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Flushing Out the Truth: Could Dietary Fiber Really Be the Magic Bullet for Colon Cancer Prevention?

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## Introduction

Colorectal cancer is the third most prevalent cancer in the United States. It is also the second leading cause of cancer morbidity in the US, accounting for approximately 47,000 deaths a year (1). Colonic tumorigenesis is a gradual process which often takes years to develop. The colonocytes first hyperproliferate, then form adenomatous polyps. Polyps themselves are benign and half of all Americans will develop them by age seventy. These might or not might progress into gross malignancy and metastasis. It now appears that this largely depends on an accumulation of genetic changes affecting numerous regulatory genes and pathways. Despite increasing molecular knowledge regarding the neoplastic process, the actual cure rate for colorectal cancer has not significantly improved in the past 30 years (2). Therefore, either primary or secondary prevention appears to be key in reducing mortality rates.

Intervention could involve arresting the process at any of the progressive stages. Due to colorectal cancer's seemingly strong correlation to diet, dietary and micronutrient approaches to prevention appeared to be a promising avenue. Indeed, numerous studies, such as the Australian Polyp Prevention Project, have reported that a high fiber diet led to an inverse relationship to colon carcinogenesis. However, the actual mechanism of fiber's role in arresting or preventing carcinogenesis has yet to be understood (3). Nor is fiber even accepted as being crucial in cancer prevention. The newly published and widely cited Fuchs study now completely dismisses any special importance of fiber in assessing one's colon cancer risk. This of course contradicts numerous studies which extolled the virtues of fiber as a cancer preventer (4). In reviewing the literature on the topic, perhaps the most striking aspect is the sheer lack of consensus regarding the matter. Therefore, it appears to be a good time to revisit the issue of dietary fiber and its possible role in colon cancer prevention.

What do you mean by fiber?

Fiber is found only in plant foods (5). Found in fruits, grains, vegetables, legumes, nuts and seeds, fiber cannot be digested. Fiber comes in both insoluble and soluble forms. In terms of cancer prevention, the danger of lumping fiber as one nutritional entity is becoming clearer. For example, poorly fermentable fibers such as wheat bran has demonstrated protective elements while readily fermented fiber such as oat actually may promote tumor development (2).

History behind the 'dogma'

The connection between dietary fiber and lowered colorectal cancer risk first began in 1971 when it was observed that black Afrikans suffered much lower rates of colon cancer than white Afrikans (6). The former group's diet was composed mainly of grains and unrefined foods. The latter adhered to a "Western Diet," which centered around animal protein and contained low amounts of plant foods. Since then, the possibility of fiber intake being the key to unlocking colon cancer's deadly mechanism had held the attention of scientists. The role of fiber as a colon protector was strengthened when in 1978 colon

cancer rates between Finnish and New York residents were compared. The study found that both had high fat diets but the former experienced less rates of colon cancer. The researchers attributed this to the Finn's higher fiber diet. Since then, numerous animal models, cohort and case-control studies have supported the fiber hypothesis (7, 8, 9). For example, the results of a 1992 paper evaluating 13 past case-control studies confirmed a statistically significant improvement in risk for the high fiber intake group (1). Central to the fiber believers' arguments were epidemiological studies showed that colorectal cancer was mainly a Western phenomenon and was relatively rare in developing nations. However, sharp increases were being detected in Eastern Europe and Japan as they incorporated a more Western style of food consumption and lifestyle.

However, it must be stated that the fiber hypothesis remained a subject of much heated debate. Epidemiological studies face the credibility obstacle of being retrospective in nature. Many argued that the results would be inevitably colored by various recall biases. Also, it was difficult to discern between the benefits of fiber and the other constituents of plant foods in one's diet. At best, many felt that the data was inconclusive and should be guarded with skepticism (10).

#### The 'new' controversy

While the exact nature of fiber's role remained subject to further investigation, many had come to accept fiber as a potent ally in the fight against colon cancer. Thus, Fuchs, et al's dramatic conclusion that dietary fiber held no special role in reducing colon cancer risk stirred up old doubts and invited new questions. The Fuchs study was deemed significant for its focused sample population (all registered nurses, between 30 to 55 years of age, with no family history of cancer or polyposis syndrome). and its prospective, meticulous cohort design (11). A semi-quantitative food- frequency questionnaire was sent every two years for a follow-up period of 16 years. Outliers for energy intake levels were taken out of the sample at the start of trial. The Fuchs project is not alone in its grim conclusions. The Health Professional Follow-up Study of 1997 which followed 16,448 men also seem to indicate that insoluble fiber conferred minimal if any benefits on actual colon cancer risk (12). However, the study did find that soluble fiber reduced the risk of adenomatous polyps of the distal colon, and the authors support the national dietary guidelines regarding fruit intake levels. These studies provided few new leads for investigation and seem to leave the quandary of colon cancer prevention back at the starting gate.

#### Possible mechanisms of protection: exploring the new molecular frontier

Originally, fiber's possible protective properties was attributed mainly to its propensity to clean house- acting as a 'colonic broom.' Foremost, fiber, being undigestible, adds fecal bulk. The increased bulk consequently dilutes or adsorbs fecal carcinogens. Another possibility is that fiber actually reduces colonic transit time, thereby minimizing carcinogens' access to the colonic mucosa. Fiber may also enhance energy excretion, thereby reducing the effects of a high caloric intake. Excess calories have been associated with positive colon cancer risk (13).

Emphasis has also been placed on fiber's connection to bile acid metabolism. It has been hypothesized that bile promotes neoplasia. Fecal bile level is in fact used as a marker for carcinogenic activity. Fibers can directly bind bile or indirectly affect the rate of conversion of primary to secondary bile acids by lowering colonic pH. However, the bile camp is losing support as hard, fast data linking it to colon cancer has proven to be elusive.

Many are now turning to fiber's molecular connection to colon function. Indeed, recent molecular investigations indicate that the role of dietary fiber in colon cancer etiology is

probably multifactorial and more fundamental. Fiber could very well possibly play a key role in the nutritional regulation of gene expression (Figure 1). Fiber also appears to impart strong influence over general intestinal mucosal structure and turnover (14). Fiber, it now seems, is not the inert material sweeping through the colon.

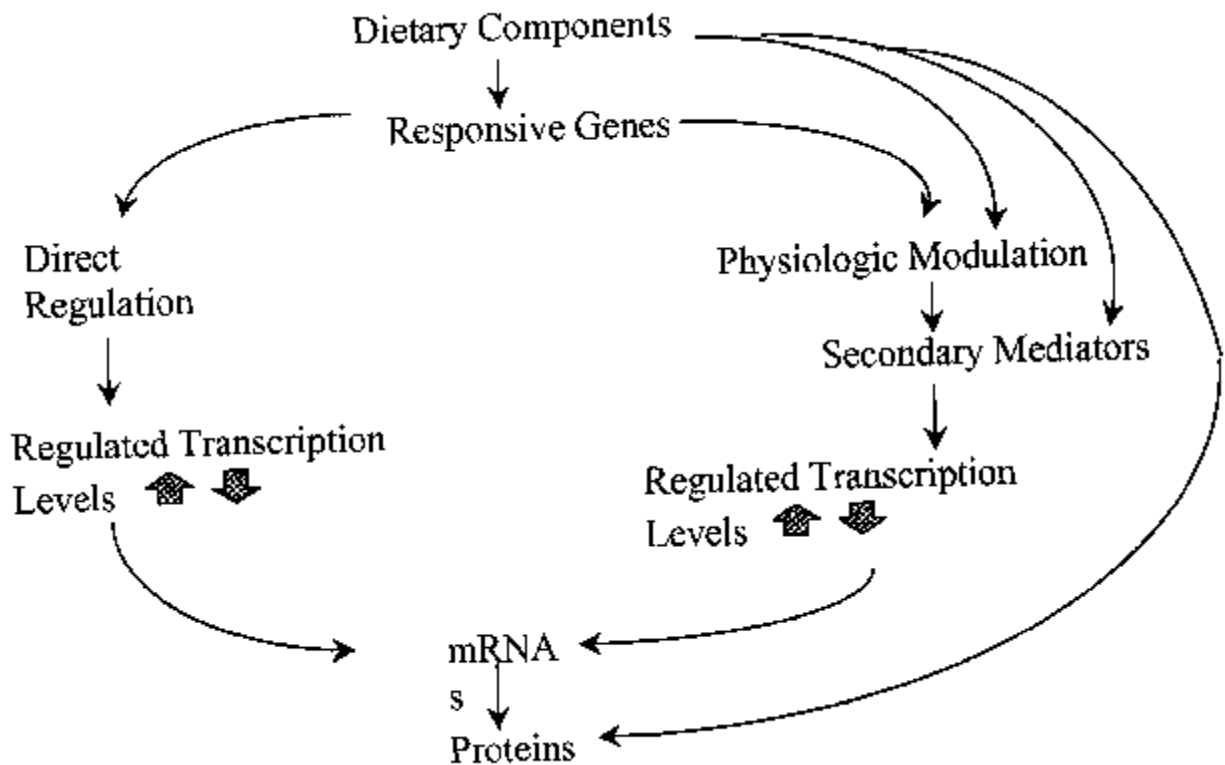


Figure 1. Dietary constituents such as fiber can influence gene expression and consequent transcription levels either 1). Directly by interacting with regulatory elements in the genome or 2). Indirectly by modulating secondary mediators, such as butyric acid (Adapted from Cousins, RJ. Nutritional Regulation of Gene Expression. Am J Med. 1999;106(1A):20S-23S).

In fact, the latest fiber research targets a group of metabolic by-product of fiber fermentation known as short-chain fatty acids (SCFA).. They are produced as a result of

bacterial fermentation of undigested dietary fiber in the bowel. There is now evidence that SCFAs mediate colonic cell proliferation and differentiation on several levels (2). Another effect of fatty acids is to alter intestinal epithelial cell's secretion of insulin-like growth factor binding proteins(IGFBP). (17). Insulin growth factor also plays an important role in intestinal cell proliferation and differentiation.

One such SCFA - butyric acid - holds particular promise. Studies show butyric acid to be a modifier of nuclear architecture, such as by leading to the transcription of p21 which leads to cellular growth arrest. Another possible molecular mechanism of butyrate involves the induction of cdk inhibitors which inhibit cell growth and prevent the transformation of a polyp into the malignant phenotype (25). Butyrate also seem to selectively induce apoptosis in colon cancer cells but not normal colonocytes (15, 16).

Various recent studies single out wheat bran, over either corn or oat, as the most consistent tumor inhibitor in vitro as well as in animal models. One study found a 40% lower incidence of colon tumors in rats fed wheat bran fiber versus those on a cellulose containing diet. Human dietary intervention studies show that wheat bran significantly reduced the level of various tumor promoters in the colon, regardless of stool bulk (7). This was true even in cases of wheat supplementation. The Australian Polyp Prevention Project detected actual reduced colorectal adenomas when fiber supplements were included in the diet. Wheat bran has been promoted because it is fermented to short chain fatty acids throughout the colon, rather than just proximally like the other more rapidly fermented fibers (10). Other promising components of wheat bran include the phytoestrogen b -sitosterol (which directly bind to the nuclear estrogen receptor and activates a tumor suppressor gene). as well as phytates which inhibit tumorigenesis (18). Interestingly, one study found a diet combining wheat and chickpeas to be less effective than if casein and wheat were administered together to tumor induced rats (19). Once again, interaction and interrelation between metabolites seem to be key. A varied diet would definitely be beneficial as evidence that butyrate alone, while a pivotal component, probably could not fend off colon cancer of in itself (14).

The widening molecular fields have both elucidated and complicated the mechanisms behind fiber's role in the colon. For example, the metabolic and physiological response to fiber has been shown to vary by gender (20). As our knowledge expands, it is, however, becoming clear that the inhibitive effects of dietary fiber varies and depends on the source and nature of the fiber, i.e. not all fibers are equal in terms of colon cancer prevention. Unfortunately, at present there just is not one clear consensus regarding diet and colon cancer in terms of plant foods. One study found fruit fiber indeed seem to confer more protection against colon cancer than cereal fiber while another investigation achieved opposite results (12, 21). There are, however, some finding which are withstanding repeated assaults. For example, folate have been consistently shown to be an effective protective agent. Fiber does not seem to act alone but in sync with other micronutrients to modulate colon physiology. The difficulty lies in the failure to achieve conclusive results in vivo despite strong correlation found in vitro.

Conclusion: Can I then forego the salad and just order the steak?

The smart answer still remains with the salad. While any direct link between colon cancer and dietary fiber remains uncertain, the Fuchs study confirmed fiber's benefits on lowering incidences of symptomatic diverticular disease, diabetes mellitus, coronary heart disease and hypertension (11). Plant foods are also leaner sources of calories, and high fat diets are directly related to high incidences of colon cancer. In addition, foods rich in fiber also tend to be plentiful in other crucial nutrients and vitamins. Fruits and vegetables confer benefits and protection in ways other than its mere fiber content (22). Environmental mutagenic factors also must play a part in determining which susceptible individuals go on to develop carcinomas. The smart choice is in arming oneself with the most diverse arsenal of nutritional resources.

Importantly, the present controversy reminds one of all which remains to be discovered in elucidating the mechanisms of colonic carcinogenesis. Ironically, such studies will probably intensify the attention given to other potentially crucial nutritional factors, such as the role sugar intake levels play in colon cancer (20, 23). Studies are now questioning the previously largely ignored relationship between insulin and colonic physiology (17, 24). Evolving ideas are part of scientific thought. Before deciding on the latest study to be the new gospel, it would be prudent to await the results of other ongoing studies such as the Polyp Prevention Trial I and the European Cancer Prevention Colon Group Study. In the end, fiber might very well prove not to be the magic bullet in colorectal cancer prevention. As future physicians in a culture increasingly obsessed with immediate gratification and quick solutions, the challenge will be in helping patients achieve long term balance in their overall diet and lifestyle.

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