek out appropriate screening in addition to any chosen dietary modifications or supplements for chemoprevention.

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