Dietary Fiber-mediated Mechanisms in Carcinogenesis

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Abstract

Dietary fiber may affect the development of cancers of the gastrointestinal tract and the breast. The biological intermediates studied most have been fecal bile acids; both human and animal studies suggest a tumor-promoting role of bile acids in the development of colon tumors, although there are conflicting data from human studies. Short-chain fatty acids are major fermentation products of bacterial degradation of dietary fiber. If short-chain fatty acids explain the tumor-inhibiting properties of dietary fiber, the readily fermentable fibers such as guar and pectin would be more protective than cellulose and wheat bran, which has not been observed. Because these two hypotheses do not adequately explain modulation of tumor growth by dietary fiber, investigation of other intermediates is indicated. These include physical characteristics of the feces, such as abrasiveness; intestinal microflora; aqueous-phase bile acids, which may represent the bioavailable pool; alterations in mucins; mutagenicity of intestinal contents; alterations in mucosal cytokinetics; activities of enzymes, such as ornithine decarboxylase or argyrol hydroxylase; neurogenic effects caused by changes in intestinal bulk or short-chain fatty acids; gut hormones or other peptide growth factors (local or systemic); enterohepatic circulation of hormones; transit time; pH; or decreased availability of total dietary energy.

Introduction

The protective role of dietary fiber against colon cancer was proposed in 1960 (1) and was extended by Burkitt in 1971 (2) to include a variety of chronic diseases prevalent in affluent societies. One of the attractions of dietary fiber for the public is that it is one of the few dietary components that are recommended to be consumed in greater quantities for improved health. The claims for dietary fiber in the biomedical literature include reductions of virtually all noninfectious disorders (3). It is generally assumed that dietary fiber has metabolic influences that counter the tumor-promoting effects of dietary fat. The original description of the fiber hypothesis rested on the ability of dietary fiber to decrease the exposure of the colonic mucosa to carcinogens and promoters (2). One significant problem in considering dietary fiber is that the definition has changed over time and there is no universally accepted method for its quantitation. Another major related factor is that there are multiple components of dietary fiber (Table 1). The broad groupings of soluble and insoluble fibers seem to have disparate effects on colonic physiology and development of colonic cancer in animal models (4, 5). There are carbohydrate and noncarbohydrate constituents of dietary fiber, and only some of the carbohydrates are well fermented when fed as isolated ingredients. In the typical diet, it has been estimated that 70% of dietary fiber is broken down by colonic flora. Eastwood (6) proposed that simply giving total dietary fiber values for food, without describing specific physiological effects, is analogous to providing a total vitamin content. In 1979, Graham et al. (7) commented on the lack of unequivocal evidence supporting the fiber-fat relationship with cancer. They believed the case for fat preventing cancer at that time. They stated, “It is likely that the etiology of colon cancer and other cancers is more complex than heretofore suspected (Ref. 7, p. 881).” Because we still do not understand the etiology of colon and other cancers, we are limited to discussing risk factors, i.e., statistical odds, rather than medical diagnoses. Most of the putative intermediates described below have been studied in normal populations (of both humans and animals) and, therefore, their relevance to development of cancer is uncertain. However, in the absence of knowledge regarding the degree of genetic influence, we are limited to assuming that dietary factors have a similar magnitude of effect across a population, even though this seems extremely unlikely.

One factor that is often overlooked is the distinction between colonic and rectal tumors, because there appear to be different risk factors in the etiology of these two tumors. This differentiation is not always easy, because of the relatively high number of tumors near the rectosigmoid junction. This raises the possibility that there are quantitative or qualitative differences in risk factors for colonic tumors at different sites within the colon. Differences in histological appearance of normal mucosa within the colon and of growth characteristics of tumors at various sites in the colon also suggest that responses of the epithelium may differ at different locations. Carcinomas of the right colon are generally bulky and rapidly growing, whereas tumors of the left colon tend to be flat and often grow in a characteristic napkin-ring configuration. In countries with low incidence of colon tumors most tumors are found in the proximal colon, but in affluent societies with high risk the majority of tumors are in the distal colon. An example of the difference in risk of colon cancer can be found in the recently published results of a large study of diet and mortality in China (8). Colon-cancer mortality ranges from 0.0 to 6.7/1000, and about one-third of the survey sites reported no colon cancer. Although the incidence rate is low by Western standards, the range of incidence within the country is greater than that seen in the United States. There was no correlation of colon-cancer mortality with total dietary fiber ($r = -0.01$) or any of its components. There were, however, significant positive correlations with schistosomiasis ($r = 0.72$) and percentage employed in industry ($r = 0.41$).

Bile Acids

Most studies on dietary fiber and colon-cancer risk have focused on the role of bile acids, and the majority of epidemiological reports have been ecological in nature. These studies are inherently weakest in their ability to link a specific nutrient or biological intermediate with risk of disease, because they almost always report average levels across a sample of the entire population. The average level may not be representative of high risk. The strength of this type of study is the wide range of disease incidence, nutrient intake, or bile acid concentration that can be seen internationally. Studies sponsored by the International Agency for Research on Cancer have contributed significantly by studying countries of similar socioeconomic status that differ 4-fold in colon-cancer incidence. One compar-
An objective of subjects in Copenhagen, Denmark, with subjects in Kuopio, Finland, found almost twice as much fiber intake in Finland but no difference in total fecal bile acid concentration per g dry weight during the spring, with a statistically significant 15% reduction during the autumn (9). A study of rural and urban areas of Denmark and Finland found that the rural areas in each country had half the colon-cancer incidence of their respective urban counterparts (10). This study, conducted during the spring, reported no differences in fiber intake but did find significantly lower bile acid concentrations in the Finns. Domellof et al. (11) compared healthy subjects in Umea, Sweden, with those in New York City and found fiber intake 2 times higher in Sweden, which corresponded to almost a 50% reduction of deoxycholic, lithocholic, and total bile acids per gram dry feces. Japanese in Hawaii have 4 times higher colon-cancer incidence than do Japanese in Akita. Although dietary fiber intake was not reported, marked differences in diet were found between the two groups, without significant differences in total fecal bile acids; there were reductions of deoxycholic acid and three minor unidentified bile acids for the subjects in Akita (12).

At the population level, the hypothesis relating fecal bile acid concentrations to colon cancer is generally supported, but case-control and intervention studies do not consistently support this relationship (13). Patients with colon cancer do not excrete significantly more fecal bile acids when fiber intake is similar to that of normal control subjects (14). Doubling fiber intake by including whole-wheat bread in the diet increased fecal wet and dry weight (15). Although there was no reported difference in the daily excretion of fecal bile acids, by inference there had to be a reduction in concentration. Reddy et al. (16) added whole-wheat and oat-fiber–enriched bread to the diets of Finnish subjects, doubling their fiber intake, and found significant reductions in secondary and total bile acids.

Animal models have been used to study the effects of bile acids on normal colonic mucosal cytokinetics and tumorigenesis after administration of a carcinogen. The earliest demonstration of this was reported by Chomchai et al. (17), who implanted the common bile duct at the midpoint of the small intestine. After carcinogen treatment, rats with bile-duct implants had a >2-fold increase in colonic tumors (with a proportionately greater increase in the distal colon) and a 2-fold increase in fecal bile acids. These data are correlative for bile acids and tumorigenesis, because other substances in bile, particularly phospholipids, may also be mediators of cytokinetics. Cholecystectomy (in species other than rats, which lack a gall bladder) should increase exposure of the mucosa to bile acids but has not shown consistent promoting effects on colonic carcinogenesis (18–20).

Although surgical diversion of bile increases exposure of the intestinal mucosa to higher but still physiological levels of bile acids, most studies that demonstrated a relationship among increased bile acid concentration, increased mucosal cytokinetics, and enhanced tumor growth used pharmacological levels of bile salts. One study that used a nonpurified diet to which fat (2 versus 25% beef tallow) and fiber (2 versus 27% cellulose) were added to change fecal bile acid concentrations within the physiological range found that fiber significantly reduced tumor yield and fecal bile acid concentrations; the difference in fecal weight between low- and high-fiber groups was approximately 8-fold, which is far more than can be achieved in humans (21). A study that specifically addressed the question of possible wheat-bran protection against colon cancer in carcinogen-treated rats during the promotion-progression phase, by dilution of colonic bile acids, was reported by Calvert et al. (22), who added small amounts of bile salts to the diets of rats fed 10% wheat bran, so that their fecal bile acid concentration was equal to that of rats fed a fiber-free diet. With equal fecal bile acid concentrations for treatment groups, wheat bran still afforded significant protection against tumorigenesis.

The mechanism whereby bile and/or bile acids are thought to affect carcinogenesis has been addressed by many studies. The most commonly cited mechanism involves cytokinetics of the colonic mucosa. Although the work of Lipkin (23) makes it clear that turnover of normal colonic epithelium is related to risk of cancer, it is not likely that transformed cells respond to the same qualitative or quantitative signals as do normal cells. There is disagreement as to the effect of cellulose on colonic mucosal cytokinetics, with some studies reporting decreased proliferation and others finding increased proliferation. Such proliferative effects do not always correlate with susceptibility to carcinogenesis (24–27).

### Short-Chain Fatty Acids

Another mechanism by which dietary fiber may modulate carcinogenesis is via fermentation to SCFAs\(^2\) in the colon. Butyrate is reported to be the preferred substrate for colonic epithelial cells. Infusions of SCFA mixtures were reported to increase proliferation at all levels of the gastrointestinal tract (28). These data suggest that fermentable fiber should increase carcinogenesis, whereas poorly fermented fiber should protect against tumor growth. Experimental results are far from unanimous on this issue (29–31). Butyric acid was reported to induce differentiation of colon-cancer cell lines in vitro (32). Two experiments were performed in which butyric acid was fed to rodents treated with carcinogens, and opposite conclusions were reported. One study found dose-dependent increases in colonic tumors of rats given 1 or 2% sodium butyrate in drinking water (33), and the other study found no difference in tumorigenesis in mice given 5% tributyric (34). The former study reported a doubling of colonic butyric acid, whereas the latter reported a 10-fold increase in fecal butyrate. Taken together, these data suggest no beneficial effect of SCFAs on reducing development of colonic tumors. The in vivo and in vitro effects of SCFAs on normal colonic epithelial proliferation also appear to be opposite (28).

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\(^2\) The abbreviations used are: SCFA, short-chain fatty acid; DMH, dimethylhydrazine; AOM, azoxymethane; ODC, ornithine decarboxylase.
Intestinal Contents

The foregoing suggests the need to search out novel biological intermediates that might be better indicators of risk or actual predictors of disease occurrence. One can make a list of multiple mediators that will be interrelated to some extent. The luminal contents are clearly modified by ingestion of dietary fiber, and this aspect of colonic physiology has been studied extensively. Alterations in colonic microflora exert marked effects on the colonic environment. These may be characterized by changes in bacterial species, functional changes in the bacteria as reflected by pH (35), or production of enzymes such as β-glucuronidase (36). Mutagenicity of intestinal contents, usually products of bacterial metabolism, may be a determinant of cancer risk that is potentially modifiable by dietary fiber. Although Reddy et al. (16) found inhibition of mutagenicity by fiber supplements to humans, Kuhnlein et al. (37) found no effect on mutagenicity of pectin or cellulose additions to rat diets. Bile acids are reported to also function as co-mutagens with DMH, which is not mutagenic by itself (38). Bile acids themselves may indirectly damage DNA, on the basis of decreased transfection efficiency in a bacterial system (39); when bile acids were preincubated with cellulose and possibly lignin (but not psyllium and pectin), transfection efficiency was not reduced. Cheah and Bernstein (39) hypothesized that cellulose catalyzed polymerization of bile acid molecules to a biologically inactive form, on the basis of UV-absorption spectra of bile acids preincubated with cellulose.

The presence of bacteria in the colon can modify susceptibility to carcinogenesis, but there appears to be no unidirectional effect. Surgical diversion of the fecal stream resulted in significantly fewer tumors in rats treated with AOM (40); a problem in interpreting this study is that all luminal factors are eliminated and there is decreased turnover of the colonic mucosa. Study of germ-free rats can distinguish between the presence of bacterial metabolites and other factors. Reddy et al. (41) reported that colonic tumorigenesis was higher in germ-free than in conventional rats treated with AOM intrarectally but lower in germ-free rats given DMH subcutaneously. Because AOM is a metabolite of DMH, these results are difficult to interpret. However, in both studies no tumors of the ear canal were found in the germ-free animals, whereas 48 and 87% of the rats given AOM and DMH, respectively, developed this tumor. This suggests that the presence of bacteria alters some aspect of carcinogen metabolism.

Other intestinal lumenal factors potentially modifiable by dietary fiber include direct binding, as was demonstrated for bile acids and steroid hormones (42, 43), which would modify enterohepatic circulation and subsequent excretion levels of the compounds mentioned, as well as carcinogens. Rather than total or specific bile acids in feces, the water-soluble portion that can contact the mucosa more intimately may be of greater biological significance. A final aspect of luminal contents that should be considered is the physical characteristics of the stool. Because excess colonic tumors occur primarily in the distal colon, after most water absorption has occurred, the abrasiveness of the stool may be an important determinant of nonspecific irritation that will increase risk of carcinogenesis. Several of the characteristics described in the original fiber hypothesis (2), such as fecal bulk and water, may contribute to aspects of abrasiveness.

Colonic Tissue Factors

Properties of the colonic mucosa itself that can be influenced by dietary fiber are likely to be important in determining risk of carcinogenesis. These include alterations in the type and amount of mucins produced (44), epithelial cytkinetins, metabolic activities of the mucosal cells, presence of and responsiveness to gut hormones and peptide growth factors, and neurogenic effects. Many enzymes were studied as indicators and as potential mediators of altered responsiveness to carcinogens. ODC was studied extensively in a variety of initiation-promotion schemes and does seem relevant for the colon, even though absolute activity is much lower than that in other organs, particularly skin. Inhibition of ODC leads to significant reductions in carcinogen-induced colonic tumors (45). Bile acids increase ODC activity, as does starvation and refeeding (46). Addition of 10% cellulose or guar gum to a fiber-free rat diet caused a 50% drop in colonic mucosal ODC, whereas 5% fiber additions had no significant effect (47). However, it appears that a specific isozyme of ODC is a more accurate marker of the malignant phenotype than is the measure of total enzyme activity (48). Protein kinase C is another marker enzyme that appears to be related to rapid growth of both normal and malignant cells. Bile acids stimulate this enzyme indirectly, by increasing the diacylglycerol content of the colonic epithelium (49), so it is reasonable to expect this is potentially modifiable by dietary fiber. Dozens of enzymes and metabolic changes that demonstrate increased glycolysis (characteristic of most tumors) and increased pyrimidine metabolism (typical of increased cell growth) have been measured in human and rodent colonic carcinogenesis (50).

An area that has only been explored by a few investigators, which should yield important information about control of normal and malignant cell proliferation, is the relationship of peptide growth factors and epithelial-cell renewal. Many peptide hormones have been shown to have trophic effects on specific sections of the gut, including gastrin, enteroglucagon, peptide YY, bombesin, epidermal growth factor, cholecystokinin, somatostatin, and insulin-like growth factor I (51–53). Consuming wheat bran reduced epidermal growth factor content of the colonic mucosa in rats by >60%, whereas small-intestinal levels were unchanged (54). Some of these peptide growth factors are responsive to caloric intake, growth, and body weight. Newberne et al. (55) showed that rats nursed in litters of four gained more weight than did rats nursed in litters of eight; the former animals were always heavier and significantly more susceptible to the tumorigenic effects of DMH. One mechanism by which caloric intake early in life may modulate susceptibility to carcinogens was presented by Albanes et al. (56), who found that, although caloric restriction did not significantly reduce the rate of DNA synthesis, the total number of colonic crypts was reduced and, therefore, the number of cells at risk was lower. This phenomenon may be mediated by systemic or local differences in one or more growth factors. We demonstrated that insulin and insulin-like growth factor I plasma levels and mammary-tumor receptor activity are modulated by caloric intake (57, 58). Both growth-factor levels and receptor expression correlate with tumor growth. Receptors for insulin and insulin-like growth factor I were identified on colonic epithelial cells (52), suggesting the possibility that these peptides regulate growth in the colon. Dietary fiber may act to decrease energy availability (59) or act through some other mechanism that would modulate levels of these growth factors.
Limited data are available concerning the relationship of dietary fiber to tumors outside the colon. A large case-control study conducted in Israel presented evidence that diet characterized by low fiber, high fat, and high animal protein was associated with higher risk of breast cancer (60). Rose (61) reviewed much of the data on this issue and suggested that dietary fiber may protect against breast cancer because of its influence on estrogen metabolism or its association with lignans.

It is clear that the alterations in bile acids and SCFA content of the colon do not adequately explain differences in colon-cancer development in humans or experimental animals. Although there are some correlations between the biological intermediates and the presence of tumors or regulation of mucosal growth, this relationship is not convincing enough to relate bile acids or SCFA causally with colon cancer. Although the evidence for most of the other potential mediators discussed above is even weaker, much less research has been carried out in these other areas. It is likely that one or more avenues of novel research will bring us closer to an understanding of how dietary fiber modulates the carcinogenic process.

References

DIETARY FIBER AND CARCINOGENESIS


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