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DIETARY FACTORS IN HUMAN COLORECTAL CANCER

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ABSTRACT

Colorectal cancer is a significant cause of mortality in Western societies. The progression of the disease from normal colonic epithelium to the acquisition of the malignant phenotype is accompanied by numerous genetic and epigenetic alterations. Compelling experimental and epidemiological evidence indicates that diet and nutrition are key factors in the modulation of colorectal cancer. A salient case in point is the recent observation that a dietary regimen based on a Western-style diet provokes in the rodent colon the appearance of preneoplastic lesions in the absence of any genotoxic insult. This review mainly describes dietary factors that inhibit the development and progression of colorectal cancer. Much is unknown about the precise mechanisms of action of chemically disparate nutrients and how they interfere with the development and progression of this disease. Current knowledge about this important issue is summarized. We believe that continuing scrutiny and precise assessment of the benefits (and potential risks) of nutrients in the treatment and prevention of colorectal cancer will prove significant to controlling this devastating disease.

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PHYSIOLOGICAL CONSIDERATIONS

The development of colon cancer initially involves one or more genetically altered cells and requires many years to evolve, with a multistep process that affords nutrients an opportunity to modify the evolution of the disease. Many different dietary factors contact epithelial cells in the colonic crypts both from the lumenal contents of the colon and from the basolateral epithelial cell membranes, thereby influencing developmental programs in both normal and transformed colonic epithelial cells.

Early studies on the structure and function of colonic epithelial cells were concerned with the spatial location of proliferating and differentiating cells and their influence on the integrity of the colonic mucosa (60, 156). More recently, much attention has been given to the process of apoptosis as central to maintaining the homeostasis of cell renewal and turnover in the colon (95, 134, 146, 155, 219, 220, 221, 224). Vast evidence shows that dysregulation of apoptosis is a contributing event to the development of neoplasia (180, 250 291, 292) and that inhibition of the apoptotic process may play a key role in modifying the effects of nutrients on tumorigenesis and on mechanisms of chemo- and radioresistance (180, 291, 292).

Major Features in Organization of the Colonic Epithelium

The lumenal surface of the colon is folded into deep cavities, aptly termed crypts, which are embedded in connective tissue. The crypt openings appear as pits on the lumenal surface of the colon. The cumulative presence of these numerous pits forms a huge surface area (60, 156, 216, 320). In the crypts of the large intestine are cells that are in a continuous process of self-renewal. Colonic cells undergo mitotic activity in the lower part of the crypts and acquire the differentiated phenotype during linear migration to the upper crypt regions. Once the colonic cells have fulfilled their biological purpose the cells die and are sloughed off into the colonic lumen. Loss of aged cells from the colonic surface occurs periodically, concomitant with replenishment by new colonocytes (60, 156, 216, 219, 320). In humans the colonic epithelium is thus completely replaced every 4 to 8 days.

The constancy of cell number along the colonic crypt axis is under stringent control to assure an accurate balance between the rate of new cell production and the rate of cell death. The nature of the molecular events responsible for the renewal, maturation, and ordered growth of the colonic mucosa continues to be elucidated. Accumulating information suggests that the phenotypes of colonic cells of various lineages depend on their positional address along the crypt continuum and on changes in simultaneous expression of genes within precise windows of time (296–298).

Apoptosis of Colonic Epithelial Cells

Among newer findings on growth, development, and homeostasis of the intestinal mucosa, the physiological deletion of distinct cells by apoptotic death is now a recognized process (90, 95, 134, 146, 155, 220, 221, 224, 264). The execution of the death program is associated with bizarre morphological changes that are remarkably similar among cell types of disparate lineages. These include loss of intercellular contact, cell shrinkage, and compaction of chromatin abutting beneath the inner surface of the nuclear membrane; DNA fragmentation at internucleosomal linker sites is observed in many cells (59, 85, 94, 172, 257, 304, 323, 324).

Apoptosis has been observed in the murine and human gastrointestinal tract, and it has become increasingly evident that the physiological deletion of rapidly renewing colonic epithelial cells by apoptotic death at a precise developmental stage is an integral part of the intricate processes controlling overall colonic tissue homeostasis. Evidence indicates that colonic cells possess an intrinsic program for their own self-destruction, normally activated once the colonocytes acquire the differentiated phenotype. Indeed, spontaneous apoptosis is observed predominantly in the upper region of colonic crypts (95, 146, 155). These findings imply that initiation and execution of the death program in colonic epithelial

cells is strictly contextual, depending on an apoptosis-permissive environment. A prevailing view is that the apoptotic process is stringently regulated along the crypt continuum by a complex interplay of local apoptosis-inducing and survival factors (95, 146, 155, 220, 221). Studies of nutritional influences on these processes have only recently been addressed. The importance of dietary factors in apoptotic events has been highlighted by the observation that chronic dietary restriction provokes a significant increase in the rate of spontaneous apoptosis (58, 130). An in-depth presentation of current knowledge of the cellular and molecular events controlling apoptosis is beyond the scope of this survey. The reader is referred to a number of recent reviews pertaining to the interdisciplinary aspect of the apoptotic process (59, 85, 94, 172, 257, 304, 323, 324).

Endogenous Growth Factors and Dietary Factors

Various effects of hormones and of cytokines on normal colonic tissue homeostasis have been recognized for some time. Earlier interest focused principally on the effects on cellular proliferation and differentiation. Recently, however, much evidence has been collected to show that these agents are an integral part of the signaling cascade involved in the regulation of cell death (257). It is obvious, therefore, that whether a colonic cell escapes from or enters the apoptosis pathway depends on contextual instructive and signaling cues originating from regulatory signals along the crypt continuum in a complex network that includes dietary factors.

A prevalent view, sustained by much experimental evidence, holds that cells are constitutively programmed for suicide and die by default unless rescued by continuous survival signals originating from neighboring cells (155, 226). This model is consonant with the localized spontaneous apoptotic death of colonic cells in intact colonic tissue (95, 146, 155) and the collective and indiscriminate suicide of colonic cells deprived of crypt habitat (90, 146, 155).

The identification of a large variety of apoptosis-inducing agents (59, 85, 94, 172, 257, 304, 323, 324) indicates that the view of apoptosis controlled by survival factors, albeit correct, is partial. Members of the bcl-2 family are a cogent example of endogenous bioactive molecules that promote the death process. One of those, BAX, is expressed predominantly in the upper zones of the colonic crypt (317).

As was outlined previously, the colonic crypt is composed of cells at distinct stages of proliferation and differentiation, and their varying phenotypes are determined by a network of inhibitory and stimulatory growth factors that exhibit a differential gradient of expression along the colonic crypt axis (95, 146, 155, 220, 221). A salient case in point is transforming growth factor-β (TGF-β), a cytokine that exerts a potent antiproliferative action on intestinal epithelial cells (13, 145, 147). TGF-β is localized primarily in nonreplicating cells

that reside in the colonic crypt cuff (12, 15, 186). Coexpression of the peptide and cognate receptors within the adult, differentiated colonocyte has recently been demonstrated (186), suggesting a determining role of the TGF-β system in the control of colon tissue homeostasis. These findings indicate a critical role of the cytokine in maintaining the differentiated state, and, possibly, in the induction of apoptosis. Indeed, TGF-β induces apoptosis in cells of various lineages, including colonic epithelial–derived cell lines (7, 35, 89, 307a).

Over the past years, a number of low-molecular-weight proteins that inhibit the activities of cyclin-dependent kinase complexes have been identified. These proteins include p21 and p27 (101, 121, 277). p21 expression induces cell cycle arrest, differentiation, and apoptosis in a variety of cells (64, 74, 328).

There is convincing evidence that the inhibitory action of TGF-β on the growth of epithelial cells is mediated, at least partly, by upregulation of the levels and activities of the cyclin-dependent kinase inhibitors p21 and p27 (reviewed in 327). It is noteworthy that butyrate-induced apoptosis of colonic epithelial cells is also associated with the induction of p21 Waf1/Cip1 and p27 Kip1 (159). Butyrate is one of the short-chain fatty acids produced in high concentrations from dietary fiber by colonic microflora fermentation. Therefore, TGF-β and butyrate-bioactive molecules of disparate chemical structure and origin seem to share a common intracellular pathway to promote death in colonic cells.

Frameshift mutations in the gene for TGF-β receptor II encoding an inactive truncated protein have been observed in colon cancer cells (20, 24, 48, 169). This upstream lesion results in escape from the TGF-β–negative regulation of growth (20, 327). Notably, the same cells insensitive to TGF-β but possessing an unimpaired p21/p27 system would remain responsive to the apoptosis-inducing action of dietary butyrate. The principle of nutrients and important cell components sharing intracellular pathways and specific receptors is being recognized more widely.

DIETARY COMPONENTS THAT MODIFY THE DEVELOPMENT OF THE NEOPLASTIC PROCESS

Dietary Fat: Epidemiologic Evidence

Diet, especially fat intake, has long been regarded as the most important nutritional influence on colorectal cancer. Marked differences internationally in colon cancer incidence, mortality rates, and increase of risk in populations migrating from low- to high-risk areas suggest that environmental factors, specifically nutritional factors, play an important role in the etiology of colon cancer. Basing their conclusions on Japanese data and case-control studies, in the late

1960s Wynder et al (325) proposed that colon cancer incidence is mainly associated with dietary fat and, furthermore, that dietary fat influences the composition of the gut flora and thus may be involved in the pathogenesis of cancer of the colon. This pioneering study led to several ecological and case-control studies on the relationship between dietary fat and colon cancer (207). Since then, a substantial amount of progress has been made in understanding the relationship between dietary fat and the development of colon cancer in humans, but the conduct and interpretation of some of these studies has been complicated by inherent problems in testing the dietary hypotheses. In question are the reliability, validity, and sensitivity of the hypotheses to reveal narrow, but biologically significant, differences and to include some degree of dose standardization. For example, the major difficulty with several earlier studies has been the lack of an accurate method of measurement of types of dietary fat in the foods of the populations under observation. The importance of measuring types of dietary fat by different fatty acid composition rather than by total fat cannot be discounted because animal model studies have provided evidence that the colon tumor–promoting effect of dietary fat depends not only on the total fat but also on the types of fat (233). Population studies and a great majority of earlier case-control studies have demonstrated that colon cancer risk increases with increased intake of dietary fat (84, 187). Continuing population studies have revealed that diets particularly high in total fat are generally associated with an increased risk of developing colon cancer. The odds ratios range from 1.3 to 2.2. One study of US nurses found that intake of dietary fat in the uppermost, versus the lowest, quintile was associated with a twofold increase in the risk of colon cancer (316). Five case-control studies that adjusted for calorie intake provided mixed results for the association of colon cancer and total dietary fat (207). Two studies found statistically significant increases in risk, whereas three found no such association (207, 211). Based on the epidemiological evidence from ecological and case-control studies, it is reasonable to conclude that diets high in total fat increase the risk of colon cancer.

Evidence for association between saturated and/or animal fat and colon cancer risk is strong. A recent ecological study suggests that mortality data of colorectal cancer for 22 European countries, the United States, and Canada correlated with consumption of animal fat (34). Several case-control studies that examined the relationship between dietary saturated and animal fat and colon cancer found that higher intakes of these types of fat increase the risk of colorectal cancer development, with odds ratios ranging from 1.5 to 2.6 (187, 207, 259, 329). In an Australian case-control study, Potter & McMichael (222) found that women in the uppermost quintile for saturated fat intake have increased risk of colon cancer, with an odds ration of 2.1, whereas males have no increased risk. Hursting et al (122) analyzed data from 10 countries and observed correlation between colon cancer risk and saturated fat intake. There

are fewer case-control studies finding no substantial association between colon cancer risk and high intakes of saturated fat (207). The results of these studies suggest that ingestion of diets high in saturated fat may increase the risk of colon cancer.

Eating a diet high in polyunsaturated fats that are rich in omega-3 fatty acids may decrease the risk of colon cancer; this has been the hypothesis in relation to fish and fish oil. A review of ecological and case-control studies of fish consumption proved these studies to be relatively few compared with studies of total fat and saturated fat consumption. Caygill & Hill (33) also reported a preliminary study of 24 European countries that indicated an inverse relationship between fish consumption and colorectal cancer. In another study, Caygill et al (34) reported an inverse correlation with fish and fish oil consumption when expressed as a proportion of total or animal fat, and this correlation was significant for colorectal cancer in both males and females. These effects were seen in populations with a high fat intake.

Laboratory Animal Studies

Laboratory animal studies have provided evidence that not only the amount but also the types of dietary fat differing in fatty acid composition are important factors in determining the enhancing effect of this nutrient in colon tumor development (233). In several earlier animal studies on dietary fat and colon cancer, interpretation of results between high-fat and low-fat diets was complicated by the use of diets that varied in caloric density and was confounded by different intakes of other nutrients. Generally, laboratory animals adjust their food intake so that similar energy intake is maintained even with diets containing substantially different energy density. Therefore, a diet with a low energy value per unit weight (low fat) will be consumed at a greater rate than a diet with more highly concentrated energy (high fat). Accordingly, in addition to the changes in fat and carbohydrate intake, the intakes of protein, minerals, vitamins, and fiber will be lower in animals fed the high-fat diet. Accordingly, it is necessary to formulate high-fat diets that ensure an intake of protein, vitamins, minerals, and fiber comparable to that of low-fat diets so that the effect of a high-fat diet on tumorigenesis can be measured. Given these limitations, numerous experiments with animals have shown that certain dietary lipids influence tumorigenesis in the colon. This promoting effect can be modified, however, by the type of dietary fat ingested. In general, the overall evidence from studies with animals is consistent with the epidemiological data.

Effect of Type and Amount of Fat

In several laboaratories, investigations have also been carried out to test the effect of diets comprising high (20–35%) and low (5%) beef fat, lard, and corn

oil on colon carcinogenesis by a variety of carcinogens: 1,2-dimethylhydrazine (DMH), azoxymethane (AOM), methylazoxymethanol (MAM) acetate,3,2′-dimethyl-4-aminobiphenyl (DMAB), or methylnitrosourea (MNU), which differ in metabolic activation (249). In these studies, semipurified diets containing high and low levels of fat were fed to rats before, during, and after carcinogen treatment to study the specific effects on the initiation and postinitiation stages of colon carcinogenesis. Animals fed diets containing 20% lard or 20% corn oil were more susceptible to DMH-induced colon tumors compared with those fed 5% lard or 5% corn oil diets. Studies by Nutter et al (203) demonstrated that Sprague-Dawley rats fed the beef fat diet had a higher incidence of colon tumors than those fed the corn oil diet. Sakaguchi et al (258) demonstrated a significantly higher incidence of colon tumors in rats fed 5% linoleic acid than in those fed 4.7% stearic acid plus 0.3 linoleic acid. Another study by Pence & Buddingh (209) indicated that DMH-induced colon carcinogenesis was increased in F344 rats fed a high-fat (corn oil) diet. Rats fed the high-beef-fat diet also developed more metastases in the abdominal cavity, lungs, and liver than did rats fed the low-fat diet. These studies indicate that, irrespective of colon carcinogens used, diet containing a high amount of beef fat, corn oil, or lard had a greater colon tumor–enhancing effect than the diet low in fat.

Effect of Types and Amount of Fat During Initiation Phase of Carcinogenesis

Bull et al (28) demonstrated that ingestion of a high-fat diet after carcinogen treatment increased the intestinal tumor incidence in rats but did not increase incidence during or before the carcinogen administration, which suggests that excess dietary fat acts at the postinitiation phase of colon carcinogenesis. The effect of various levels of polyunsaturated (corn oil) and saturated (lard) fats ingested during the initiation phase of colon carcinogenesis was investigated (241). When the animals were fed diets containing 23.5% corn oil during the stage of initiation (before and during carcinogen treatment), there was no increase in the incidence of colon tumors compared with that of animals on a 5% corn oil diet. When the 23.5% corn oil diet was fed during the postinitiation stage of carcinogenesis, there was a significant increase in colon tumor incidence compared with that of animals fed either the 5% corn oil diet or the 23.5% corn oil diet during the initiation stage. These results suggest that the effect of a high corn oil diet in colon carcinogenesis is observed mainly during the postinitiation stage. In contrast, animals fed the 23.5% lard diet during the initiation period showed an increase in colon tumor incidence. Animals fed the 23.5% lard diet during the postinitiation period also had a higher colon tumor incidence than did those fed the 23.5% lard diet during initiation as well as those fed the 5% lard diet during the promotion stage. In contrast to diets high in corn

oil and lard, diets high in fish oil rich in omega-3 fatty acids [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] had no colon-tumor promoting effect (238, 240). Also, a significant reduction in colon tumor incidence in animals fed the high fish oil diet was observed when compared with those fed the high-corn-oil diet during the initiation phase of carcinogenesis. These results indicate that the enhancing effect of colon carcinogenesis by dietary fat during the initiation phase depends on the types of fat and their fatty acid composition.

Effect of Type and Amount of Fat During Postinitiation Phase of Carcinogenesis

The role of type and amount of dietary fat during the postinitiation phase of colon carcinogenesis was investigated, and the effects of corn oil, olive oil, safflower oil, and fish oil differing in fatty acid composition were studied (238, 240, 241). Animals fed the diets containing high corn oil or high safflower oil (23.5%) had a higher incidence of AOM-induced colon tumors than did those fed diets low in fat (5%). By contrast, diets high in olive oil or menhaden fish oil had no colon tumor–promoting effect compared with diets high in corn oil or safflower oil (238). Corn oil and safflower oil are very high in omega-3 fatty acids (linoleic acid), olive oil is rich in monounsaturated fatty acid (oleic acid), and fish oil is rich in omega-6 fatty acids (DHA and EPA). The varied effects of different types of fat on colon carcinogenesis suggest that fatty acid composition is one of the determining factors in colon tumor promotion.

In another study, the efficacy of varying levels of fish oil and corn oil on colon carcinogenesis was investigated to determine the optimum dietary levels at which the combination of two sources of fat differing in fatty acid composition elicits maximum tumor inhibition (238). Ingestion of high-fat diets containing 17.6% corn oil plus 5.9% fish oil, 11.8% corn oil plus 11.8% fish oil, or 5.9% corn oil plus 17.6% fish oil significantly inhibited colon carcinogenesis as compared to a 23.5% corn oil diet. High-fat diets containing high levels of fish oil and low levels of corn oil induced fewer colon adenocarcinomas than did diets high in corn oil alone. Further studies also demonstrated that feeding of increasing levels of fish oil altered the incorporation of fatty acids into the membrane phospholipids of colonic mucosal cells and tumors (241). Compared with membranes prepared from rats fed the 23.5% corn oil diet, membranes from the animals fed the increasing levels of fish oil diets were enriched with omega-3 fatty acids such as EPA and DHA at the expense of omega-6 fatty acids such as linoleic acid (LA) and arachidonic acid (AA) in colonic mucosa and tumors.

In summary, laboratory animal studies have provided useful data for evaluating the role of dietary fat in the development of colon carcinogenesis. The majority of studies in which intakes of all nutrients and total calories

were controlled in both high- and low-fat diet groups clearly suggest that not only the amount but also the types of fat differing in fatty acid composition are important factors in determining the modulating effect of dietary fats in colon tumor development. The stage of carcinogenesis at which the effect of dietary fat is exerted is apparent mostly during the postinitiation phase of carcinogenesis. However, certain dietary fats, such as lard or fish oil, also act during the initiation phase of colon carcinogenesis. The strong association between dietary fat and colon cancer risk, experimental evidence, and biological plausibility indicate that these associations are real.

Possible Mechanisms of Action of Types of Dietary Fat in Colon Carcinogenesis

With regard to the mechanism of colon tumor–promoting effect of dietary fat, diets high in beef tallow, lard, or corn oil increase the concentration of colonic luminal (fecal) secondary bile acids, i.e. deoxycholic acid and of lithocholic acid (234), whereas diets high in fish oil have no such enhancing effect. Laboratory animal studies demonstrated that these secondary bile acids induce cell proliferation (27, 310) and act as promoters for cancer of the colon (231). Metabolic epidemiologic studies indicate that populations at high risk for colon cancer excrete high levels of secondary bile acids (231). In humans, individuals at increased risk for colon cancer have abnormal patterns of cell proliferation, including higher rates of DNA synthesis in normal-appearing colorectal mucosa (49, 157). These changes precede tumor development and therefore constitute a key step in colon carcinogenesis (157). It is important to note that high concentrations of luminal secondary bile salts also increase colonic epithelial cell proliferation (157, 288).

One of the mechanisms through which high dietary fat increases colon tumor promotion is the alteration of membrane phospholipid turnover and prostaglandin synthesis. This conclusion is based on observations that secondary bile salts stimulate the membrane phospholipid turnover through the activation of phospholipases, especially phospholipase PLA_2 (46). Also, DHA and EPA from fish oil can partially replace AA and LA in the phospholipid pool (246, 249) and modulate the activity of PLA_2 and phosphatidylinositol-specific phospholipase C (PI-PLC) involved in the release of fatty acids from phospholipids (246). As a result of increased phospholipid turnover and the release of free AA and other products of phospholipid breakdown, a number of biologically active compounds that might alter cellular proliferative activity are generated locally in the colon (47). Consonant with this view, other studies show that PLA_2 activity is significantly higher in colon tumors than in normal mucosa of rats (144, 230). Also, a high-fat diet containing corn oil was found to increase colonic mucosal and tumor PLA_2 as well as PI-PLC as compared

with a low-fat diet containing corn oil, or a diet high in fish oil (46, 144, 230). It is important to note that increasing levels of fish oil in the diet increase the omega-3 fatty acids, namely DHA and EPA, at the expense of the omega-6 fatty acids such as LA and AA (247). Only after liberation from membrane phospholipid is AA available for further enzymatic modification by cyclooxygenases (COX), lipoxygenases (LOX), and monooxygenases.

AA released from phospholipids is metabolized via COX to a number of prostanoids (41). It is of great interest that omega-3 fatty acids present in fish oil, namely DHA and EPA, have been shown to inhibit the COX pathway as well as AA metabolism, resulting in inhibition of prostaglandin (PG) synthesis (43). Consistent with the observations, there are studies to demonstrate that diets rich in omega-6 fatty acids increase the total COX activity in colonic mucosa and tumors during the promotion and progression stage compared with diets low in omega-6 or high in omega-3 fatty acids (230, 279). It is important to note that there are at least two COX isozymes of which COX-1 is thought to be constitutively expressed, whereas the isoform COX-2 is induced by cytokines, growth factors, and tumor promoters (61). Intestinal epithelial cells overexpressing the COX-2 gene develop altered adhesion properties and are resistant to apoptosis (301). Therefore, overexpression of COX-2 may alter the tumorigenic potential of intestinal epithelial cells. Mitogen-inducible COX-2 expression is upregulated in human colorectal carcinomas (61, 136, 301). A markedly elevated expression of COX-2 but not COX-1 gene expression has also been observed in colonic mucosa and tumors of rats (56). Decreased expression of COX-2 has been found in the colonic mucosa and tumors of rats fed a low-fat corn oil diet as compared with those fed a high-fat corn oil diet (279).

DIETARY FIBER AND COLON CANCER

Epidemiologic Evidence

The hypothesis that a diet high in fiber may protect against colon cancer was first proposed by Burkitt (29), who observed that African Blacks consuming high-fibrous and low-fat foods had lower death rates due to colon cancer than did their white counterparts with low-fiber and high-fat diets. Subsequent studies demonstrated that, in populations consuming diets high in total fat, the intake of diets high in total fiber, fibrous foods, and certain whole-grain foods reduces risk for colon cancer (132, 245). Intra-country comparisons of dietary fiber and colon cancer mortality rates strongly support the hypothesis that dietary fiber, especially fiber from cereal sources and pulses, protects against colon cancer (182). Prospective studies have been only somewhat supportive of a protective effect of dietary fiber against colon cancer, showing either a protective association (285) or no association (77). Case-control studies on the relationship

between the dietary fiber and colon cancer provided convincing results. Out of 19 case-control studies assessing the role of fiber and fiber-containing foods, 3 reported no protective effect, 2 found an increased risk, and 13 reported a protective effect of fiber-containing foods and vegetables (214). Howe et al (113) examined the results of a combined analysis of 13 case-control studies of diet and colon cancer with respect to the intake of fiber and micronutrients. In this analysis, the individual data records for 5,287 colon cancer cases and 10,470 control subjects were pooled for a common analysis, which provided substantive evidence that intake of fiber-rich foods is inversely related to colon cancer risk, with odds ratios of 1.0, 0.8, 0.7, 0.6, and 0.5 for each quintile of consumption from lowest to highest. The cogent implications of this study were that risk of colon cancer in the US population could be reduced by about 31% with an average increase in fiber intake. Similar findings were reported in a meta-analysis of 16 case-control studies, with an odds ratio of 0.6 for the highest, versus the lowest, intake of fiber (299). In human clinical trials, supplements of wheat bran produced a reduction in the incidence of rectal polyps among the individuals genetically predisposed to these lesions (45). Metabolic epidemiologic studies demonstrated that wheat-bran supplementation favorably altered a number of biomarkers related to the risk of colorectal cancer, including fecal mutagenicity (236), fecal secondary bile acids (5, 237), and rectal cell proliferation (4). The evidence generated thus far suggests that high dietary fiber, including wheat bran, reduces the risk of colon cancer.

Laboratory Animal Studies

The concept of dietary fiber involvement in colon carcinogenesis is of great importance. Studies examining the possible role of various types of dietary fiber in animals appear to have provided some conflicting results. These discrepancies might in part be due to the nature and amount of the carcinogen used, to differences in the susceptibility of a particular rat strain to carcinogen treatment, to variation in the composition of the diets, to qualitative and quantitative differences in the intact fibers and their components administered, to relative differences in food intake by the animals, and/or to differences in experimental design and duration. Conflicting results from several studies may also in part stem from a failure to define the source of dietary fiber and/or the intake of other nutrients, such as fat and trace minerals. The protective effect of dietary fiber, which comprises a heterogeneous group of nonstarch polysaccharides such as cellulose, hemicellulose, pectin, and gums and a noncarbohydrate substance (lignin), depends on the nature and source of fiber in the diet (235).

The anticancer effect of semipurified diet containing 15% pectin or wheat bran and 20% fat was evaluated against colon carcinogenesis induced by azoxymethane in F344 rats by Watanabe et al (311). The addition of pectin or wheat bran to the diet greatly inhibited colon tumor incidence induced by AOM. The

effect of dietary wheat bran and corn bran at levels of 15% on intestinal carcinogenesis induced by DMAB and/or AOM was studied in male F344 rats (239, 242, 243). The composition of diets was adjusted so that all animals in different experimental groups consumed approximately the same amount of protein, fat, minerals, and vitamins. The animals fed the wheat bran and treated with AOM or DMAB had a lower incidence and multiplicity of colon tumors than did those fed the control diet, whereas those fed a 15% corn bran diet showed an increase in the multiplicity of colon adenocarcinomas. Diet containing 7.5% lignin inhibited the multiplicity of DMAB-induced colon adenocarcinomas (239). Nigro & Bull (202) reported that diets containing 35% (high-level) beef fat plus wheat bran or cellulose showed no inhibitory effect on AOM-induced colon carcinogenesis, whereas the diets containing 5% fat plus either 20% or 30% wheat bran or cellulose inhibited colon carcinogenesis in rats. Although fat and fiber levels were very high in this study, the data indicate that in assessing the effect of fiber on colon cancer, the amount of fat in the diet is important because dietary fat in large amounts appears to be a stronger promoter of colon cancer than an inhibitor.

The effect of fiber fractions such as cellulose and guar gum on DMH-induced colon carcinogenesis has also been examined (69, 127). Experiments in which guar gum was present at a 5% level and fat at a 19% level demonstrated no effect on colon carcinogenesis, whereas another study in which guar gum was present at a 10% level in a 7% fat diet showed an increase in colon tumors. Several studies have shown an inhibitory effect of dietary cellulose on DMH-induced colon carcinogenesis (69). In a separate study, dietary cellulose had no effect on colon carcinogenesis (127). Several of these reports are difficult to interpret because dietary components such as fat, minerals, and other nutrients were different in the experimental diets compared with those in the control diets. The results of several of the studies reported above have been confounded by the use of very high doses of carcinogen.

In conclusion, the results thus far on the effect of dietary fiber in colon carcinogenesis suggest that (*a*) the inhibitory effect depends on the type of fiber and that (*b*) wheat bran appears to inhibit colon tumor development more consistently than other sources of fiber in animals with colon cancer. The varying conclusions regarding diets with other types of fiber appear to be due to differences in experimental protocols, the amount and type of carcinogen used to induce colon tumors, and, perhaps even more important, elements in the diet other than the fiber. Several of the diets used to study the effect of fiber were deficient in certain micronutrients that are involved in carcinogen metabolism or detoxification.

Fermentation of Fiber to Short-Chain Fatty Acids

Fiber starch polysaccharides also are subjected to anaerobic fermentation by the microflora of the large intestine and break down to acetic, propionic, and

butyric acids (44). These short-chain fatty acids occur in millimolar concentrations in the colon and are rapidly absorbed. Butyrate, a four-carbon compound, provides a main local energy source for the metabolism of colorectal epithelium (44, 252, 263).

There is vast evidence that suggests that butyrate is a principal mediator of the effects of dietary fibers on the human mucosa. The precise molecular mechanisms that mediate the growth effects of butyrate remain to be elucidated. Recurring observation shows that butyrate induces histone hyperacetylation of chromatin core proteins (269). This effect would result in the separation of DNA and histones, allowing the access of transcription factors to DNA sequences (91, 191). As previously noted, butyrate is able to induce the expression of the p21 and p27 proteins in colonic cells (159).

The consumption of a diet rich in fiber has been associated with decreased incidence and growth of colon cancers: Does butyrate contribute to mediating this salutory effect? In vitro results are convincing. The compound, at millimolar concentration, inhibits the growth, induces differentiation, and triggers apoptosis in colon cancer cells (9, 10, 14, 18, 92, 102a, 104, 159, 278, 289, 315).

How do we reconcile the growth-restraining, apoptosis-inducing action of butyrate in vitro with the contradictory observation that, in vivo, normal colonocytes are able to grow in the environment of about 20 mM butyrate produced by bacterial fermentation? Indeed, an in vivo increase of the butyrate supply results in growth stimulation of cells in the colonic crypts. The growth-enhancing effect on normal colonic epithelial cells was previously observed in vivo and has been recently confirmed by continuous infusion of butyrate into rat colons (124). Therefore, butyrate has apparently opposite effects: it serves as an important energy source for normal colonic epithelium and as an inducer of the growth of colonic mucosa, and yet in colonic tumors it impedes growth and promotes differentiation and apoptosis (102a). It is reasonable to surmise that butyrate may act differently on normal cells compared with transformed cells, or it may be metabolized differently in the different cells. Several plausible explanations for these contradictory observations have been offered (176a), and the reader is referred to an incisive commentary on the butyrate "paradox" (93). The point of importance pertaining to dietary factors and colorectal cancer is that butyrate impedes the growth of colonic cancer, acting, at least partly, as an inducer of apoptosis.

CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA), a naturally occurring nutritional substance, describes collectively one or more positional and geometrical isomers of linoleic acid (*cis*-9, *cis*-12 octadecadienoic acid), a minor fatty acid found predominantly

in the form of triglycerides in beef and in dairy products. Conjugated double bonds are at positions 9 and 11 or 10 and 12, and each double bond can be in either the *cis* or *trans* configuration (208). Milk fat is the richest natural dietary source of CLA. Studies of anticancer properties of CLA have been conducted on mammary carcinogenesis. In rats with mammary tumors, CLA has proven to be a potent chemopreventive agent (126). Very little work has been done to investigate the chemopreventive activity of CLA in colon carcinogenesis. In cell culture systems, physiological concentrations of CLA ranging from 1.87 to 7.14×10^{-5} M inhibited the proliferation of HT-29 colorectal cancer cells by about 37–47% (268). Administration of CLA in the diet protected against 2-amino-3-methylimidazo[4,5-*f*] quinoline (IQ)-induced adduct formation in the rat colon, as well as in the number of aberrant crypt foci (ACF) in the colon, early preneoplastic biomarkers of malignant potential in the process of colon carcinogenesis (154). In the last study, CLA had no effect on the size of foci, but it inhibited significantly the number of aberrant crypt foci in the colon, from 4.3 to 1.1 in control rats. The mechanism by which CLA exerts its anticancer activity is not clear.

SPHINGOMYELIN

Both exogeneous and endogenous sphingomyelin (SM) are present in the intestinal tract. The exogenous SM is derived from dietary nutritional sources including milk, soybeans, and animal tissues (208).

In addition to its structural function as a component of plasma membrane, SM plays a central role in transmembrane signal transduction and cell regulation (208, 283, 330). The interaction of extracellular agonists with specific membrane receptors activates sphingomyelidases that cleave SM to generate ceramide and phosphocholine (55, 208, 283, 330). It is well established that ceramides are second messengers that convey signals to the nucleus via tiers of downstream effectors (82). Ceramide-related pathways are related to three important cell-regulating functions: inhibition of cell growth, induction of cell differentiation, and induction of apoptosis (82, 208, 283, 330). Of note, ceramide is also hydrolyzed to sphingosine, a long-chain sphyngoid base that exerts antigrowth actions similar to those of the parent compound (82, 208, 283, 330).

Recent studies in rodents indicate that the digestion of exogenous SM in the intestinal lumen and the hydrolysis of endogenous SM in the intestinal mucosa are of relevance to colon cancer (54, 55, 57, 265, 266). It is interesting that the activity of all isoform types of sphingomyelidases is markedly decreased in human colorectal carcinomas (55, 105). This decrease is particularly prominent in the alkaline isoform of the enzyme resident in the intestinal brush border region that plays an essential role in the digestion and absorption of dietary SM (55).

Recently, a significant reduction of alkaline sphingomyelidase activity in polyps from FAP patients was reported (55, 105). It is noteworthy that the transformation of normal mucosa to colonic adenomas and carcinomas is accompanied by progressive resistance to apoptosis. Of relevance is whether the decreased sphingomyelidase activity and consequent decreased production of ceramide/sphyngosine is responsible for the attenuation of the apoptotic cascade in the transformed colon cells.

Administration of dietary SM may, therefore, impede colon carcinogenesis in the early stages of the neoplastic process by exerting cumulative antiproliferative, differentiation, and apoptosis-inducing actions (36, 321) on aberrant colonic cells that still retain sphyngomyelinase activity. The precise mechanism of action of SM in exerting an anticancer action remains to be clarified.

CALORIES AND COLON CANCER

Currently there is considerable interest in the relationship between calorie intake and carcinogenesis. When investigating their relationship with any chronic disease it is difficult to distinguish between the energy intake and intake of dietary fat; thus the question has been raised several times whether the effect of dietary fat on carcinogenesis is due to specific action of fat or to an associated caloric effect (31, 232). Pioneering studies by Tannenbaum & Silverstone (290) and others (254) indicated that calorie restriction reduces the formation of spontaneous and chemically induced tumors in mice. Epidemiological evidence indicating the role of calories on colon carcinogenesis came from case-control studies (84, 187). Further studies have shown decreased oxidative damage to DNA by calorie restriction.

Klurfeld et al (139) demonstrated that DMH-induced colon tumors were inhibited by calorie restriction in rats, although the calorie-restricted rats ingested twice as much fat as ad libitum–fed animals. They concluded that calorie ingestion may be a greater determinant than dietary fat in enhancing tumorigenesis. Calorie restriction by 25% exerted an inhibiting effect on colon carcinogenesis when the initiating agent was MAM acetate (requiring host activation) but not when it was MNU (direct-acting carcinogen), which suggests that the metabolic activation of MAM was interrupted in the rats on the restricted dietary regimen (217). The effect of a high-fat, semipurified diet ingested ad libitum and of a 30% calorie-restricted diet on AOM-induced colon carcinogenesis during the postinitiation phase was investigated by Reddy et al (248). The animals on the calorie-restricted diet consumed about 30% fewer calories from carbohydrate, protein, and fat but consumed the same amount of vitamins, minerals, and fiber. They developed significantly fewer colon tumors and had a lower colon tumor incidence than did the rats in the ad libitum group. In the second study, the dose-response effect of 10%, 20%, and 30% calorie restriction was investigated

(141). The incidence and multiplicity of colon tumors were significantly inhibited in animals fed 20% and 30% calorie-restricted diets. The regression coefficient representing the dose-response effect of different levels of calorie restriction is significant.

ADDITIONAL FOOD COMPONENTS PROTECTIVE IN REDUCING RISK FOR COLON CANCER

Dietary Calcium and Vitamin D

Human diets in developed or Western countries tend to have a high fat content (i.e. 30–40% of calories). A small amount (2–4%) of dietary fat remains unabsorbed and appears in the colon as free fatty acids, in conjunction with a small amount of unconjugated bile acids. These acids are both highly irritating to colonic epithelium and are believed to act as promoters of colonic tumorigenesis (171). Adequate dietary intakes of dietary calcium and vitamin D actually form insoluble bile and fatty acid complexes to protect the colonic epithelium. Calcium has direct antiproliferative and differentiating-inducing effects on colonic epithelial cells (29a). Evidence is available that calcium induces apoptosis in a variety of cells (178, 179, 201, 300). Vitamin D restrains proliferation and induces differentiation and apoptosis in a variety of normal and cancer cells, including cells of the large intestine (63, 68, 100, 102, 129, 218, 287). Eisman et al (62) reported that 1,25(OH)2D3 markedly inhibited the in vivo growth of human cancer xenografts in immunosuppressed mice. Belleli et al (19) observed a protective role of vitamin D in chemically induced rat colon carcinogenesis.

It has been suggested that increasing dietary calcium and vitamin D in Western high fat diets could reduce colorectal cancer risk (200). Subsequent studies in rodents indicated that high-fat and bile acids induced hyperproliferation and hyperplasia, and this was prevented by increasing dietary calcium (309, 310). This was further confirmed in the colonic mucosa of human subjects at increased colon cancer risk (158). Other subsequent studies largely confirmed the effect of increased dietary calcium in reducing hyperproliferation in the colon epithelium of human subjects (17, 22, 205, 261, 308; reviewed in 261).

The biochemistry and physiology of calcium and vitamin D are highly interrelated. In longer-term studies of effect on chemical carcinogen-induced colonic carcinogenesis, both calcium and vitamin D supplementation inhibited high dietary fat–promoted colonic carcinogenesis (209, 280).

A diet with increased fat, reduced calcium, and vitamin D designed to mimic the Western diet produced hyperproliferation and hyperplasia of colonic epithelium in short-term studies in mice and rats (199). Long-term administration in mice produced polypoid hyperplasias and dysplasias in the colonic epithelium (251).

The molecular basis of the protective effect of vitamin D remains to be elucidated. Although the case for vitamin D action via the mediation of calcium ions is well documented, the possibility should be considered that the secosteroid may also exert an antitumor effect in colonic neoplasia by acting at the genomic level of colonic cells (1, 99, 107). Many, but not all, epidemiologic studies indicate a decreased risk of colorectal cancer with increased dietary intake of calcium and/or vitamin D (8, 23, 71–73, 135, 143, 152, 165, 168, 175, 198, 211, 213, 253, 281, 282, 286, 322). Several recent studies in Sweden (225), Uruguay (52), and the United States (137) indicate significant reduction of colorectal cancer risk with a higher regular dietary intake of calcium and/or vitamin D.

Several recent epidemiologic studies of human calcium intake and risk of colorectal adenomas (a precancerous lesion) suggest that a high intake of calcium is associated with a decreased incidence (173, 174) and also decreased risk of recurrent adenomas, especially for those on a high-fat diet (123). A large randomized controlled trial of calcium supplementation to prevent colorectal adenoma recurrence indicates that calcium supplementation can prevent a significant proportion of individuals from a recurrence of colorectal adenomas, the clinical precursor of most colorectal cancers (16).

In summary, some protective effects of increased dietary calcium and vitamin D against risk of colorectal cancer in high-fat diets are now recognized. However, the protective effect appears to be modest, or partial. From the original hypothesis (200), the protective effect would be largely at the early promotion stages of tumorigenesis. No effect has been found on the initiation or late stages of colon tumorigenesis. However, within this narrow range, primarily during high-dietary-fat promotion of early stage colon tumorigenesis, increased dietary calcium and vitamin D may be useful. Regarding dietary levels of calcium required for risk reductions, it is interesting that animal, epidemiologic, and intervention studies suggest a preferred total intake of about 1800 mg of calcium daily, very similar to the level proposed for prevention of osteoporosis. Likewise, a level of 400 IU of vitamin D daily, suggested by results of colon cancer studies of rodents, is similar to that suggested for osteoporosis. Current recommendations of daily adequate intake (AI level) for adults include 1000–1300 mg of calcium, and up to 600 IU of vitamin D (207). Thus, the moderate protective effect of increasing dietary calcium and vitamin D can be achieved with dietary levels similar to that currently recommended for prevention of other diseases (i.e. osteoporosis) and well within current long-term safety guidelines.

Selenium

Several epidemiologic and experimental studies of laboratory animals have led to consideration of the protective role of selenium in human cancers.

Epidemiological studies indicate an increased incidence of colorectal cancer in humans in geographic regions where selenium is deficient (26), and cancer mortality rates were significantly lower for total cancers of the lung, colon and rectum, bladder, breast, esophagus, and cervix in areas with high selenium levels (274, 303). Comparisons between and within countries have also indicated that levels of dietary selenium intake may be related to differences in cancer incidence in human populations (26, 274, 303).

Further support for the protective role of selenium came from the discovery by Rotruck et al (255) of its essential role in the functions of glutathione peroxidase (GSH-Px), an enzyme that is responsible for preventing damage due to peroxidation, and also from experiments demonstrating that selenium is a chemopreventive agent in chemically or virally induced tumors in animals (86–88, 192). A recent multicenter, double-blind, randomized, placebo-controlled cancer prevention trial by Clark et al (37) demonstrated that daily oral administration of 200 μg of selenium supplied as 0.5 g of high-selenium brewer's yeast significantly reduced total cancer mortality (relative risk, 0.50) and incidence of colorectal cancer (relative risk, 0.42).

Studies with animals indicate that supplementation of the diet with inorganic selenium protects against chemically induced cancers, including cancers of the colon, mammary gland, pancreas, liver, and skin. Studies using supplemental sodium selenite in the drinking water show that selenium at a level of 4 ppm reduces the incidence and/or multiplicity of chemically induced colon tumors, and that maximal inhibition is usually achieved following continuous exposure of the animals to selenium. Reddy et al (244) demonstrated that inorganic selenium administered in diet in the form of Na_2SeO_3 is effective when it is given only during the postinitiation stage of chemically induced colon carcinogenesis.

Although inorganic selenium compounds have been shown to inhibit carcinogenesis, their toxicity is a matter of concern. Chronic feeding of inorganic selenium compounds at levels >5 ppm is toxic to animals because the liver is a key target. Because selenium occurs predominantly in the form of selenomethionine in cereals, grains, and vegetables, and human exposure to it is primarily through ingestion of organic selenium forms, a rationale exists for developing less-toxic organoselenium compounds with potential chemopreventive properties. Synthetic organoselenium compounds have been designed to achieve greater chemopreventive efficacy and to reduce toxic side effects. On the basis of mechanistic and short-term efficacy studies, 1,4-phenylene-bis(methylene)selenocyanate (*p*-XSC), a second-generation synthetic organoselenium compound, was evaluated for its chemopreventive activity against AOM-induced colon carcinogenesis in male F344 rats. This study demonstrated that dietary *p*-XSC administered at dose levels equivalent to 10 or 20 ppm, as selenium significantly

inhibited AOM-induced colon carcinogenesis at both initiation and postinitiation stages. In contrast, sodium selenite (4 ppm as selenium) inhibited colon carcinogenesis only during the postinitiation stage. In another study, it was shown that administration of *p*-XSC during or after the initiation periods in diets containing high and low levels of fat inhibited AOM-induced colon carcinogenesis in male F344 rats. The chemopreventive effect of *p*-XSC was more pronounced when the compound was administered with a low-fat diet compared with high-fat diets, emphasizing that a low-fat diet along with chemopreventive agents provides a desirable approach for secondary prevention of colon cancer in high-risk individuals. With regard to mode of action in colon carcinogenesis, *p*-XSC inhibited prostaglandin E_2 (PGE_2) levels and enhanced GSH-Px activity and apoptosis in the rat colon. This may in part account for the chemopreventive activity of *p*-XSC during the postinitiation stage of carcinogenesis.

Inositol and Inositol Phosphates

Inositol is a cyclic alcohol (cyclohexanehexol) closely related chemically to glucose. Of the nine inositol isomers, only *myo*-inositol is of importance in plant and animal metabolism. It is found in plants, usually as phytic acid, and in animal tissues, primarily as a constituent of phospholipids in biomembranes (109).

The *myo*-inositol content of tissues is provided primarily by the diet and through biosynthesis (3, 153, 185). *myo*-Inositol is synthesized from D-glucose by the hydrolytic action of inositol-1-phosphatase on inositol-1-phosphate derived from cyclization of glucose-6-phosphate (11, 25, 110). Adult humans consume approximately 1 g of inositol/day from animal products, as well as from plants, which are particularly rich in inositol hexaphosphate (phytic acid, phytate). Inositol is also present in high concentration in breast milk. Serum-inositol concentration in normal subjects averages 29.0 μmol/liter (0.5 mg/dl) (11, 25, 110). Dietary *myo*-inositol has not been shown to produce any known deleterious effect to any organ system when given in amounts often far greater than those present in normal diets (96). Several full reviews pertaining to the nutritional and biological importance of inositol are available (3, 26, 223).

Free inositol is actively transported across the intestinal mucosa by a mechanism dependent on sodium and energy and is taken up in most tissues against a concentration gradient (11, 25, 32, 109, 110). The *myo*-inositol transporter is distinct from the glucose carrier (11, 25, 32, 109, 110).

In mammalian cells *myo*-inositol exists in its free form and as phosphorylated derivatives. The importance of *myo*-inositol as a key bioactive molecule is well established (11, 21, 25, 110). Briefly, the biochemical pathway includes phosphatidylinositol, which is sequentially phosphorylated to phosphotidylinositol

1-4,5-biphosphate. This intermediate is cleaved by phospholipase C in stimulated cells when receptors are occupied by various agonists and thereby leads to the formation of the second messengers, inositol 1,4,5-triphosphate, involved in intracellular calcium mobilization and 1,2-diacylglycerol, with resultant activation of protein kinase C (PKC) and phosphorylation of key intracellular substrates (11, 25, 110). Membrane phosphatidylinositol can also serve as a source of arachidonic acid for the synthesis of eicosanoids (including prostaglandins, leukotrienes, and thromboxanes) (11, 25, 110).

A polyphosphate inositol derivative, inositolhexaphosphate (IP6), is a ubiquitous compound in the plant kingdom, present as phytic acid (11, 25, 110). It is also the most abundant inositol phosphate found in mammalian cells, occurring at the concentration range of 10–100 μM (11, 25, 110). Much of ingested IP6 is hydrolized to free inositol by intestinal phytases (11, 25, 110).

In their incisive studies since 1989, Shamsuddin et al (272–274) and Vucenik and colleagues (306, 307) have used phytate, with or without inositol, as an ancillary dietary component to inhibit tumorigenesis in the colon, as well as other organs, of rats and mice, indicating systemic absorption and anticancer effectiveness in vivo of both of these agents. They have convincingly shown (272–274) that inositol hexaphosphate suppressed hyperproliferation and tumor formation in the mouse colon after injection with the colonic carcinogens DMH or AOM. Similar inhibition also occurred with *myo*-inositol (272, 273), a more common, and safer, dietary component. Both phytate and inositol are active inhibitors in initiation and postinitiation stages of DMH-induced colonic carcinogenesis.

Vucenik et al (306, 307) reported that both phytate and *myo*-inositol inhibited DMBA-initiated mammary carcinogenesis in rats. Wattenberg and Estensen (312, 313) reported a chemopreventive effect of inositol in two different models of lung carcinogenesis in mice. Jyonuchi et al (134a) have recently reported that myoinositol exerts a protective effect against carcinogenic insult in immortalized human small airway epithelial cells.

The use of phytate as a chemopreventive agent poses problems in that it chelates cations (40, 192), particularly iron, zinc, and calcium (40, 192), reducing their bioavailablility. In contrast, *myo*-inositol, which does not have phosphate groups, is devoid of this potentially harmful attribute. It can be consumed at high-dose levels without evidence of toxicity. *myo*-Inositol has been used clinically to minimize diabetic neuritis and cataract formation (38). The administration schedules employed used dose levels of several grams per day over a long period of time (87, 88), and in none of those studies was toxicity encountered. Restoration of nerve conduction velocity has been demonstrated in patients with diabetic neuropathy following the addition of *myo*-inositol to their diets (86, 88, 177, 318).

Still to be addressed is the question of the mechanism(s) of action of *myo*-inositol and IP6 as antiproliferative anticancer agents. Shamsuddin et al (273) have hypothesized that IP_6 exerts an anticancer effect by entering the intracellular inositol phosphate pool with the subsequent production of lower inositol phosphates compounds. Therefore, it may be that changes in Ca^{2+} fluxes inside the cell are provoked by the sustained delivery of *myo*-inositol and phosphorylated derivatives thereof. It is noteworthy that in cells of disparate lineages, including colonic cells, an increase in intracellular Ca^{2+} is associated with antiproliferative, differentiation-inducing effects (29a, 157).

Philipps and colleagues (212) recently reported that colorectal tumors exhibit enhanced phosphatidylinositol 3-kinase (PI-3K) activity. The enzyme phosphorylates inositol phospholipids at the D-3 position of the inositol ring and plays a pivotal role in the control of cell growth. PI-3K has been implicated in tumor promotion in a variety of cells (103, 114). It is interesting that recent in vitro findings suggest that IP6 inhibits cell transformation and activator protein 1 activation by targeting PI-3K (115). One may argue therefore that the constant delivery of dietary *myo*-inositol, although providing the enzyme with the appropriate substrate(s), would, in turn, maintain and expand the intracellular pool of IP6 with a subsequent inhibition of PI-3K activity in a kind of negative-feedback loop.

It has been also recently reported that IP6 upregulates the tumor-suppressor gene *p53* and *WAF1* gene expression in the human colon carcinoma cell line HT-29 (256). A putative similar action of IP6 in vivo on cancer cells may be envisaged.

Finally, the alternative possibility is that influx of inositol impedes normal glucose oxidation, thereby depriving the cell of energy. This is consistent with the observation that although the pathway for *myo*-inositol to cross the brush border area is distinct from that of D-glucose (11, 25, 32), the two compounds seem to interact at the level of the translocation step, as sugars that interact with and utilize the translocation step of glucose transport for entry into the intestinal mucosa exert a noncompetitive inhibition on the transport of *myo*-inositol (32).

So far, the information regarding inositol (and/or its phosphorylated derivatives) for risk reduction of experimental colon cancer is very promising, but further work is needed to firmly establish the usefulness of inositol as an agent for human colon cancer inhibition.

Dietary Substances with NSAID Properties

The observation that dietary components exhibit biochemical and physiological properties analogous to NSAIDs (nonsteroidal anti-inflammatory drugs) has fostered increased interest in research on the use of those dietary substances as potential agents in reducing the risk of colorectal cancer. Data from a wide

variety of sources strongly, and almost unanimously, support the conclusion that NSAIDs reduce the incidence of, and mortality from, colorectal cancer and the risk of developing the precursor lesions (adenomas) of colon cancer (75, 78, 142, 206, 302). Several NSAIDs are known to antagonize colon tumor formation in rodent models of colon cancer induced by chemical carcinogens. Several substances in foods, particularly some plant phenolic compounds found in cereals, fruits, vegetables, beverages, and spices, have shown NSAID-like activity as inhibitors of arachidonate metabolism by inhibiting COX and/or LOX activity in laboratory studies (228). A few of these dietary components have been selected for testing as inhibitors of colon carcinogenesis, partly because they can reach significant levels in human diets and because they also have potent antioxidant activity. They appear to pose less risk than NSAID-tailored pharmaceutical drugs for inducing side effects and therefore might be better tolerated over long periods of dietary intake necessary for colon cancer prevention.

Laboratory rodent studies suggest inhibition of colonic carcinogenesis induced by chemical carcinogens for some plant phenols in this category. A description of each follows.

CURCUMIN Curcumin (diferuloylemthane; 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (*a*) has been identified as the major yellow pigment in turmeric (the powdered form of the root of the plant *Curcuma longa* Linn), curry, and mustard, (*b*) is an approved food additive in the United States, and (*c*) is available commercially at a low cost, particularly 97% pure formulation of curcumin (with minor amounts of demethoxycurcumin and bisdemethoxycurcumin) (83, 193). It is noteworthy that the use of medicinal plants, or their crude extracts, in the prevention and/or treatment of several chronic diseases has been traditionally practiced in different ethnic societies worldwide. Turmeric, the powdered rhizome of *Curcuma longa* Linn, has been used to treat a variety of inflammatory conditions and chronic diseases (6, 260, 284). It is also used as a coloring and flavoring additive to foods. Curcumin possesses both antiinflammatory (118–120) and antioxidant properties (276). It has been demonstrated that topical application of curcumin inhibits 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced epidermal DNA synthesis and tumor promotion in mouse skin (39, 118, 119). Topical application of curcumin has also inhibited benzo-[*a*]-pyrene (B[*a*]P)-induced DNA adducts and skin tumors as well as DMBA-induced skin tumors in laboratory animals (120). With regard to cancer of the colon, Rao et al (228) showed that 0.2% curcumin in the diet significantly suppressed AOM-induced formation of colonic aberrant crypt foci, early preneoplastic lesions, in male F344 rats. In addition, dietary administration of curcumin significantly inhibited the incidence (percentage

of animals with tumors) of colon adenocarcinomas by 42% and the multiplicity (tumors in rats) of invasive and noninvasive adenocarcinomas by about 56% (210). Dietary curcumin also significantly suppressed the colon tumor volume by >57% (210). Pereira et al (210) reported that dietary administration of 0.8% and 1.6% curcumin significantly inhibited the incidence and multiplicity of AOM-induced colonic adenomas in a dose-dependent manner. The incidence and multiplicity of adenomas in the animals fed the control diet were 47% and 0.58%, respectively, whereas the incidence and multiplicity of adenomas in animals fed 0.8% and 1.6% curcumin were 19% and 0.22% and 0.06% and 0.08%, respectively. The results of these studies strongly indicate potential chemopreventive activity of curcumin against cancer of the colon.

With regard to the mode of chemopreventive action, curcumin exhibits a diverse array of metabolic, cellular, and molecular activities, including inhibition of arachidonic acid formation and its further metabolism to eicosanoids (295). Dietary administration of curcumin significantly inhibited phospholipase A_2 in colonic mucosa and tumors, leading to the release of arachidonic acid from phospholipids, altered COX activity, and modified PGE_2 levels (210). Several lines of evidence also indicate that the mechanism of action of curcumin is not limited to prostaglandin inhibition. Curcumin inhibits LOX activity and the production of the LOX metabolites 5(*S*)-, 8(*S*)-, 12(*S*)-, and 15(*S*)-HETE in the colonic mucosa and in tumors (210). It is important that LOX metabolites such as 12(*S*)-HETE have been shown to promote tumor cell adhesion, stimulate the spreading of tumor cells, and augment metastatic potential. Also, a positive correlation was observed between the levels of 8(*S*)-HETE and hyperproliferation and tumor development induced by TPA (133). Moreover, curcumin inhibited several mediators and enzymes involved in cell mitogenic signal transduction pathways (161, 326) and AP-1 and NF_KB activation. Hanif et al (98) provided evidence that curcumin inhibits cell proliferation and induces cell cycle changes in the colonic adenocarcinoma cell lines HT-29 and HCT-15, and that this effect is independent of its ability to inhibit prostaglandin synthesis. The inhibitory effect of curcumin is associated with increased apoptosis, which suggests that increased cell death through apoptosis may be one of the mechanisms by which dietary curcumin affects this inhibition. Thus, it appears that curcumin exerts its chemopreventive effect on colon tumorigenesis by a combination of PG-dependent and PG-independent mechanisms, thereby reducing cell proliferation and inducing apoptosis (229).

Methodology for measurement of blood and tissue levels of curcumin and/or its metabolites is generally not yet available. However, current data (228) indicate that some absorption occurs from the gastrointestinal tract, but rapid conjugation and secretion to the bile occurs so that the bulk of the metabolites appears in the feces and less than 1% in the urine. Clinical studies are currently

under way, including phase 1 (tolerance) and biomarker indicators for effect on colonic epithelium.

QUERCETIN AND RUTIN Quercetin is a flavonoid present in varying amounts in most fruits and vegetables. It is often present in the glycoside form, such as rutin (the rutinose glycoside of quercetin), or in other glyocosides in onions, teas, apples, etc. These glycosides are largely hydrolyzed in the colon, although some may be hydrolyzed in the upper GI tract. Thus, rutin is a prodrug that is metabolized to the active compound, quercetin, largely in the colon. The net result of the biotransformation of rutin is the release of active quercetin for absorption, which can occur in the colon (166) and also in the upper portion of the GI tract. This metabolic conversion of rutin bears similarity to the pharmacological behavior of sulindac, which is also a prodrug and is converted, by colonic bacteria, to its active COX- and LOX-inhibitory moiety, sulindac sulfide. Both quercetin and rutin are frequently present in a large variety of fruits and vegetables consumed by humans, but at widely variable concentrations. Estimates suggest that the daily intake of flavonoids in the United States may be up to 1 g, with quercetin and its glycoside, rutin, representing between 50 and 500 mg/day. Both are inhibitors of AOM-induced colonic neoplasia in mice on a low-fat AIN-76A diet and of AOM-induced focal adenomatous dysplasia in mice on a high-fat–modified AIN-76A diet (50, 51). Quercetin appears to be more active than rutin. These data suggest that, regardless of dietary fat intake, quercetin and rutin can modulate molecular events in the genesis of carcinogen-induced colon neoplasias. Quercetin has been reported to be a potent concentration-dependent inhibitor of epidermal LOX activity and is purported to have COX inhibitory activity as well (138, 195). In addition, quercetin has a broad range of other activities. It can inhibit Na+K+-ATPase, PKC, various tyrosine kinases, HIV-associated reverse transcriptase, sarcoplasmic reticulum Ca^{2+} ATPase, $pp60^{src}$ tyrosine kinase, phosphatidyl-3-kinase, and 1-phosphatidyl inositol-4 kinase (196). Methodology to detect blood and tissue levels of quercetin and its metabolites has recently been reported (108, 166, 167). The inhibitory effect of dietary quercetin on mammary carcinogenesis in rats suggests that the circulating form, primarily conjugates of quercetin and the 3′-methoxy metabolite, may also be active in vivo (305). The relationship between circulating and colonic lumenal levels of these compounds is being studied in relation to effects induced in the colonic mucosal epithelium (67).

FOLATE Folate is a generic term for compounds that have vitamin-like activity similar to that of pterolymonogutamic acid (also called folic acid), the chemical that is added to supplements or fortified foods. Folic acid commercially is synthetic, heat stable, and approximately twice as bioavailable as the folate

that occurs naturally in food. In nutritional regulations and customary use, the terms folic acid and folate are interchangeable.

The current recommended intake in the United States is 400 μg of folate per day, but this is not achieved in the average diet. The US Food and Drug Administration has required that enriched grains be fortified with folate effective January 1, 1998, to supply an extra 100 μg/day to the basic (low) diet, primarily as a means of reducing neural tube defects (66, 67a). The low intake of dietary folate and its known important role in methylation reactions and nucleic acids biosynthesis prompted studies of folate dietary adequacy in relation to colon cancer risk (80, 164, 204).

In general, epidemiological studies support an inverse relationship between folate status and the rate of colorectal neoplasia (176). Two large, well-controlled, prospective studies support the inverse association between folate intake and incidence of colorectal adenomatous polyps (79) and of colorectal cancers (76). In these two studies, moderate-to-high alcohol intake greatly increased the neoplastic risk of a low-folate diet. There was a significant, 35% lower risk of adenoma among those in the highest quintile of folate intake ($\sim$800 μg/day) relative to those in the lowest quintile [$\sim$200 μg/day, relative risk (RR) $\sim$0.65]. The adverse effect of high-alcohol intake coupled with a low-folate diet was confirmed by Glynn et al (81): an observed significant fourfold increase in risk of colorectal cancer. Participants in the Physicians' Health Study pertaining to methylenetetrahydrofolate reductase polymorphism had reduced risk of colon cancer, but low folate intake or high alcohol consumption appeared to negate some of the protective effect (164).

Patients with chronic ulcerative colitis are at increased risk for colonic cancer and coexisting folate deficiency. Sulfasalazine, a drug taken chronically by these patients, inhibits folate absorption (97) and metabolism (270). Lashner et al (150) observed that the rate of colonic neoplasia was 62% lower in folic acid–supplemented patients with chronic ulcerative colitis compared with unsupplemented patients, and that sulfasalazine therapy was associated with an increase in the risk of dysplasia. These observations were not statistically significant but pointed to an important area of investigation. In an additional study Lashner (149) prospectively compared the red cell folate concentrations in patients with neoplastic changes in the colorectum with those for disease-matched controls without neoplasia. The results were 1000 nmol/liter or 454 ng/ml compared with controls, 1200 nmol/liter or 520 ng/ml, still well within the normal range, which is in line with observations in the uterine cervix (30).

Animal studies appear contradictory, in that whereas folate deficiency can reduce the growth of several tumors (204), and a folate antagonist, methotrexate, is used clinically to retard the rate of tumor growth clinically, dietary folate deficiency can enhance the growth of tumors in some rodents (204). However, a recent report suggests that dietary folate deficiency increases the risk of

malignancy when there is an underlying predisposition to colorectal cancer in dimethylhydrozine-induced tumors in rats (42).

More evidence for or against a causal relationship between folate status and colorectal cancer will be provided by data from prospective controlled intervention trials that are currently under way.

OLIVE OIL AND SQUALENE Epidemiological studies of populations in the Mediterranean area suggest that breast, colon, and perhaps pancreatic cancer are lower in areas with a high intake of olive oil. Squalene, a triterpene found at low levels in many foods and in human and animal tissues, is uniquely high in olive oil compared with other common human foods. It has been proposed as the active agent in olive oil for reducing cancer risk (197). A study of AOM-induced aberrant crypt foci in rat colon epithelium suggests that squalene may be a useful dietary agent for reduction of risk of colon cancer (227). However, more work is needed to confirm and establish squalene as an effective preventive agent for colorectal cancer.

SELECTED FOOD COMPONENTS BELIEVED TO BE RISK FACTORS FOR COLORECTAL CANCER IN HUMANS

Heterocyclic Amines

Heterocyclic amines (HCAs) are formed on the surface of high-protein foods such as meat or fish on exposure to high-temperature cooking processes such as frying or boiling, and particularly to charcoal broiling. At these aerobic high-temperature conditions, the meat-muscle component, creatinine, reacts with Maillard reaction products from the interaction of the protein amino acids and carbohydrates present to produce a series of HCAs. These are potent mutagens and in rats induce cancer in breast, colon, and pancreas, depending on structure. Several of the more prominent HCAs are potent colon carcinogens in rats (2, 151, 314). Reduction of HCAs in food can be accomplished by avoiding high-temperature cooking (frying or broiling), addition to the meat or fish of high antioxidant–containing foods, i.e. tea polyphenols, apples, etc, or processing to reduce creatinine content (short microwave and drain before cooking further), or addition of soy protein (65, 314). An estimate of dietary intake and cancer risk suggests that meat and fish products represent about 80% of the risk from HCAs (151).

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are largely formed by high-temperature pyrolysis of fuels associated with direct flame cooking of feed, and are ubiquitous in foods, environment, and soils, usually at very low levels. In

studies of rodents, they were mostly not carcinogenic to the colon, with the possible exception of B[*a*]P, but they are known to be potent carcinogens to other organs. It is not known whether the chronic intake of the low levels in human food represents a significant risk of colon cancer (188).

CONCLUSION

An impressive body of observation supports the concept that dietary factors are key modulators of colorectal cancer. A major challenge of modern nutrition is to gain insight into the biochemical sites of chemopreventive (or cancer-inducing) action of dietary agents at various tiers of cellular organization. In this context much interest is presently focused on the functional interaction between dietary agents and gene expression not only as a fascinating subject of basic research but also as mandatory knowledge of clinical relevance. A salient case in point is represented by recent intriguing findings showing that, at least in vivo, the nuclear peroxisome proliferator-activated receptor (PPAR)-γ, a transcription factor activated by endogenous fatty acids and cicosanoids (303a,b), may serve as a molecular link between high-fat diets and increased risk of colorectal cancer (152a, 255a).

Much progress in our understanding of the functional relationship between dietary factors and intestinal cancer has been provided by nutritional studies using knockout mouse models exhibiting phenotypic and genetic similarities to the human disease (326a). The emerging results reiterate the view that dietary components cross-talk, either in a beneficial or detrimental way, with the intestinal cell.

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