Chemoprevention of Colorectal Cancer: Dietary and Pharmacologic Approaches

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Colorectal cancer is a major cause of death in the United States, where it accounts for approximately 57,000 deaths per year. Thus, the prevention of this disease would have a significant impact on public health. Chemoprevention is defined as the use of natural or pharmacologic agents to disrupt the process of carcinogenesis. Substances explored as chemopreventive agents in colorectal cancer include: (1) the nonsteroidal anti-inflammatory drugs (NSAIDs), which may inhibit the evolution and formation of adenomas by their inhibition of cyclooxygenase and decrease of prostaglandin synthesis; (2) antioxidants, such as vitamin E or C, which may modulate carcinogenic substances; and (3) folate and calcium, which may interfere with tumor cell growth and replication. Dietary intervention can be accomplished by decreasing fat intake and increasing fiber consumption, both of which have been linked to a lower incidence of colon cancer in multiple epidemiologic studies. This field is continuing to evolve. Hopefully, ongoing research efforts will offer a better understanding of the role of these and other substances in chemoprevention. This article summarizes the available data regarding dietary and pharmacologic approaches to colorectal cancer chemoprevention. [ONCOLOGY 1(13):89-98, 1999]

Introduction

Colorectal cancer is the third most prevalent cancer and third most frequent cause of cancer death in the United States.[1] Evidence suggests that colorectal cancer arises from preexisting adenomatous polyps.[2] Many of the current colorectal prevention strategies focus on the identification and removal of these premalignant lesions. Given the morbidity and mortality of colon cancer, as well as the number of individuals at high risk for this cancer (Table 1), chemopreventive interventions directed toward preventing the formation and development of colorectal carcinomas and adenomas could have significant public health benefit.[3]

Cancer development is a continuous process that occurs over several years, during which time damage to numerous regulatory genes eventually may result in premalignant, malignant, and then metastatic disease. Thus, chemoprevention may target various or even multiple stages in the cancer process (Table 2).

This article summarizes much of the available data regarding dietary and pharmacologic approaches to colorectal cancer prevention. Specifically, it addresses the effects of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, dietary fiber and fat, calcium, folate, and vitamins.

Aspirin and NSAIDs

Potential Mechanisms of Cancer-Preventing Effects

Experiments in human and animal models have shown that tumors produce large amounts of prostaglandins (particularly, prostaglandin E\textsubscript{2}).[4] The synthesis of prostaglandins is limited by cyclooxygenase. Nonsteroidal anti-inflammatory drugs reversibly interrupt prostaglandin synthesis by inhibiting cyclooxygenase. Aspirin works differently from NSAIDs. It acetylates prostaglandin H synthase and thereby irreversibly inactivates cyclooxygenase. Early studies in rodents demonstrated that administration of NSAIDs several weeks after a carcinogen prevented colorectal carcinoma.[5]

Nonsteroidal anti-inflammatory drugs may prevent tumor formation by their actions on prostaglandins, which may have an immune-modulating effect. High levels of prostaglandin E\textsubscript{2} may suppress the immune system, which keeps malignant cells in check. Nonsteroidal anti-inflammatory drugs reduce the production of prostaglandin E\textsubscript{2}.[6] An alternative prostaglandin-based theory suggests that inhibition of cyclo-oxygenase prevents formation of free radicals, which could damage cells and lead to malignant transformation.[7]

Alberts et al[8] studied the effect of different NSAIDs on colon tumor formation and also evaluated
prostaglandin E₂ levels in an azoxymethane-induced colon carcinogenesis rat model. In this model, a regimen of sulindac and piroxicam reduced the number of tumors per rat. The same investigators also studied a novel agent, sulindac sulfone, that lacks antiprostaglandin synthase activity. Rats treated with sulindac sulfone had a reduced number of tumors. Sulindac and piroxicam decreased levels of prostaglandin E₂, as compared with placebo, but sulindac sulfone alone did not. These findings suggested that NSAIDs may also prevent colorectal cancer by prostaglandin-independent pathways.

Other mechanisms that may explain the antiproliferative/antitumor effects of NSAIDs include: interference with membrane-associated processes, such as G-protein signal transduction and transmembrane calcium influx, and inhibition of other enzymes, such as phosphodiesterase, folate-dependent enzymes, and cyclic adenosine 5' monophosphatase–dependent protein kinase, as well as enhancement of immunologic responses and of cellular apoptosis.[6]

**Clinical Studies of NSAIDs**

Wadell et al[9] detected a decreased number of rectal polyps in patients with familial adenomatous polyposis who took sulindac. The prophylactic effects of this drug were further supported by the subsequent demonstration of reappearance of polyps after therapy was discontinued.

Labayle et al[10] conducted the first randomized, placebo-controlled, double-blind, crossover study using NSAIDs in patients with familial adenomatous polyposis. The results of this study demonstrated a reduced number of polyps in the group receiving sulindac, as compared with the control group. The effect of sulindac disappeared when the therapy was discontinued.

Giardello et al[11] conducted a randomized, double-blind, placebo-controlled trial of oral sulindac vs placebo in 40 patients with familial adenomatous polyposis. Patients in the sulindac group had significantly fewer polyps at 9 months than the control group. In fact, patients in the sulindac group had a 44% decrease in the total polyp number from baseline levels.

**Clinical Studies of Aspirin**

Human studies evaluating the use of aspirin in colorectal polyp chemoprevention have shown a promising reduction in rates of colorectal cancer as well. In a prospective, cohort study conducted by Giovannucci et al[12] 51,529 US health professionals 40 to 75 years of age responded to a mailed questionnaire on use of aspirin and other NSAIDs. The regular use of aspirin (ie, more than two times per week) correlated with a lower risk of colorectal cancer (relative risk [RR], 0.68; 95% confidence interval [CI], 0.52 to 0.92).

In another cohort study that followed 121,701 US female registered nurses, Giovannucci et al again demonstrated a statistically significant reduction in colorectal cancer risk among subjects who took aspirin consistently for 20 years.[13] One concern raised about the results of this study was the possibility that the beneficial effect may have been a consequence of earlier detection resulting from aspirin-induced gastrointestinal bleeding.

Thun et al surveyed a cohort of 622,424 adults about medication use from 1982 to 1988. More frequent aspirin use was correlated with a decrease in death from colon cancer.[14]

The Physicians' Health Study was a prospective, randomized trial assessing the effects of aspirin, 325 mg on alternate days, and beta-carotene vs placebo on the incidence of cardiovascular disease and cancer in 22,000 US male physicians. The study was terminated early because the men in the aspirin group experienced fewer myocardial infarctions than did the men in the control group. The incidence of colorectal tumors in the aspirin group was not decreased. However, the study lasted only 5 years. Therefore, the duration of treatment and follow-up may not have been sufficient to detect an effect on colon cancer incidence.[15]

A recently published follow-up analysis of the study, with a mean follow-up of 12 years, also showed no association between the use of aspirin and the incidence of colorectal cancer.[16]

**Clinical Studies of COX-2 Inhibitors**

The discovery that overexpression of the gene for cyclooxygenase type 2 (COX-2) is an early, central event in colon carcinogenesis has led to the investigation of COX-2 inhibitors as potential chemopreventive agents.[17] Cyclooxygenase type 2 appears to be distributed only in inflamed tissues and affects cell proliferation, cell adhesion, tumor growth, and immune responsiveness. Some investigators have previously reported increased COX-2 expression in human colorectal adenocarcinomas, as compared with normal adjacent colonic mucosa.[18]

In an experiment evaluating rats for aberrant crypt formation (a commonly accepted preneoplastic lesion), administration of either a COX-2 inhibitor or sulindac significantly suppressed the total number of aberrant crypts, compared to placebo.[19] Other studies using tissue culture support the concept that overexpression of COX-2 leads to increased expression of BCL-2, which can lead to resistance to apoptosis.[20]
The role of COX-2 in intestinal tumorigenesis was also demonstrated in a study comparing mice genetically deficient in both the COX-2 and adenomatous polyposis coli (APC) gene with mice defective in APC alone. The mice with the double defect had a marked diminution in the number of intestinal polyps.[21]

In concordance with these findings, human studies have revealed that colon cancer cell lines have increased amounts of COX-2 messenger RNA.[18] Cyclo-oxygenase type 2 selective inhibitors are particularly promising in that they may prove to be potent chemopreventive agents that have minimal toxicity.

**Summary**

Overall, these studies support a potential role for aspirin and NSAIDs in the prevention of colorectal carcinoma. At present, the use of aspirin or NSAIDs is not widely recommended for the prevention of colorectal cancer because better information is needed about the duration of therapy, dose, and possible adverse effects. It is also unknown whether a particular NSAID affords better protection than any others.

Perhaps future studies, such as an ongoing Cancer and Leukemia Group B (CALGB) Cooperative Group trial, will help clarify the use of aspirin in colorectal chemoprevention. After curative surgical resection, this phase III trial will randomize approximately 900 patients with a history of colorectal cancer to either aspirin (325 mg) or placebo, one pill daily for 3 to 4 years. The goal of the study is to observe any effect of aspirin on the development of new adenomas and cancer in such patients.

**Calcium**

Epidemiologic and experimental findings indicate an association between high calcium and vitamin D intake and decreased risk for colorectal cancer.[22,23] Increased levels of calcium in tissue have been shown to decrease cell proliferation and induce normal cell differentiation, whereas low levels of intracellular ionized calcium contribute to cellular proliferation.[24]

**Possible Mechanisms of Cancer-Preventing Effects**

Several theories exist as to how calcium may decrease the risk of colon cancer. Calcium may act by binding fatty and bile acids. The typical high-fat western diet (100 to 150 g/d of fat) produces hyperproliferative changes in the colonic mucosa of humans and rodents. These hyperproliferative changes are induced, in part, by the toxic effects of increased bile and fatty acids on the colonic epithelium; they may also represent compensatory hyperproliferation by the colonic epithelial cells aimed at providing repair and regeneration.[25] Calcium may inhibit colon cancer by binding to fatty and bile acids in the lumen of the colon, forming insoluble calcium complexes, and by inducing terminal differentiation of colonic epithelial cells.[26]

Studies in humans have shown a possible relationship between calcium supplementation and a decrease in epithelial cell hyperproliferation.[27] An increased calcium concentration may also directly inhibit the development of malignancy by inhibiting the proliferation of pluripotent stem cells in colonic crypt epithelium.[28] It has been hypothesized that there is a calcium gradient concentration differential along the crypt. This gradient could provide a signal to calcium receptors in colonic cells and trigger different set points in the cell-cycle processes of the colonic crypt cells, as well as providing stability to the cells in the crypt. Therefore, increasing the calcium concentration may arrest and modulate crypt cell proliferation. Disabling or losing calcium receptors along the crypt cells could promote colon carcinogenesis as the responsiveness of cells to the antiproliferative properties of calcium is lost.[29]

**Clinical Studies**

Clinical trials have not borne out this hypothesis, however. A randomized, double-blind, placebo-controlled trial conducted by Bostick et al failed to detect any difference in epithelial cell proliferation rates between the control and calcium arms.[30] A study done in Norway showed no protective effect of calcium in combination with vitamins on adenoma recurrence or growth.[31] Similarly, Rooney et al noted no effect of calcium on adenoma incidence or mucosal proliferation after 2 years of follow-up.[32]

**Summary**

At present, the role of calcium in colon carcinoma prevention is unclear. However, additional ongoing studies are evaluating the chemopreventive effects of calcium. These include a randomized, phase III study by Baron (Dartmouth College), which is comparing the effects of 3 years of calcium carbonate (1,200 mg/d) and on colonoscopy-proven polyp recurrence.[33] and a multicenter, randomized, placebo-controlled European study by Faivre et al aimed at testing the efficacy of oral calcium supplementation (2 g/d) in preventing adenoma recurrence.[34]
Fat

Epidemiologic Studies
Dietary factors are thought to be an important cause of colon cancer. Many hypotheses on the etiology of colon cancer were generated from epidemiologic studies and clinical observations. For example, Doll and Peto suggested that differences in diet may account for approximately 90% of the variation in rates of colon cancer among countries.\[35\] Other groups have found that per capita consumption of dietary fat correlates with the incidence of colon cancer.\[36,37\]. In a review of colon cancer epidemiology, Potter et al evaluated 13 epidemiologic studies focusing on the associations between fat, meat, and protein consumption and colon cancer. Of the 13 studies, 12 demonstrated correlations between increased fat intake and mortality or incidence of colorectal cancer.\[38\] Only the study by Jensen et al failed to demonstrate such an association.\[39\] The scientific basis for the dietary prevention of large bowel neoplasia in humans has not been well established.\[40\] Drasar and Irving evaluated dietary information from 37 countries and found that colorectal cancer incidence was highly associated with animal fat intake.\[41\] Results from some analytical studies, including case-control and cohort studies, corroborate the findings of the epidemiologic studies with regard to fat intake and colon cancer. One prospective study with 20 years of follow-up demonstrated an inverse association between the intake of saturated fats and the risk of colon cancer among Japanese-Hawaiian men.\[42\] Likewise, the Nurse’s Health Study demonstrated that a higher consumption of red meat and fat from animal sources was associated with an increased incidence of colon cancer.\[43\] On the other hand, a randomized, prospective study from Chicago that followed 2,107 subjects for 19 years showed no association between fat intake and colon cancer.\[23\] Overall, the results of epidemiologic studies are suggestive but do not conclusively define an association between dietary fat and colon cancer.

Potential Mechanisms of Cancer-Promoting Effects
Several mechanisms have been proposed to explain how fat intake might increase the risk for colorectal carcinoma. Newmark et al\[26\] suggested that fatty and bile acids cause irritation of the colonic epithelium, leading to a compensatory increase in the rate of cellular proliferation. This, in turn, causes cells with abnormal DNA to produce altered progeny, leading to malignancy (Table 3). Another more recently described mechanism for the role of fat in colon carcinogenesis involves an interaction among fat, bile acids, and bacteria. This interaction produces excess intraluminal diacylglycerol, which subsequently mimics and/or amplifies cell-replication signals.\[44\] Recent studies in rats demonstrated that a diet containing high levels of high-fat corn oil promoted colon tumorigenesis (by increasing ras-p21 expression), and a diet containing high levels of high-fat fish oil inhibited colon tumorigenesis (probably by post-transcriptional modification and membrane localization of ras-p21).\[45\]

Studies of Dietary Fat Modification
Two large institutional studies have attempted to describe the relationship between fat and the incidence of colorectal adenomas, which are premalignant lesions. The Australian Polyp Prevention Project, a prospective, randomized trial, involved 424 patients with a history of resected colorectal adenomas. The goal of the study was to determine the effect of reducing dietary intake of fat (to 25% of total calories) and supplementing the diet with wheat bran and beta-carotene for 4 years on the incidence of recurrent adenomas. The study revealed no evidence that any intervention protected against adenoma recurrence. Further analysis revealed that subjects on a low-fat and high-wheat-bran diet had a significant (P = .03) decrease in the formation of large adenomas (> 10 mm). Overall, however, the study did not convincingly support the hypothesis that these dietary modifications alter large-bowel risks.\[40,46\] This could have been secondary to the small sample size and timing of colonoscopies. A study from Canada also explored the effect of diet on adenoma recurrence. In this study, 201 men and women with prior colorectal adenomas were randomized either to receive counseling on a low-fat (< 50 g/d), high fiber (50 g/d) diet or to continue their usual western diet. Follow-up colonoscopy was performed in 165 subjects an average of 2 years after study enrollment. A relative risk of 1.2 (95% CI, 0.6 to 2.2) for adenoma recurrence was observed in the intervention group, as compared with the treatment group.\[47\]

Summary
At present, it is unclear whether dietary modifications aimed at reducing fat consumption can prevent colorectal adenomas. The Polyp Prevention Trial I is an ongoing, multicenter, randomized, controlled trial sponsored by the...
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Published on Cancer Network (http://www.cancernetwork.com)

National Cancer Institute (NCI) that is evaluating the effect of a low-fat, high-fiber, high-fruit-and-vegetable diet on large bowel adenoma recurrence. The dietary intervention consists of a goal of 20% of daily caloric intake from fat, 18 g of dietary fiber per 1,000 kcal/d, and five to eight servings of fruit and vegetables per day. The study should complete follow-up in 1998, after 4 years of dietary intervention. On the basis of sample size (approximately 2,079 participants), this trial has sufficient statistical power (90%) to detect a 24% reduction in adenoma recurrence, and hopefully will provide more conclusive information about these relationships.[48]

**Fiber**

**Epidemiologic Studies**

In the early 1970s, Burkitt observed that colon cancer was rare in Africans, whose diets are high in unrefined foods, as compared with people from industrialized countries, whose diets generally contain less fiber. Based on this observation, he proposed that dietary fiber may protect against cancer of the large bowel.[49]

Another population-based comparison was made by Reddy et al in 1978. They found that even though residents of both New York City and Finland consumed high-fat diets, the incidence of colon cancer was decreased in the Finnish population, presumably secondary to their higher intake of fiber, leading to increased stool bulk.[50]

Many animal studies support the hypothesis that diets high in fiber prevent colon cancer, although the results are mixed.[51]

In 1990, Trock et al reported the results of a meta-analysis of the available epidemiologic studies concerning colorectal cancer and fiber intake. They found that diets rich in fiber and vegetables were associated with a lower risk of colon cancer.[52]

Howe et al analyzed the combined results of 13 case-control studies examining the relationship between dietary intake of fiber, beta-carotene, and vitamin C and colorectal cancer. They calculated relative risk by quintiles of intake. Those in the highest quintile of fiber intake had about half the risk of colorectal cancer as those in the lowest quintile. Of note, when analyzed individually, 8 of the 13 studies showed a statistically significant decrease in colon cancer in the groups with high-fiber intake.[53]

**Possible Mechanisms of Anticarcinogenic Effect**

Several potential mechanisms by which dietary fiber may have an anticarcinogenic effect in the colon have been proposed. One hypothesis holds that bile acids may be promoters of neoplasia,[54] and that fiber binds bile acids in the gut.

Fiber may also dilute the effects of potential dietary carcinogens by increasing stool bulk, which decreases the time during which they are in contact with the intestine.

A third possible mechanism is that fiber may act as a substrate for bacterial fermentation.

Fermentation results in an increase in bacterial mass and the preferential production of short-chain fatty acids, which may be less carcinogenic than longer-chain fatty acids.

Another indirect effect of fiber may be mediated by a lowering of gut pH, resulting in a decreased rate of conversion of primary to secondary bile acids via pH-dependent bacterial enzymes (Table 4).[55]

**Prospective Studies**

Recent prospective studies have evaluated the association between fiber consumption and colorectal cancer. The Nurses’ Health Study showed a modest, nonsignificant negative correlation between cancer and fiber intake.[43]

The Iowa Women’s Health Study, a prospective, population-based study, examined the incidence of colon cancer in postmenopausal women after 5 years of follow-up. The association of decreased risk of colon cancer and dietary fiber intake was weak, not reaching statistical significance.[55]

**Randomized Studies**

Randomized studies evaluating the role of fiber in the prevention of colorectal adenomas have had mixed results. A randomized study by De Cosse and coworkers evaluated the effect of high-dose wheat bran fiber and vitamins C and E vs low-dose wheat bran fiber plus placebo vs low-dose wheat bran and vitamin supplements on rectal polyps in 58 patients with familial adenomatous polyposis.[56] An intention-to-treat analysis revealed a nonsignificant reduction in adenoma number and size in the retained portion of the rectum in the high-fiber group compared to the other groups.

The Health Professionals’ Study prospectively evaluated patients who were found to have adenomas of the descending and sigmoid colon and rectum on sigmoidoscopy. All sources of dietary fiber (fruits, vegetables, and grain) were protective against the development of adenomas. The study’s
results support the hypothesis that high intake of dietary fiber and low consumption of animal or saturated fat substantially reduce the risk of colorectal adenomas.[57]
A group from Toronto reported that, after an average follow-up of 2 to 4 years, the relative risk of adenoma recurrence was 1.2 among individuals who received 12 months of dietary counseling, as compared with those who did not receive any intervention.[47] When evaluated by gender, women who underwent counseling had a reduced risk of adenomas (RR, 0.5), but their male counterparts actually had an increased risk (RR, 2.1).
In an Australian study,[46] a diet calling for 11 g/d of wheat bran and < 25% total calories from fat did not reduce the incidence of new adenomas.

Summary
Overall, the clinical evidence and epidemiologic data suggest a protective effect of a diet high in fiber against colorectal carcinoma/polyps. In addition, ongoing trials are evaluating the role of fiber in colorectal cancer. The European Cancer Prevention Colon Group Study is evaluating the effectiveness of supplementation with ispaghula (a type of fiber) and calcium in decreasing adenoma recurrence.[34] Another large study being conducted in the United States is the Polyp Prevention Trial I (described above in the section on fat).[48] Results of these ongoing trials, which should be available in the next few years, will help to better define this relationship.

Vitamins
The antioxidant vitamins, in particular, vitamin E, vitamin C, and beta-carotene, may have a role in the prevention of cancer in humans.[58,59] These antioxidants have been indirectly linked to a decreased risk of colorectal cancer in many studies that have examined dietary intake.[58,60]

Potential Mechanisms for Anticarcinogenic Effects
Basic research has demonstrated that beta-carotene can trap organic free radicals and/or deactivate excited oxygen molecules, both of which may have an anticancer effect by preventing tissue damage.[61] Beta-carotene also may prevent genetic changes by preventing DNA damage directly induced by free radicals. Enhanced cell-to-cell communication has been described with the use of beta-carotene; this would restrict clonal expansion of initiated cells.[62]
Vitamin E functions as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids, which may be carcinogenic. It has also been suggested that vitamin E supplementation may increase production of humoral antibodies and enhance cell-mediated immunity.[63]
Vitamin C acts as a free radical scavenger, thus possibly protecting genetic material from the initiation and promotional stages of carcinogenesis. Research has also demonstrated that vitamin C has an effect on the immune system and, thus, enhances tumor immune surveillance in the promotion and progression of cancer.[64]

Studies in the General Population
Since vitamin intake may be modified by changing the diet and vitamin supplements are considered to be “natural” rather than pharmacologic interventions, vitamins are seen by many as attractive means of preventing cancer. Several studies have addressed this issue.
The Iowa Women’s Health Study, a recent large cohort study, examined the relationship between dietary vitamins A, C, and E and colorectal cancer incidence. Vitamin E was associated with a decreased cancer risk, but vitamins A and C were not.[65]
As mentioned above, the Physicians’ Health Study, a randomized, double-blind, placebo-controlled trial, examined the effects of aspirin and beta-carotene on the prevention of cardiovascular disease and cancer. After 12 years of beta-carotene or placebo, no difference in the incidence of colorectal malignancy or overall malignancy (RR, 0.98; 95% CI, 0.91 to 1.06) was found between groups.[66] 
In a large double-blind, placebo-controlled, chemoprevention study from Finland, 29,133 males were randomized to receive vitamin E and beta-carotene (alone or in combination) or placebo and were followed for the occurrence of various cancers. After a follow-up of 5 to 8 years, (median, 6.1 years), patients receiving beta-carotene experienced no decrease in cancer occurrence (including colorectal cancer) and exhibited an 8% excess in overall mortality that was statistically significant (P = .02). Patients in the vitamin E group did show a nonsignificant,16% reduction in colorectal cancer incidence.[67]

Studies in Patients With Colon Polyps
The role of vitamin supplements in colon cancer prevention also has been investigated in patients with a history of colonic polyps. Most of these studies do not convincingly demonstrate a benefit.
In 1982, Bussey et al published the results of a randomized, double-blind trial evaluating the effect of vitamin C (3 g/d) in 36 patients with adenomatous polyposis coli who had undergone colectomy and
ileorectal anastomosis. They found a nonsignificant reduction in the number of rectal polyps at 9 and 12 months of follow-up in patients taking vitamin C, as compared with those taking placebo. Although the reduction in the number of rectal polyps did not reach statistical significance, the difference in polypl area was significant at 9 months of follow-up (P < .03).

Another randomized, double-blind, placebo-controlled study of 58 patients with familial adenomatous polyposis by De Cosse et al. compared three treatments: (1) low-wheat bran plus placebo, (2) low-wheat bran plus vitamins C and E, and (3) high-wheat bran supplementation plus vitamins C and E. The analysis revealed a nonsignificant trend toward decreased polyps relative to baseline colonoscopy in the high-fiber group (P < .97). The vitamin supplementation groups showed a nonsignificant reduction in the number of rectal polyps, as compared with the no-vitamin group.

A Canadian study by McKeown-Eyssen et al. published in 1988 investigated the use of vitamin C plus vitamin E vs placebo in patients with a history of colonic polyps. In 185 subjects followed over 2 years with periodic colonoscopy, no difference was found between treatment groups with respect to adenoma recurrence.

A similar finding was noted by Greenberg et al. In their study, 864 patients with history of large bowel adenoma, were randomly assigned to: (1) placebo; (2) beta-carotene plus placebo; (3) vitamins C and E plus placebo; or (4) beta-carotene plus vitamins C and E. Colonoscopy was performed 1 and 3 years after the baseline study. No differences were seen among the treatment groups with regard to the number of new adenomas. The Oslo study was a randomized, controlled study of 116 polyp-bearing patients that examined the effects of antioxidants and calcium vs placebo on recurrence and growth of colorectal polyps. The study failed to demonstrate an advantage of various combinations of beta-carotene, vitamin E, vitamin C, selenium, and calcium on adenoma re-currence or growth after yearly colonoscopy over a 3-year period.

In contrast, a positive study from Italy was reported by Roncucci et al. They randomized 209 individuals after polypectomy to one of three treatment groups: (1) vitamins A, E, and C; (2) lactulose; or (3) no treatment. Subjects were followed for 18 months after their initial postoperative colonoscopy. The group treated with vitamins showed a significant reduction in the incidence of adenomas compared to the no-treatment group (P < .002).

Summary
Despite this last study, overall, vitamins and antioxidants have not been convincingly shown to reduce adenoma or cancer occurrence. Consequently, at present there is no support for their use in colon cancer prevention.

Folate
Epidemiologic studies suggest an inverse correlation of dietary folate with colorectal neoplasia. In a study by Lashner et al, low levels of red cell folate were associated with an increased risk of adenomas and cancer in patients with ulcerative colitis. Another case-control study by Bird et al revealed a weak association between red cell folate levels and recurrence of polyps in the rectosigmoid area.

Potential Mechanisms of Anticarcinogenic Effect
The role of folate in cancer chemoprevention is also currently being studied, and its mechanism of action is a matter of debate. One theory focuses on the role of folate in DNA methylation. Several studies have noted abnormal DNA methylation patterns in colorectal adenomas and adenocarcinomas. The transfer of a one-carbon group from 5-methyl-tetrahydrofolate permits the transformation of homocysteine into methionine, a precursor of S-adenosylmethionine (Adomet). Adomet is a major methyl-group donor, and interference with its production by inadequate folate could lead to abnormalities in DNA methylation.

A study by Cravo et al supports this theory. They demonstrated that pharmacologic doses of folic acid reversed genomic DNA hypomethylation present in the normal-appearing rectal epithelium of individuals harboring either colorectal adenomas or cancer.

Clinical Study
In a recent study, Glynn et al followed 29,133 male smokers in Finland for an average of 5 to 8 years and evaluated them for the effects of 50 mg/d of alpha-tocopherol and 20 mg/d of beta-carotene on the occurrence of various types of cancer. Serum folate was not significantly
associated with either colon or rectal cancer. The study did, however, suggest that high dietary folate combined with a low-alcohol, high-protein diet may have a protective effect against colon cancer.

**Summary**

Further studies are needed to clarify the role of folate in the chemoprevention of colorectal cancer. Some data support the hypothesis that greater intake of folate may decrease the risk of colorectal cancer by affecting methyl donors, but evidence is insufficient at present.

**Conclusions**

At present, we believe that it is premature to make recommendations concerning the use of NSAIDs, calcium, folate, and antioxidant vitamins as chemopreventive agents in colorectal carcinomas. Much of the data from epidemiologic studies suggest that a diet that is low in fat and high in fiber and that includes substantial amounts of vegetables and fruits may help prevent colorectal cancer. Some of the recommendations for the prevention of cancer by the World Cancer Research Fund include:

1. Choose predominantly plant-based diets rich in a variety of vegetables and fruits, legumes and minimally processed starchy staple foods.

2. Avoid being underweight or overweight and limit weight gain during adulthood to less than 11 pounds.

3. Maintain physical activity. If occupational activity is low or moderate, take an hour’s brisk walk or similar exercise daily, and also exercise vigorously for a total of at least 1 hour per week.

4. Eat 15 to 30 ounces of five or more portions per day of a variety of vegetables and fruits, all year-round.

5. Eat 20 to 30 ounces or more than seven portions per day of a variety of cereals (grains), legumes, roots, tubers, and plantains. Preferably choose minimally processed foods.

6. Alcohol consumption is not recommended. If consumed at all, limit alcoholic drinks to fewer than two drinks a day for men and one for women.

7. If eaten at all, limit intake of red meat to no more than 3 ounces daily. Preferably choose fish, poultry, or meat from nondomesticated animals in place of red meat.

8. Limit consumption of fatty foods, particularly those of animal origin. Reduce total fat intake to less than 25% to 30% of total calories and saturated fat to less than 10% of total calories.

9. Limit consumption of salted foods and use of cooking and table salt. Use herbs and spices to season foods.

10. Do not smoke or chew tobacco.

In the future, the utilization of drugs or natural products alone or in combination with dietary modifications may effectively control the development of colorectal adenomas and carcinomas. There is still much to be accomplished in this area despite the multitude of studies that have been conducted to date (Table 5). Ongoing clinical trials continue to address the usefulness of colorectal chemopreventive agents. Further knowledge of the mechanisms of carcinogenesis will hopefully lead to the development of agents that are specific, effective, and nontoxic. Also, the introduction of new surrogate end point biomarkers (such as fecal carcinoembryonic antigen; mucosal polyamine measurements; vas-p21 oncoprotein expression; fecal PKC beta II and beta mRNA levels; and GST activity and ODC activity) is a promising area toward which research in this field may be directed.

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