

## Prevention of Colorectal Cancer: Diet, Chemoprevention, and Lifestyle

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This article describes primary prevention of colon cancer (ie, interventions that do not involve the removal of diseased tissue or chemotherapy for known colon cancer). Although screening with ablation of adenomas has a significant impact on colon cancer [1], the logistics of screening are complicated [2–4]. These issues are addressed in accompanying articles. This article focuses on preventing the initiation and promotion of neoplastic growth, particularly with dietary measures. A goal of dietary epidemiology is to identify chemopreventive agents and strategies. The effects of diet are analyzed by observational approaches and experimental dietary, nutritional, or chemopreventive interventions.

The adenomatous polyp or adenoma is an important surrogate endpoint for colon cancer [5–7]. The adenoma often remains indolent for years, so prevalence can be analyzed. The adenoma is common among older individuals, especially those more than 50 years old. As many as 30% to 50% of individuals older than 50 years of age harbor one or more adenomatous polyps [8].

The adenoma is usually asymptomatic and is generally discovered only during routine screening. The adenoma is the key premalignant lesion that leads to colon cancer [5,6]. Many, if not most, adenomas never progress to colon cancer, but most colon cancers emerge from adenomas (adenoma-to-carcinoma sequence). As the adenoma is more common than colon cancer and new adenomas develop in individuals who have had previous adenomas that were ablated, studies of interventions designed to prevent colon cancer usually analyze the adenoma as a surrogate marker. This strategy is based on preventing colon cancer by preventing adenomas. The weakness of this strategy is that the formation of adenomas does not guarantee that an individual is at increased colon cancer risk, but this weakness has not deterred investigators from studying the adenoma as a surrogate marker for human colon cancer.

The proportion of colon cancer attributable to genetic syndromes—familial adenomatous polyposis and hereditary nonpolyposis colon cancer—seems to be small, so that screening for these two syndromes is unlikely to substantially reduce the incidence of colon cancer. Although these syndromes are powerful

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predictors of colon cancer, they are uncommon and contribute a relatively small proportion to the total colon cancer burden.

## OBSERVATIONAL EPIDEMIOLOGY

The epidemiologic literature is replete with studies that claim that various dietary factors affect colon cancer risk, either by reducing or increasing the risk. This epidemiologic literature must be read critically. The possibility of small-sample variation and of outright bias in studies is great. In addition, the study design—the means by which data were collected—may affect the nature and quality of the findings. A historically important study design has been the ecologic method. In this design, political entities, rather than individuals, are the unit of analysis. The cancer risk or mortality of several countries is analyzed together with the typical exposure level within each country; the analytic task is to then correlate each country's cancer risk or mortality with the country's mean exposure level [9].

A better and more common study design is the case-control method, in which a sample of cases diagnosed with the disease is enrolled along with a sample of controls. The prior exposure of cases versus controls is then analyzed. If a given exposure increases the risk for disease, those who have the disease should have experienced greater exposure than the controls [10]. Case-control studies are efficient and are relatively inexpensive to perform.

The cohort method is regarded as the scientifically most valid observational epidemiologic study design. The exposure of each member of an assembled cohort is assessed using a standardized measure, such as a questionnaire [11]. Occasionally, the exposure data are obtained from a biologic sample, such as blood. After exposure data are procured, the cohort is followed over time, and the analysis considers whether those who have greater exposure to a putative risk factor experience a greater incidence of the disease. Because the risk for a particular cancer within a brief period is small, cohort studies must be large, and the cohorts must be followed for several years.

## CLINICAL TRIALS

Several dietary hypotheses have emerged from observational studies, such as case-control and prospective cohort studies; in almost every case, however, attempts to experimentally validate these findings have failed.

Because of the ambiguities of observational studies, researchers have increasingly instituted prevention trials to identify means of preventing colon cancer. A key element in these trials is random assignment to one intervention or another, or nonintervention, so that intervention is independent of any other characteristic of trial participants. Experimental and control subjects tend to be alike in baseline height, weight, smoking, social class, physical activity, and other characteristics.

Prevention trials directly test an intervention; they evaluate whether dietary, nutritional, or chemopreventive intervention alters the risk for an individual. Observational studies merely focus on the association between dietary practice

or nutrient exposure and risk for disease (ie, whether variance in practice or exposure predicts elevated or diminished disease risk). Analyses based on cross-sectional variance in practice assume that changing an individual's exposure can alter individual risk. If, for example, greater red meat consumption predicts elevated risk for colon cancer, individuals who have above-average intake should decrease their colon cancer risk by decreasing their red meat consumption. This assumption, although reasonable, is largely unproved. Furthermore, the length of time required for the risk to change is generally unknown and would be daunting to accurately specify empirically.

A complication of prevention trials involving altered behavior or environmental exposure is that they often cannot be administered under conditions of blinding: subjects know whether they are assigned to an intervention. In addition, behavioral change is difficult to implement and to maintain long term. The Polyp Prevention Trial required subjects to adopt and maintain a dietary change for 4 years [12]. Recidivism among experimental subjects diminishes the differences between them and control subjects. Behavioral changes rarely happen in isolation. The goal of experiments is often to identify the impact of a single change, such as smoking cessation, increased physical activity, or a dietary change.

## DIET AND COLON CANCER PREVENTION

The analysis of dietary data is highly complex. Hundreds of food items are commonly consumed in Western societies, and the number of dietary elements—macronutrients, micronutrients, and minerals—extracted from foods, is in the thousands. Analysis of these items is therefore complex.

### The Western Diet: Fat and Fiber

Dr. Burkitt [13] observed in 1971 that the diets and stools of the native peoples of South Africa were much different from those of Westerners and they had a different incidence of colon cancer. He proposed that the high fiber content of these peoples could protect against colon cancer. Formal analyses of ecologic data revealed strong positive associations of dietary fat, and strong negative associations of dietary fiber, with colon cancer risk [9]. An early case-control study indicated that a history of elevated dietary fat intake increased risk [14]. Although a study based on a large, hospital-based sample of cases and controls provided no evidence that dietary fat was associated with increased risk [15], an equally large and well-executed case-control analysis revealed a strong association of dietary fat with colon cancer risk [16]. One of the best studies of diet and colon cancer, the prospective Nurses Health Study, indicated that dietary fiber does not affect the risk for subsequent colon cancer [17]. Although some fruits and vegetables, which contribute fiber to the diet, may be protective, dietary fiber alone seems to have no impact on colon cancer risk [17].

Alberts and colleagues [18] directly tested Burkitt's provocative hypothesis in a double-blind, placebo-controlled clinical prevention trial. They randomized 1429 patients who had adenoma to a high-fiber versus a low-fiber

cereal supplement. Compliance with the study protocol was high. Recurrence rates among experimental and placebo subjects were virtually identical. Although experimental subjects were slightly less likely than placebo patients to take their supplement, adjustment for imperfect compliance made no difference; assignment to the high-fiber supplement did not affect the risk for recurrence.

Although interest in the role of dietary fat and fiber in the genesis of colon cancer has persisted, the accumulated evidence has been unconvincing. The strongest of the cohort studies indicates that dietary fat, per se, does not increase the risk for colon cancer [17,19], but that some foods that contribute fat to the diet, especially red meat, may increase the risk [19].

### Fruit and Vegetable Consumption

The analysis by Graham and colleagues [15] indicated that intake of cruciferous vegetables, such as broccoli, cabbage, and cauliflower, decreased the cancer risk. A subsequent report by Graham and colleagues [20], with a more detailed dietary assessment, showed cases consumed fewer fruits and vegetables than controls. Nonetheless, no association between cruciferous vegetable consumption and risk was observed. A recently published compendium of case-control studies indicated that cruciferous vegetable consumption was associated with a modest (15%) decrease in colon cancer risk [21]. Cohort and prospective studies provide stronger evidence that dietary cruciferous vegetable intake decreases the colon cancer risk by approximately 25% [21]. The evidence regarding colon cancer protection is stronger for cruciferous than for other vegetables. A meta-analysis of case-control studies suggests that fruit and vegetable consumption in general is associated with a slight decrease in the risk for colon cancer [22]. For example, fruit consumption is associated with a 13% decrease in colon cancer risk, and vegetable consumption is associated with a 40% decrease. The strength of the association is, however, variable. Furthermore, the cohort evidence is less compelling [22,23].

The Polyp Prevention Trial constitutes an important attempt to analyze the effect of dietary intervention among patients who have adenomatous polyps in preventing polyp recurrence [12,24]. The intervention achieved statistically significant changes in dietary practice, whereas the diets of the control subjects did not change, as confirmed by analysis of blood tests [12]. Nevertheless, dietary intervention had no impact on the recurrence of adenomatous polyps compared with control subjects, including the total number of adenomas, the number of adenomas by site, or the number of high-risk or advanced adenomas [12]. A 17-year follow-up revealed no impact of this 4-year dietary intervention on the total adenoma rate or colon cancer risk [25]. The Women's Health Initiative dietary intervention trial reported similarly disappointing results [26]. In this randomized trial of dietary intervention of some 48,000 women followed for an average of more than 8 years, the subsequent risk for colon cancer for experimental and control patients was virtually identical [26].

### Antioxidants

There is excellent evidence that oxidative stress contributes to the risks for chronic diseases, including cancers [27]. Whether this mechanism is important in colorectal cancer is not completely clear. It was hoped that antioxidant dietary constituents, including vitamins C and E and carotenoids, might protect against oxidative stress and thereby decrease cancer risk [28]. An important interventional trial reported no evidence of reduction of the risk for adenoma recurrence from administration of beta carotene and vitamins C and E, however [29]. Compliance with study medications, as reflected by blood nutrient levels, was extremely high.

### NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Interest in the use of nonsteroidal anti-inflammatory drugs stemmed from the observation that individuals who chronically used large amounts of aspirin had decreased mortality from colorectal cancer [30]. This finding was supported by other studies [31–33]. Subsequent reports based on clinical trials have generally supported this observation. In a study of 635 patients randomized to receive either 325 mg/d of aspirin or placebo after colorectal cancer surgery, the relative risk for adenoma among those randomized to aspirin was approximately 0.65 [32]. In a study of 1121 patients who had a history of adenoma randomized to receive placebo, 81 mg aspirin, or 325 mg aspirin daily, the relative risk for adenoma recurrence was 0.81 in the 81 mg group and 0.96 in the 325 mg group [34]. Why 81 mg/d of aspirin significantly decreased adenoma recurrence, while 325 mg/d did not, is puzzling [34]. Although these results are encouraging, the use of aspirin as a chemopreventive agent entails risks: as an anticoagulant it can lead to excessive bleeding, and as an inhibitor of cyclooxygenase 1 activity it can lead to intestinal bleeding. Other anti-inflammatory drugs were therefore studied [35,36]. These agents unfortunately have cardiovascular toxicity that renders them unsuitable for chemoprevention [37].

### SELENIUM

The trial by Clark and colleagues [38] of selenium supplementation among patients who had nonmelanoma skin cancer was partly motivated by ecologic data indicating that regions of the United States where ambient soil selenium levels were low had elevated risks for several cancers. This intervention resulted in a nearly 50% decrease in colon cancer risk among patients receiving selenium supplementation; unfortunately, the statistical significance of the decrease in risk was marginal because of the small number of patients in the study who developed colon cancer. Extended follow-up analysis of the data reveals that assignment to selenium supplementation was also associated with a decreased risk for developing adenomatous polyps [39]. Numerous animal studies have shown that selenium has antineoplastic properties [40]. In addition observational studies have revealed decreases in colon cancer risk among those who have elevated selenium intake [41].

## CALCIUM

Observational epidemiologic evidence suggests that calcium protects against colon cancer [42]. The [34] randomized, controlled trial reported by Baron and colleagues [34] provided even stronger evidence. The relative risk for adenoma recurrence among those assigned to receive calcium was 0.85, and the ratio of adenomatous polyps among experimental versus control patients was 0.76. Both effects were statistically significant. The decline in adenoma risk associated with calcium supplementation was only 15%, however. Whether this small decrease would justify widespread calcium supplementation is debatable. No subgroup of subjects was affected enough to alter the standard colon cancer screening schedule.

## FOLATE

Evidence derived from in vitro and in vivo models strongly suggests that folate should protect against colon cancer [43,44]. Baron and colleagues [45] in a cohort study conducted within a randomized clinical trial found that folate intake at baseline was associated with a statistically significant reduced risk for adenoma recurrence. Adjustment for likely confounders, for total energy, and for dietary fiber intake, however, obliterated this effect. On the other hand, alcohol intake, which diminishes folate levels, was associated with a greater than twofold increase in adenoma recurrence [46]. The reduction in risk with folate may be as high as 40%. In a study of male health professionals, a high dietary folate intake was weakly associated with a decreased risk for colon cancer [47]. A more recent study found that folate intake for more than 15 years was associated with a sizeable, statistically significant decrease in colon cancer. In these studies, alcohol intake was again associated with increased colon cancer risk, and this association was stronger than that for folate.

## LIFESTYLE

Several aspects of lifestyle, including body mass, physical activity, and smoking, have been analyzed as possible colon cancer risk factors.

### Body Mass

Elevated body mass, or obesity, partly represents energy balance, or the juxtaposition of energy intake and expenditure. On an ecologic level, Western industrialized countries have increased obesity and an increased colon cancer risk. The epidemiologic literature is relatively consistent: case-control and prospective studies show obesity is associated with increased risk [42]. The mechanisms of the association are not well understood; hormonal factors for women or insulin metabolism have been proposed [42]. Alteration of inflammatory processes is possible; Martinez and colleagues [48] reported a strongly positive association between body mass index and prostaglandin E<sub>2</sub>, a marker of inflammation and inflammatory responses. There have been no experimental evaluations of this association or whether weight loss can decrease colon cancer risk.

### Physical Activity

Physical activity, a component of energy expenditure and energy balance, may by itself be associated with decreased colon cancer risk [42]. Much of the recent literature has emphasized recreational physical activity [48,49]. The mechanisms of this effect are poorly understood. Martinez and colleagues [48] showed a statistically significant, positive association between rectal mucosal prostaglandin E2 levels and body mass, and a negative association between rectal mucosal prostaglandin E2 levels and physical activity.

### Smoking

The pathogenicity of tobacco smoking for pulmonary and urologic cancers and for heart and lung disease is well established and understood. Early studies of colon cancer did not show smoking to be associated with increased risk [50]. It now appears that the effects of smoking on colon cancer require decades of exposure. Only individuals who have long periods of smoking have increased risk for adenomatous polyps [41,42]; this risk may be increased as much as threefold. The increased risk for colon cancer may take even longer to manifest; competing causes of death may diminish the impact of smoking.

The association between smoking and colon cancer is not as strong as those between smoking and pulmonary cancers. Nonetheless, the effect is significant, and attempts to prevent colon cancer should include control of smoking. The risk for colon cancer among long-term smokers is approximately doubled [51,52]. Smoking thus increases the risk for colon cancer more than any known chemopreventive agent decreases the risk. The mechanisms of this association are poorly understood; carcinogenic smoking byproducts are carried in the blood and could infuse the colon, whereas smoke entering through the mouth could be ingested with food and transported to the colonic lumen.

## CHALLENGES FOR FUTURE PROGRESS IN COLON CANCER PREVENTION

Major questions concerning the etiology of colon cancer remain to be resolved. Two major exposure routes are possible: the fecal stream within the colonic lumen and transmission by way of the blood circulation to the colon. For example, the concentration of deoxycholate and related compounds in stool has received much attention [53]. Blood is the major, if not only, means by which compounds initiating and promoting neoplastic growth could be transmitted to many other tissues—breast, prostate, liver, brain. Factors transmitted by the circulatory system could be related to the cause, and hence to the prevention, of colon cancer. Clearly, further understanding of the etiology of colon cancer is needed.

Several options are available to prevent colon cancer. The most important is screening [1,2,4]. The costs of screening are considerable [4], however, and there are at present not enough trained medical personnel to screen the entire eligible population of the United States.

Diet may play a moderate role in colon cancer risk, but the effect of diet may be underestimated because of imprecise dietary measurements attributable to the complexity of the diet [54,55]. Short-term trials that alter intermediate biomarkers that are more sensitive than the adenoma to interventions may be necessary. The same logic needs to be applied to chemoprevention. Nonsteroidal anti-inflammatory drugs, calcium, and selenium have some individual effects that could be potentiated if added together. The current evidence is that the combined effect of all three agents is modest, compared with the effects of screening, or even those of smoking cessation.

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