Colon Cancer Prevention: Intervening in a Multistage Process (44177)

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Abstract. **Colorectal cancer, one of the most common human malignancies, is also one of the best understood. The epidemiology of this disease, and its relationship to environmental influences, particularly diet, has been extensively studied. New insights into the molecular biology and genetics of colorectal cancer also provide clues to its etiology, and high-risk populations that are most likely to benefit from preventive measures can be identified. Using this information, promising strategies for prevention of colorectal cancer are under investigation. These strategies include dietary modification, screening and adenoma removal, and antitumor agents from both natural and synthetic sources.** [P.S.E.B.M. 1997, Vol 216]

"An ounce of prevention is worth a pound of cure."
—old adage

"If I'd known I was going to live this long, I'd have started misbehaving earlier."
—George Burns

To prevent an undesired outcome, the cause of the outcome must be understood, or at least identified. The pursuit of colorectal cancer prevention, therefore, leads us to fundamental questions about the nature of this disease. How does colorectal cancer develop? What causes the malignant changes in the intestinal epithelium? What is the earliest evidence of cancer development, and are the early changes reversible? Because cancer is a complex, multifactorial process, the answers to these questions have been elusive, and prevention has been difficult to achieve.

This review begins by addressing what is known about the nature of colorectal cancer; how it develops; how early changes are identified. Following this is a brief discussion of the epidemiology of colorectal cancer, describing the known environmental influences in lower intestinal carcinogenesis. After outlining what is known about the causes of colorectal cancer, we will discuss the strategies for prevention that are based upon this knowledge.

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The Multistage Hypothesis: Redefining the Adenoma-Carcinoma Sequence

There is one central, unifying element of cancer etiology: genetic change. The common denominator in all theories of carcinogenesis is alteration of the cell's genome, either by direct damage from radiation or chemicals, integration of viral genomic sequences, or an inherited defect in DNA repair capacity. The study of cancer etiology is presently focused upon the molecular events required for malignant transformation, particularly the interplay between genetic and environmental influences in carcinogenesis.

Experience tells us that "what can go wrong, will." It is therefore instructive to study normal regulatory processes to understand the derangements that occur with carcinogenesis. To achieve homeostasis in tissues, renewable cell populations such as the colonic epithelium must perform four related functions. They must: (i) proliferate with proper timing and fidelity of DNA content, (ii) differentiate in a pattern consistent with normal function of the tissue, (iii) involute in a manner such that the proliferation and involution rates are balanced, and (iv) repair any damages to their DNA resulting from exposure to mutagens such as radiation, toxins, and transforming viruses (Fig. 1). A defect in any one of these functions can result in tumor formation.

The gastrointestinal epithelium is a complex microenvironment, made up of at least five different types of interrelated cells and characterized by a tightly regulated program of cell renewal, maturation, and death. The enterocyte is the primary functional cell of the intestinal mucosa. During its life span in the human large intestine, the enterocyte is produced from a stem cell in the colonic crypt, matures and migrates up toward the top of the crypt, and then be-

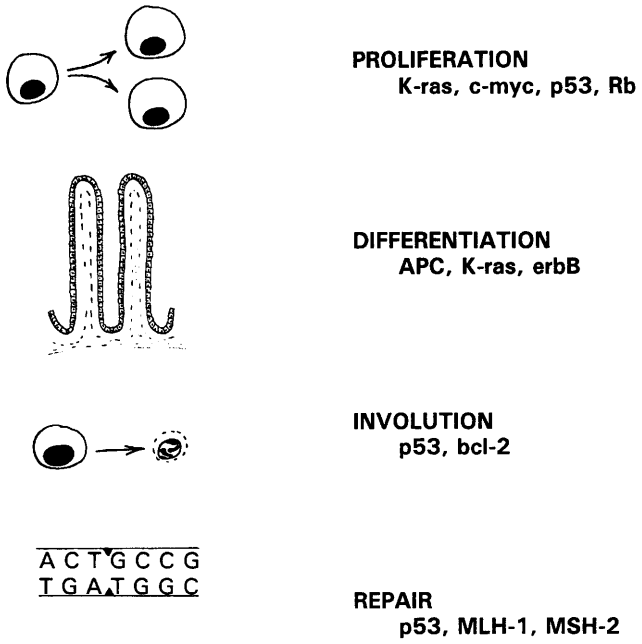

Figure 1. Regulation of Homeostasis in the Intestinal Mucosa. Renewable tissue populations such as the intestinal epithelium must coordinate several balancing processes in order to maintain normal tissue function. In the colon, some of these processes can be associated with genetic changes observed during carcinogenesis.

comes senescent and is shed into the lumen of the bowel. Carcinogenesis in the intestinal mucosa is characterized by the progressive loss of normal controls and balance of proliferation, maturation, and senescence (apoptosis) in the enterocyte population. A clinical cancer is present when the properties of invasion and metastasis develop in a population of abnormally functioning enterocytes. There are, however, many changes in the mucosal epithelium that precede a clinical cancer. Measurements of precancerous alterations in enterocyte proliferation, maturation, and apoptosis are broadly termed intermediate biomarkers for carcinogenesis. The best characterized premalignant epithelial lesions constitute actual changes in the architecture of the colonic crypts. Microscopic premalignant changes in the colonic mucosa are termed aberrant crypt foci, whereas macroscopic lesions are known as adenomas. There is abundant epidemiologic, clinical, pathologic, and molecular evidence to support the assertion that, with time and accumulation of transforming mutations, colorectal adenomas may progress to colorectal carcinoma, a concept known as the adenoma-carcinoma sequence (1–4).

Carcinogenesis in the gastrointestinal epithelium is likely the result of successive accumulation of multiple genetic mutations, resulting in a transformed phenotype and eventual progression of the enterocyte to invasive cancer. In 1988, Vogelstein *et al.* (1) published a report describing specific mutations in colorectal cancer and defining their relationship to the adenoma-carcinoma sequence. This report led to wide acceptance of the multistep hypothesis as the basis for malignant transformation and gave a genetic perspective to the processes of tumor initiation, promotion, and progression. Recent data suggest that, not only are specific mutations essential for carcinogenesis, but, in addition, the order in which these defects are acquired is important (5, 6). Although the multistep hypothesis is incompletely understood, it gives us a useful framework for defining the genetic nature of carcinogenesis (7).

The mutations associated with carcinogenesis are either inherited or acquired through interaction with mutagens in the environment. An inherited tendency to develop cancer is now thought to be associated with 1%–5% of all colorectal cancers. For colorectal cancer, the best-characterized inherited cancer predisposition mutations are the APC mutation, which is associated with familial adenomatous polyposis (FAP), and the family of mismatch repair mutations associated with hereditary nonpolyposis colon cancer (HNPCC). Most, if not all, colorectal cancers arise as a combination of genetic and environmental factors. For example, an inherited defect in mismatch repair is not, in itself, sufficient for cancer development. This defect, however, may set the stage for rapid accumulation of additional acquired, or somatic, mutations, many of which are diet associated. Because the inherited cancer predisposition syndromes involve germline mutations in genes that are also associated with sporadic colorectal cancers, these syndromes present a unique opportunity to study carcinogenesis and cancer prevention in models that are also relevant to more common, nonfamilial malignancies.

In spite of great advances in the field of cancer genetics during the last five years, we still are far from a precise understanding of the molecular biology of colon cancer. Many fundamental questions remain, including (i) What is the relative importance of inherited genetic and environmental influences in colorectal carcinogenesis? (ii) What combination(s) of mutations is necessary and sufficient for the development of invasive cancer? (iii) What environmental influences are most important to carcinogenesis, and what mutations are produced or prevented as a result of these influences? and (iv) Can modulation of environmental factors prevent cancer in patients with an inherited cancer predisposition syndrome such as FAP or HNPCC? Although we lack full answers to these questions, the study of cancer epidemiology provides many clues, and suggests possible approaches to cancer prevention.

Epidemiology: Clues to Cause and Prevention

Cancer epidemiology involves the search for associations between environmental or genetic factors and cancer incidence or mortality. The results of such studies provide a starting point for development of cancer prevention strategies. Because colorectal carcinogenesis is a multifactorial process that occurs over many years, it is difficult to prove a direct cancer-inducing effect of any single agent. Nevertheless, insights derived from epidemiologic studies help to define both the causes of colorectal cancer and the means to achieve tumor prevention.

Evidence that environment plays a major role in colon

carcinogenesis began with the observation that colon cancer incidence rates vary significantly between different parts of the world. In general, industrialized nations have up to eight times higher rates of colon cancer than those of developing nations (8). Although this may be ascribed to either environmental or genetic factors, an environmental role is strongly supported by evidence that immigrants from countries of low incidence to areas of high incidence develop a risk of colon cancer similar to individuals in the new country of residence (9). Most of the data related to colon cancer concerns dietary constituents, such as fat, fiber, or meat intake, and lifestyle factors, such as activity level or alcohol and medication use.

Role of Diet in Colorectal Cancer. Diet is thought to be a major etiologic factor in the development of colorectal cancer. Determining the relationship between diet and cancer is difficult, however, because of the long interval required for carcinogenesis as well as multiple confounding interactions between dietary constituents. As a result, studies of the relationship between single dietary constituents and colorectal cancer yield many conflicting results. In spite of this, strong cumulative data from both human epidemiology and animal studies links several dietary components to colorectal cancer risk (Table I).

In 1969, Burkitt noted that consumption of dietary fiber was strikingly different between inhabitants of Africa, who had a high-fiber diet and a low incidence of colon cancer, and residents of Western countries, who consumed little fiber and in whom colon cancer is common (21). Prospective and case-control studies confirm a relationship between fiber intake and colorectal neoplasia (22). An analysis of 13 case-control studies demonstrates that dietary fiber consumption in inversely related to risk of colorectal cancer (23). Dietary fats, particularly the saturated fat present in red meat, may contribute to colorectal cancer (24). Multiple case-control studies also demonstrate an association between high fat consumption and increased colorectal cancer risk (25, 26). Animal studies suggest that high fat intake, particularly saturated fat, induces abnormal proliferation of colonic mucosa and may even produce aberrant crypt foci, one of the earliest cancer-associated structural changes in the gut (27). Bile acids are agents with mitogenic effects upon intestinal epithelium whose production is increased by high fat intake (28, 29). Secondary bile acids (deoxycholic and lithocholic acid) are at high levels in the colon of populations at increased risk for colon cancer. Because this group also has an increased fat and decreased fiber diet, the exact relationship of these components to cancer is unclear (30).

Table I. Diet and Colorectal Cancer

Associated factor	Possible impact upon carcinogenesis
Dietary fiber	Dilute toxins and bile acids through increasing stool bulk; alter carcinogen production by intestinal flora; increase fermentation and production of short chain fatty acids necessary to prevent high colonic lumen pH, supply nutrient (butyrate) to colonic enterocytes, and aid in differentiation (10, 11)
Dietary fat	High intestinal bile acid levels and fatty acid concentration result in tumor promotion; fat is a source of increased diacylglycerol (DAG) in the colon lumen, a molecule important in cellular activation (12, 13)
Consumption of red meats	Mutagens (colon carcinogens) are produced by heterocyclic amines formed in fried meats (14, 15)
Consumption of fruits and vegetables	Contain indole derivatives that act as detoxifying enzyme inducers or direct inhibitors of carcinogenesis; contain plant phenolics or antioxidants that are arachidonate modulators (16)
Dietary micronutrients (selenium, calcium, vitamin D)	Cause fixation of bile acids and fatty acids; antagonize proliferation induced by a high-fat diet (17–20)

High consumption of red meat correlates with increased colon cancer risk in numerous case-control and cohort studies, an association which is even more consistent than that linking fat and colon cancer (26, 31). In addition to containing saturated fats, cooking of red meat produces genotoxic substances such as heterocyclic amines and polycyclic hydrocarbons that may contribute to intestinal tumor formation. Red meat also supplies a high level of phosphate and a low level of calcium to the diet, and is a major source of myoglobin, an agent suspected as a source of oxidative damage in the colon. In numerous epidemiologic studies, populations with a high intake of vegetables and fruits and a low intake of red meat have a decreased incidence of colon cancer (25, 32).

A number of additional dietary agents, such as vitamins, micronutrients, and other minor dietary components may be important to the process of cancer development. For example, some studies suggest that a high intake of calcium or vitamin D is associated with reduced risk of colorectal cancer (33, 34), perhaps by binding bile acids and reducing their exposure to colonic mucosa. Substantial work in animal models supports this hypothesis (35). A recent large study of diet and cancer risk, however, failed to demonstrate an association between total calcium intake and colorectal adenoma risk (36). For women, this study suggested that vitamin D from supplements, but not from diet, may be inversely associated with colorectal cancer risk. Antioxidant vitamins, such as vitamins C, E, and β-carotene, are free radical scavengers that can theoretically prevent DNA damage resulting from a local inflammatory response. Selenium is an essential trace element important for the function of glutathione peroxidase, an enzyme that also protects against oxidative tissue damage (37). A number of studies in both animals and humans suggest that increased intake of anti-

oxidant vitamins or selenium reduces the incidence of cancer (38–41). In spite of these data, conflicting results were reported from a recent clinical trial in patients with colorectal adenomas which tested the relationship between adenoma development and dietary intake of β-carotene, vitamin C, vitamine E, or a combination of all three. This study found no change in adenoma recurrence with follow-up colonoscopy after 1 and 3 years of antioxidant administration (42). Folic acid contained in leafy green vegetables may prevent intestinal tumors by preventing DNA methylation imbalances, a theory supported by a reduced risk of colon cancer observed in individuals with high folic acid intake (43). Fruits and vegetables contain additional compounds such as phenols, flavonoids, isothiocyanates, and indoles, all of which have tumor-preventing activity in animal and cell models (44, 45).

Because the consumption of fiber, fat, red meat, fruits, vegetables, antioxidants, or micronutrients are all closely linked, it is difficult to point to any one of these as a cause or a preventive agent for colorectal cancer. It is clear, however, that the best diet for prevention of colorectal neoplasia is one relatively high in vegetable, fruit, and fiber consumption, and low in saturated fat and red meat.

Lifestyle and Colorectal Cancer risk. Obesity may be associated with an increased risk of colorectal cancer, particularly in women (46). Individuals with sedentary occupations have a higher incidence of colon cancer when compared with those whose occupations require a higher level of physical activity (47, 48). Although not tested in human trials, these studies suggest that regular exercise and maintenance of ideal body weight contribute to cancer prevention. Alcoholic beverages contribute to many solid tissue tumors, particularly breast, oral, and esophageal cancer, and may also increase the risk for colon or rectal cancer (49, 50).

Another lifestyle factor associated with colorectal cancer risk is the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin and NSAIDs have been associated with inhibition of colorectal carcinogenesis in both animal tumor models and human epidemiology. Regular use of aspirin or NSAIDs by humans correlates with a decrease in colorectal cancer by as much as a 40%–50% in several large epidemiologic studies (51, 52). In carcinogen-induced rodent colon tumor models, piroxicam (53–55), sulindac (56, 57), and to a lesser extent, indomethacin, ketoprofen, ibuprofen, and aspirin (58–62), all inhibit tumor formation. In a rat model of azoxymethane (AOM)-induced large bowel tumors, sulindac inhibits tumors in the promotion/progression period as well as during initiation of carcinogenesis (57). The mechanism by which anti-inflammatory drugs inhibit intestinal carcinogenesis is not fully understood. Most data suggest that the antitumor efficacy of these agents resides in their ability to inhibit prostaglandin synthesis, specifically, by inhibition of cyclooxygenase-2 (Cox-2), an inducible primary enzyme of the prostaglandin metabolic pathway.

Strategies for Prevention

The epidemiology of colorectal cancer provides valuable insight into the causes of lower intestinal tumors and the ways to prevent them. The most direct method of preventing colorectal cancer is by identification and removal of precursor adenomas. Because colorectal neoplasia is linked to dietary intake of various chemicals with cancer-preventing properties in animal studies, an intense effort is also underway to develop effective, safe chemopreventive agents. The ideal chemopreventive agent is simple to administer with extremely low toxicity, as it would likely require almost lifelong use. A number of promising agents have been identified that modulate basic determinants of carcinogenesis such as cellular activation and differentiation. Some of these agents, described in the following section, are presently under investigation in both animal and human colon tumor studies.

Evaluating the efficacy of a chemopreventive agent is difficult because the time required for development of sporadic colorectal cancer is long, in the range of 20–40 years. Unlike cancer treatment studies, where the end points of disease-free survival and overall survival are measured in a few years, most chemoprevention analyses must rely upon measurement of intermediate biomarkers for cancer development. The most commonly utilized intermediate biomarkers for colorectal neoplasia are intestinal adenoma formation, aberrant crypt formation, and alterations in colonic epithelial differentiation. It may one day be possible to follow the structure and expression of genes responsible for tumor development as predictors of tumor development and progression.

Endoscopic Screening and Adenoma Removal. Over the past several years, there has been a gradual decline in colorectal cancer incidence and mortality, and this trend may at least in part be attributable to endoscopic polypectomy (63). It is now widely accepted that most colorectal carcinomas arise from preexisting adenomas. The sequence from normal mucosa to adenoma to carcinoma provides clinicians with a unique opportunity to prevent colorectal carcinoma by removing its premalignant precursor. A growing body of literature supports the efficacy of polypectomy in reducing colorectal cancer-associated mortality.

In a unique study performed during the pre-endoscopic era, longitudinal follow-up was provided on 226 patients who were discovered to have a polyp during barium studies of the colon (64). In these untreated patients, 21 invasive cancers developed at the site of the index polyp after a mean follow-up of 9 years. An additional 11 invasive cancers developed at sites remotely located to the index polyp. Cumulatively, these data reaffirm the adenoma-carcinoma sequence, and highlight the concepts of synchronous and

metachronous colorectal neoplasms, the potential importance of neoplasms that arise in the proximal colon, and the potential inadequacies of barium studies to detect early, relatively small tumors within the colon. Just over two decades ago, Dr. V. Gilbertsen suggested that polypectomy reduces the incidence of colorectal cancer (65). This study employed rigid sigmoidoscopy to detect and remove distal large bowel adenomas. As a result, an 85% reduction in cancer incidence was noted in the portion of the colon that was examined and cleared of adenomas annually. This observation has been confirmed by numerous case-control studies (66–68). The subsequent development of fiberoptic and video-endoscopic equipment has had a dramatic impact on the diagnosis and treatment of colorectal adenomas. For routine screening of older individuals, flexible sigmoidoscopy has replaced rigid sigmoidoscopy for screening because it provides a more comprehensive examination that has the potential to detect up to 50% of all colorectal neoplasms (69–72).

Colonoscopy, performed with intravenous sedation as an outpatient procedure, allows visualization and adenoma removal for the entire colon. Compared with flexible sigmoidoscopy, which requires minimal bowel preparation and no anesthesia, full visualization of the colon by colonoscopy is a more costly and invasive endeavor. Despite this, the benefits of full colonoscopy in individuals at high risk for colorectal cancer are well documented. Approximately half of all colorectal neoplasms arise proximal to the splenic flexure, beyond the reach of flexible sigmoidoscopy. Moreover, up to 30% of asymptomatic individuals have adenomas limited to the right colon without any coexistent adenomas in the distal colorectum (70), and the proportion of proximal colorectal neoplasms increases with age (69). Individuals with an index adenoma are also at increased risk of having synchronous and metachronous colorectal neoplasias (73–75). Finally, nonendoscopic methods of adenoma detection, such as fecal occult blood testing, are limited by poor sensitivity and predictive value for detecting colorectal neoplasms (76, 77).

These observations have led some to question the efficacy of sigmoidoscopic examination to screen for colorectal carcinoma, and to propose full colonoscopy as the optimal method for adenoma detection and removal. Two prospective trials have been performed to evaluate the merits of colonscopic screening compared with sigmoidoscopic screening in asymptomatic individuals over the age of 50 (69, 70). In both studies, 41% of the evaluated subjects were demonstrated to have adenomas. Examinations to a level of 55–60 cm from the anal verge detected 44%–54% of all adenomas. A substantial portion (46%–56%) of adenomas were detected only following complete colonoscopy. Analysis of the data from the National Polyp Study Workshop revealed a lower incidence of colorectal cancer among the cohort of individuals with an index adenoma that had subsequently undergone periodic surveillance colonoscopy (78). Compared with historical controls, the reduction of colorectal cancer incidence was lowered by as much as 90% in the cohort that underwent periodic surveillance after discovery of an index adenoma. This study also showed that surveillance intervals of 3 years provides a level of protection against the development of clinically significant adenomas (>1 cm or high-grade dysplasia) and carcinomas equal to that of more frequent examinations (79). These observations strongly support the long-held belief that colorectal carcinomas arise from precursor adenomas, and that removal of the precursor lesions can effectively lower the rate of subsequent cancer development within the colon. As a result of studies such as these, colonoscopy has become the standard screening technique for individuals at increased risk of colorectal neoplasia. These individuals include those with a known history of colorectal adenomas or colorectal cancer, and those with a strong family history of colorectal tumors.

Chemoprevention of Colorectal Cancer. Chemoprevention is defined as the administration of specific chemicals to prevent the development of invasive cancer. Hundreds of natural and synthetic compounds have been studied for their effects upon carcinogenesis in intestinal mucosa.

Dietary intervention. Although the exact role of individual dietary constituents in colorectal cancer development is unknown, a lage body of cumulative evidence supports some specific cancer-preventing dietary recommendations. A healthy diet should be high in vegetables and fruits, with carbohydrates consumed as whole grains to add dietary fiber. The fat content of the diet should be low (approximately 20%–25% of total calories), and added fats should be unhydrogenated forms derived mainly from plants, such as olive oil. Saturated fats, red meats, salt, sugar, processed grain products, and excessive alcohol intake should be avoided. A diet such as this naturally contains many of the microingredients found to inhibit intestinal carcinogenesis.

It is possible that humans can benefit from supplementation of the diet with many of the minor dietary components associated with colorectal cancer prevention in epidemiologic and animal studies. Although not proven by prospective, randomized study, there is consistent evidence that adding additional calcium, vitamin D, and folate to the diet may help to prevent colorectal neoplasia. This supplementation should not exceed well-established recommended daily allowances (RDA) for these substances. Increased intake of ω-3 fatty acids, which are present in fish oils and certain vegetable oils, has been shown in clinical studies to decrease proliferation of colonic epithelium, and may therefore be beneficial as a dietary additive (80). Studies to document the efficacy of these and other agents in colorectal cancer prevention are underway (Table II).

Naturally occurring compounds with chemopreventive properties, such as the plant phenolics, isothiocyanates, indoles, tannins, and organosulfur compounds, are consumed in human diets high in vegetables and fruits. Many of these natural substances demonstrate antitumor effects in carcino-

Table II. Possible Agents of Colorectal Cancer Prevention: Dietary Supplements

Dietary additives	Antitumor effect
High fiber: wheat bran	Decrease fecal diacylglycerol; decrease protein kinase C activation (10, 11)
Calcium	Bind bile salts; direct antiproliferative effect on enterocytes (18, 19)
Vitamin D	Normalize differentiation in colonic epithelium (20)
Folic acid	Correct DNA methylation imbalances (43)
Selenium	Antioxidant activity (37)
Allyl sulfides, isothiocyanates, indoles	Induce glutathione-*S*-transferase and other detoxifying enzymes (81)
Vitamin C, vitamin E, β-carotene, flavonoids	Scavenge oxygen radicals, preventing DNA damage (82)
inositol, phytic acids	Modulate transmembrane signaling (83)
Caffeic acid, other plant phenolics	Inhibit nitrosation to form carcinogenic nitrosamines, antioxidants *in vivo;* reduce arachidonate metabolism (16, 84)
ω-3 fatty acids	Reduce arachidonate metabolism, thereby reducing prostaglandin activity (80, 85)
Conjugated linoleic acid	Alter membrane phospholipids; decrease enterocyte proliferation; induce epithelial differentiation (86)

gen-induced animal models of colorectal cancer (87, 88). These agents exert a variety of activities associated with antitumor effects including inhibition of prostaglandin synthesis, mutagenesis, nitrosation, ornithine decarboxylase activity, and protein kinase C activity. As already mentioned, some dietary compounds may also protect against tumors as a result of natural antioxidant activity. Some plant phenolics are weak phytoestrogens that can bind to estrogen receptors, resulting in a mild antiestrogen effect (89, 90). Because these compounds are naturally occurring dietary components, they are potentially better tolerated during the long-term (lifelong?) administration required of a chemopreventive agent.

Chemopreventive medication and colorectal cancer. Some of the most promising colorectal cancer prevention studies involve the administration of NSAIDs or aspirin. The regular use of aspirin or NSAIDs is associated with a decreased incidence of colon cancer in human studies (91–93). In patients with FAP, the NSAID sulindac is effective in mediating regression of colorectal adenomas. A prospective, randomized trial is presently underway to evaluate the efficacy of aspirin for prevention of colorectal adenomas in individuals who have undergone curative treatment for colorectal cancer. These compounds share the ability to block the activity of cyclooxygenase, an enzyme responsible for conversion of arachidonic acid to prostaglandins. Prostaglandins have been implicated in epithelial carcinogenesis as stimulators of cell growth, inhibitors of apoptosis, and suppressors of immune surveillance. Widespead use of aspirin and NSAIDs for colorectal cancer chemoprevention is hampered by side effects of intestinal upset and increased bleeding tendency. New drugs, specific for inhibition of inducible cyclooxygenase (cyclooxygenase-2), may provide effective tumor prevention with reduced side effects (94, 95).

Table III. Possible Agents of Colorectal Cancer Prevention: Chemoprevention Drugs

Chemopreventive drug	Antitumor effect
Sulindac and related nonsteroidal anti-inflammatory drugs	Block prostaglandin activity; induce apoptosis (91–93)
Aspirin	Block prostaglandin activity (58)
Specific cyclooxygenase-2 inhibitors	Block arm of prostaglandin pathway responsible for cellular activation (94, 95)
DFMO (difluoromethylornithine)	Inhibit ornithine decarboxylase (96)
N-Acetyl-L-cysteine protease inhibitors	Increase DNA repair capability (97)
Oltipraz	Induce glutathione-*S*-transferase and other detoxifying enzymes (98)

Several additional drugs are under investigation for their ability to mediate antitumor effects in animal models (Table III). These include difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase and resultant polyamine activity, Oltipraz, a drug originally developed for treatment of schistosomiasis that induces production of detoxifying enzymes (98, 99), and various protease inhibitors (97). These agents demonstrate chemopreventive activity in animal tumor models but have yet to be tested in human studies.

Summary

Many compounds, both synthetic and diet derived, exhibit antitumor activity in cell line and animal models of

Table IV. Recommendations for Colorectal Cancer Prevention

Prevention method	Recommendation
Dietary modification	20%–25% of calories as fat; increased cereal bran fiber, fruits, and vegetables
Lifestyle modification	Moderate, regular exercise; maintain ideal body weight; low alcohol intake
Medication use	Regular low-dose aspirin use; supplementation with calcium and vitamin D
Adenoma screening and removal	Endoscopic examinations beginning at age 50 with polypectomy if indicated; increased screening for those with identified genetic risk

colorectal carcinogenesis. Although most potential chemopreventive agents await study in human trials, some of them, such as dietary fiber, calcium, vitamin D, and the anti-inflammatory drugs, show promise in limited human tumor studies. Table IV summarizes the current recommendations for colorectal cancer prevention. In the future, the ability to better characterize both genetic and environmental determinants of colorectal cancer will undoubtedly lead to more effective methods of tumor prevention.

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