Grist for the Mill: Role of Cereal Fiber and Calcium in Prevention of Colon Cancer

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Investigation into the causes and prevention of colon cancer has always been a fascinating area of cancer research. It remains so because of the complex interplay of genetics and environment in the etiology of this common malignancy (1,2). The dietary milieu probably provides mutagens that initiate colon carcinogenesis, altering critical genes involved in its genesis, and is the source of substances that promote the tumorigenic process. Fortunately, as the epidemiologic evidence underscores, the diet is seemingly rich in factors that modulate risk for the disease (3-5).

An impressive amount of experimental evidence, especially in laboratory animal studies, supports protective roles for cereal fiber and calcium in influencing risk for colon cancer. In carcinogen-treated rodents, research studies (6-13) have consistently implicated dietary fiber from wheat and supplemental dietary calcium as potentially protective in terms of reducing colon cell hyperproliferation upon short-term feeding and in reducing and protecting against the development of colon cancer in the longer term. The results have been inconsistent regarding the cancer preventive effects of other forms of cereal fiber. Some studies even suggested an adverse effect on the colon; i.e., some soluble forms of fiber have been shown to enhance cellular proliferation in the colon (14,15).

From the human standpoint, relatively few studies have addressed the possible mechanism of action of added dietary fiber and calcium in the prevention of colon cancer. One hypothesis that has withstood the test of time suggests that the digestion of a diet rich in fat enhances the release of primary and secondary bile acids, which are thought to act as tumor promoters in colon cancer (16-19).

In this issue of the Journal, Alberts et al. (20) report the findings of a randomized, double-blinded, placebo-controlled clinical trial in Arizona of supplemental wheat bran fiber and calcium on the excretion of fecal bile acids over a period of 9 months in subjects at increased risk for colon cancer. The salient findings of the Arizona intervention trial are as follows: 1) A 9-month supplementation of the diet with 13.5 g/day of wheat bran fiber resulted in documented reductions in the excretion of total fecal bile acids and the decreased production of primary and secondary bile acids suggested to promote colon cancer, and 2) supplementation of the diet with 1500 mg/day of elemental calcium led to a more modest reduction in total bile acids and primary and secondary bile acids. The Arizona team failed to find that the combination of a high-fiber diet and increased use of calcium supplements improved on either supplement taken alone in curbing the excretion of fecal bile acids.

Several other aspects of the Arizona trial are worth mentioning. Phase II cancer control clinical trials allow limited, mechanistic hypothesis testing that may have an impact on larger trials focusing on recurrent disease. Often these trials are unique opportunities to pilot test more difficult interventions, such as dietary change. The ability to hold other aspects of the diet constant while keeping the study subjects adherent to the dietary change was extremely well controlled in this study, in that nearly all subjects consumed at least 75% of their assigned intervention supplements for the 9-month trial.

While a protective effect for wheat bran supplementation was previously reported in patients with familial polyposis, adherence to the dietary plan diminished significantly by the end of the trial (21). It will be of interest to know if the ongoing randomized, adenoma recurrence trial of wheat bran supplementation in the metropolitan Phoenix, AZ, area initiated by the Arizona group maintains the high level of adherence reported in this issue of the Journal. The question of dietary adherence looms all the more important in view of the recent findings of the Australian Polyp Prevention Project, where a possible inhibitory effect of a low-fat/increased fiber diet on recurrence of adenomas was reported (22). As implied by Schatzkin et al. (23), the need to have and keep adequate numbers of subjects adherent in cancer control trials is vital to the interpretation of their success.

Increased output of bile acids into the colon has long been known to accompany a diet high in dietary fat (18,24,25). In animal studies, the long-term feeding of high-fat diets or dietary exposure of carcinogen-treated rats to primary and secondary bile acids has been shown to promote the development of colon cancer (26). It is interesting that high levels of dietary fat may...
cause an increase in the propensity for development of colorectal adenomas (24). Interventions designed to lower the output of bile acids (through fiber or calcium), specifically cholic acid and deoxycholic acid, have also resulted in an abrogation of their tumor-promoting potential (6). Alberts et al. (20) have found that the better of the two interventions in this regard was wheat bran fiber.

Both wheat bran fiber and calcium have the ability to bind dietary lipids, including bile acids. Although the Arizona trial did not quantitatively analyze fecal water and solids for bile acid binding, both interventions resulted in a reduction in total output and a diminution in quantity of cholic and deoxycholic acids, among the other bile acids assayed. Cholic acid and deoxycholic acid are known to stimulate proliferation of colonic epithelial cells when incorporated into rodent diets (26,27). Both bile salts have been shown to increase the incidence of premalignant and malignant tumors of the colon in a rat model (28). Therefore, the statistical reduction in fecal output reported by Alberts et al. (20) when the trial participants consumed wheat bran or calcium is biologically noteworthy. It will be of interest to see if adherence to the fiber diet translates into protection from recurrence of colonic adenomas in this study population.

Dietary fiber is a complex entity, and a reduction in bile acid output may not totally explain its potential benefit in the human colon. Likewise, calcium supplementation may have additional effects beyond those measured in the current study. Both fiber and calcium supplementation can dramatically alter the pH of the colon, resulting in changes in the physicochemical state of the bile acids and their ability to interact with cellular membranes (16,17,29-33). Wheat bran fiber, when utilized in the colon by the microflora, may generate appreciable quantities of butyrate, long suspected to aid in the redifferentiation of potential tumor cells (34,35). Additionally, Reddy et al. (36) have observed that short-term supplementation with wheat fiber in the diet of women reduced the output of fecal diacylglycerols, currently thought to act inappropriately signal cells to proliferate (37). Butyrate, long suspected to aid in the redifferentiation of potential tumor cells, may be involved in this process (38). Furthermore, calcium supplementation results in a reduction in the output of neutral sterols, are tumor promoters in the colon in man and in rodents. Environ Health Perspect 1992;100:685-92.

While not yet proven, evidence is mounting that changing the composition of the diet in areas of the world where colorectal cancer remains a significant health problem may lead to prevention of this neoplastic disease. The findings of the Arizona trial are encouraging; taken together with the completion of other ongoing colon cancer prevention trials utilizing dietary change as the preventive vehicle, these results should soon provide a much clearer picture of the role of diet in the etiology and prevention of colon cancer.

References

(2) Potter JD. Colon cancer—do the nutritional epidemiology, the gut physiology and the molecular biology tell the same story? J Nutr 1993;123:418-23.


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