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# Colon Cancer

## *Nutritional Strategies for Prevention*

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**M**any of us have known, or will know, someone who suffers with colon cancer. In its Facts and Figures for 2000, the American Cancer Society estimates that there were 93,800 new cases of colon cancer in the United States in 2000 and 47,700 deaths from the cancer. Commonly recognized risk factors for colon cancer include obesity and low consumption of vegetables, fish, and whole-grain cereals.<sup>1</sup> Additional risk factors include a genetic predisposition, as in the case of familial polyposis, and other conditions, such as chronic ulcerative colitis. This article reviews a portion of the growing evidence that nutrition and supplementation may have very significant roles to play in maintaining a healthy, cancer-free colon.

### **What is the Role of Fiber?**

Since it was first suggested that a high-fiber diet was protective against colon cancer,<sup>2</sup> several potentially preventative mechanisms against cancer have been proposed and studied to varying degrees, including the reduction of irritating secondary bile acids, decreasing transit time, and lowering the pH of the colon.<sup>3-5</sup> Some attention has recently focused, however, on two significant studies, both published in the *New England Journal of Medicine*,<sup>6,7</sup> which have failed to show the benefit of fiber consumption. The first study, a prospective nurses' study, was published in 1999 and reported no protective effect of total dietary fiber or fiber from cereals, fruits, or vegetables against

colon cancer or adenomas.<sup>6</sup> While this study was large, and apparently extremely well-done, an interesting perspective is added by another prominent researcher, Bandaru S. Reddy of the Nutritional Carcinogenesis and Chemoprevention Program, Valhalla, New York. In a lecture presented at the 90th Annual Meeting of the American Association for Cancer Research, Dr. Reddy pointed out that, in the nurses' study, median total daily dietary intake ranged from 9.8 g in the lowest fiber consumers to 24.8 g in the highest fiber consumers, 1.0-4.8 g of which was cereal fiber. In contrast, Finnish researchers reported an *average* daily intake of 35 g/day and a cereal fiber intake range of 17-21 g/day.<sup>8,9</sup> This difference leads to the suggestion that it is vital to consider the effects of specific kinds of fiber. While the results of the nurses' study are certainly real, it may be that the consumption of cereal fiber, in particular, was just not high enough in the study population to produce significant results.

The second study, published in 2000, explored the effects of a low-fat, high-fiber diet on the recurrence of colorectal adenomas, which are precursors to colon cancers.<sup>7</sup> The study results showed no difference in recurrence rates between the 958 subjects in the intervention group, who lowered their fat intake and increased their dietary fiber and fruit and vegetable intake substantially, and the 947 subjects in the control group. As was pointed out in correspondence regarding the study,<sup>10</sup> it may be difficult to assess subject compliance accurately in a study like this and introducing new diet regimes successfully is a difficult task to accomplish. However, it just may be the case that this study represents the truth

and that, in patients who have had previous colon adenoma, a low-fat, high-fiber diet does not hold as much promise as had been hoped. It is also important to realize that, even if this is the case, it does not mean that the results of the study can be translated to the general population who have not had previous colon adenomas. And there are several reasons to think that cereal fiber may be beneficial.

The fiber from wheat bran, for example, is deserving of special attention, as it may be able to decrease the risk of colon cancer via various mechanisms. One of the principal ways in which a high cereal-fiber diet may be beneficial is by decreasing the amounts of secondary bile acids that are irritating to the colonic mucosa. In fact, at least one of these secondary bile acids, deoxycholic acid, increases the proliferation of colonic epithelial cells.<sup>11</sup> Research has shown that these bile acids, including deoxycholic acid, were significantly reduced when subjects consumed 10 g per day of wheat bran, but not oat bran, as an addition to their typical Western diet.<sup>12</sup>

In addition, research has shown there are several parts of wheat bran that may have complementary actions in maintaining a healthy colonic environment. For example, phytic acid, or inositol-6-phosphate as it is also known, is an antioxidant and inducer of increased natural-killer cell activity that, in animal studies, has been shown to inhibit chemically induced carcinogenesis.<sup>13</sup> In addition, it may be important to bear in mind that dietary fiber makes up less than half of wheat bran, with other constituents such as phenolic acids, lignans, and flavonoids also being present.<sup>14</sup> In fact, the core structure of the flavonoids, flavone, has recently been shown to be a

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### Factors That Increase the Risk of Colon Cancer

- Low levels of antioxidants (vitamins A, C, and/or E)
- Daily consumption of beef
- High intake of refined carbohydrates
- Multiple juvenile polyposis
- Gardner's syndrome
- Crohn's disease
- Ulcerative colitis
- Previous history of polyps or colon cancer
- Familial polyposis
- Family history of colon cancer or polyps

more potent inducer of apoptosis in human colon cancer cells than the established antitumor agent camptothecin.<sup>15</sup>

Moreover, in a recent study, the lipid-soluble portion of wheat bran was shown to inhibit chemically induced colon-tumor growth.<sup>16</sup> In this study, the researchers started rats on diets that were fortified with different fractions of wheat bran. At 7 weeks, the rats were injected twice per week with azoxymethane, a carcinogen. For the rats who initially received wheat bran that was missing phytate and lipids, the wheat bran was subsequently fortified with bran oil and phytic acid. These rats had a decreased incidence and number of tumors. Other rats were fed wheat bran that was missing phytate and lipids and the wheat bran was subsequently fortified with only phytic acid and not bran oil. These rats experienced no decrease in incidence or number of tumors. Thus, this study indicated a protective effect of the bran oil against cancer. In addition, rats who were given normal wheat bran were compared to those who were given wheat

bran that was deficient in oil and phytic acid. The rats on the deficient wheat bran had increased total COX and COX-2 enzyme activities.

### Nutritional View of Intestinal Inflammation

The role that inflammatory processes, such as those modulated by COX-1 and -2 have in colon cancer may well be significant; in fact, several studies have demonstrated a definite inverse relationship between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of colon cancer.<sup>17,18</sup> In fact, this has led some authorities to recommend aspirin as a preventive. One of the proposed mechanisms of protection by NSAIDs is that, by inhibiting the action of the COX enzymes, production of potentially tumor-favoring prostaglandins is reduced. While it may be the case that the advent of specific COX-2 inhibitors will allow for benefit in this regard without the side-effects (such as gastrointestinal bleeding and renal damage) of less-specific NSAIDs, there may be distinct advantages to taking a more broad anti-inflammatory approach that includes supplementation with  $\omega$ -3 fatty acids, such as those found naturally in fish oil such as docosahexaenoic acid and eicosapentaenoic acid. Several reviewers have pointed out various mechanisms via which  $\omega$ -3 fatty acids can fight inflammation.<sup>19,20</sup> For example, they can be released from cell membranes instead of arachidonic acid (AA) and compete with AA for subsequent oxidation via the COX, lipoxygenase (LOX), and monooxygenase pathways. These fatty acids may also, at least par-

tially, inhibit these pathways directly. A broader approach than exclusive COX-2 inhibition makes sense because products of COX action are not the only concern in colon cancer. For example, one of the products made in the lipoxygenase pathway, 12(S)-HETE, may increase the ability of tumors to metastasize.<sup>21</sup>

An additional note regarding different types of fatty acids is worth mentioning—at least in chemically induced colon cancer, the incidence and volume of tumors in rats who are fed fish oil is significantly lower than in groups who are fed beef tallow, soybean oil, or alkana oil.<sup>22</sup> And, while a diet high in cereal fiber and containing enough  $\omega$ -3 fatty acids is certainly important, there are also other factors to consider. A recent review of European studies suggests the importance of maintaining a reasonable body weight and including regular exercise in order to decrease colon cancer risk.<sup>23</sup>

There is also evidence that draws attention to the importance of healthy gut microflora. For instance, ingestion of fermentable probiotics, such as oligofructose and inulin have been shown to lead to an increase in the growth of friendly bacteria, such as bifidobacteria.<sup>24,25</sup> An increase in friendly bacteria has been reported to decrease colonic mucosal cell proliferation and to decrease tumor biomarkers, such as tumor ornithine decarboxylase and *ras*-p21.<sup>25</sup> One of the products made by bifidobacteria, butyrate, may be of special interest in colon cancer. In fact, in a model that included rats with induced colitis (itself a risk factor for colon cancer) or with colitis plus induced colon cancer, rats that received butyrate enemas showed a significantly

**In a significant study, intake of greater than 400 µg of folic acid per day at the beginning of the study was associated with a significant decrease in colon cancer risk.**

lower incidence and size of induced tumors. An added finding was that the rats with colitis showed a normalization of glutamine metabolism,<sup>26</sup> the most abundant amino acid in intestinal tissue.

In addition to telling your patients to consume generous amounts of cereal fiber and foods that are rich in ω-3 fatty acids, while maintaining healthy gut microflora, there are several other key nutrients that may be considered in an effort to maintain a healthy and cancer free-colon (see box entitled Preventing Colon Cancer: What to Tell Your Patients).

### Key Nutrients

#### *Folic Acid*

One nutrient to that is especially important for colon health is folic acid. In 1998, the results of a significant prospective study of more than 88,000 nurses suggested that intake of greater than 400 µg per day at the beginning of the study was associated with a significant decrease in colon cancer risk, even after controlling for other factors such as intake of vitamins A, C, D, and E, and calcium. In addition, women who consumed multivitamins that contained folic acid, for 15 years throughout the study, had a dramatic decrease in colon cancer risk compared to women who did not consume such vitamins.<sup>27</sup> In fact, the relative risk (RR) was 0.25 (confidence interval [CI], 0.13–0.51) for women ages 55–69 who used a multivitamin that contained folic acid. This dramatic decrease in risk after a number of years may be not only be an important indication of the benefits of folic acid but also of the synergistic benefit of tak-

<b>Preventing Colon Cancer:</b>	
<i>What to Tell Your Patients</i>	
Suggested for prevention. . .	Tell your patients. . .
Increase intake of cereals	Aim for roughly 20 g per day of cereal fiber.
Increase ω-3 fatty acids	Include cold water fish in the diet (such as salmon) weekly; also, include cold-pressed flaxseed ( <i>Linum usitatissimum</i> ) oil, 2000 mg 3 times per day.
Support healthy gut flora	Eat a variety of fresh fruits and vegetables that contain the oligosaccharides that are necessary for the growth of friendly bacteria; consider a quality probiotic supplement containing bifidobacteria and lactobacillus.
Folic acid	Take a quality multivitamin that provides at least 400 µg/day.
Vitamin E (D-α tocopherol)	Take 400–1200 international units per day.
Curcumin	If you have evidence of gut inflammation, diagnosed by a licensed health care provider, take as directed by that health care provider.
Selenium	Take 200 µg per day.
Calcium	Take 1200 mg per day.

ing the needed vitamins and minerals supplied in multivitamins consistently over a significant portion of the lifetime. Also, it is useful to remember that it can take years before a study is able to detect a statistically significant difference between groups that are and are not getting supplements.

Another prospective trial highlights the importance of assuring adequate folate intake, especially when methionine levels are low and alcohol consumption is heavy.<sup>28</sup> In this study of almost 48,000 men, those who drank more than 2 drinks a day had a substantially increased risk (roughly double) of developing colon cancer compared to those who drank less than or equal to a quarter of a drink per day. In men who drank more than 2 drinks per day and had a low-folate, low-methionine diet, their risk roughly

tripled for occurrence of any kind of colon cancer and was higher still for cancer of the distal colon.

While there may be several mechanisms via which folic acid helps to prevent colon cancer, recent research suggests that one important role may be maintaining the genetic integrity of the DNA coding for the important tumor-suppressor gene, p53.<sup>29</sup>

#### *Vitamin E*

Another vitamin that has been associated with decreased colon cancer risk is vitamin E as shown in another prospective trial that included more than 35,000 women, ages 55–69.<sup>30</sup> While the data from this study did not show lowered risks for developing colon cancer with intake of other vitamins, the data did show a substantial decrease in risk for women in the study who consumed the

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most vitamin E. Women who had the highest intake of vitamin E had an RR of developing colon cancer of 0.32 (95% CI, 0.19–0.54) compared to women who had the lowest intake of vitamin E.

### Curcumin

Curcumin is also worthy of continued research. This nutrient is one of the constituents of the spice turmeric. Widely used for its anti-inflammatory actions, curcumin has been shown to inhibit AA metabolism and to prevent the occurrence of chemically induced preneoplastic colon lesions in rats.<sup>31</sup> Some of curcumin's anti-tumor effects also extend beyond the initial stage of initiation to the late premalignant progression stage, during which curcumin is associated with an increased rate of apoptosis.<sup>32</sup> Curcumin's ability to block initial DNA damage and to limit progression make curcumin a very promising preventive agent.

### Selenium

Another key nutrient is selenium. The importance of this nutrient was initially suggested by epidemiologic data that showed an inverse relation between its levels and colon cancer occurrence.<sup>33</sup> This relationship seems to be confirmed by the results of data from a prospective human study with brewer's yeast that had been fortified with selenium.<sup>34</sup> Subjects who consumed 200 µg per day of selenium over the course of the study had significantly lower levels of colon, lung, and prostate cancers, compared to subjects in a control group. In one animal study, selenium, in the form that it occurs in broccoli, provided protection against chemically induced preneoplastic lesions, indicating that this natural and available source might be an effective chemopreventive.

### Calcium

A final nutrient that has been well-studied in colon cancer recurrence and prevention is calcium. In a study of 930 patients who had recently been diagnosed with colorectal adenoma, subjects received either 3 g of calcium carbonate (1200 mg of elemental calcium) per day or placebo.<sup>35</sup> The subjects were then followed for 4 years. Of the 913 subjects who had at least one follow-up, there was a moderate, although significant, decrease in the risk for recurrence of adenoma. At least one adenoma was diagnosed in 127 of the subjects in the calcium-treated group (31%) and in 159 subjects in the placebo group (59%). However, as in the earlier-cited study of fiber in the recurrence of polyps, it is still uncertain if the results of this study in patients with histories of adenoma can be translated to patients with no past histories of adenoma. In fact, the results of a significantly sized prospective trial in cancer-free men produced nonconclusive results; initially calcium appeared to offer a statistically significant protective effect, but that effect became nonsignificant when factors in addition to age and total energy intake were taken into account.<sup>34</sup> The conclusion of the study was that, while a strong protective effect of calcium was not apparent, a modest one could not be excluded. Because calcium is a very inexpensive and widely available intervention, it makes sense to emphasize its inclusion in a prevention strategy.

### Conclusion

In light of the evidence, it is evident that there are still many questions to be answered concerning the central role of

nutrition in colon cancer prevention. Certainly, future research will help to elucidate the roles that different kinds of fiber play—or do not play—in the prevention of colon cancer. There is much to be understood, as yet, concerning the proper ecology of gut microflora and the importance of limiting gut inflammation. Moreover, there are a variety of key nutrients that will, no doubt, continue to be studied and that may play pivotal roles in preventing colon cancer, such as folic acid, vitamin E, curcumin, selenium, and calcium. By nourishing the body with a spectrum of these vital nutrients, the combined effects of their unique and complementary actions may best improve our patients' chances of avoiding this all-too-common form of cancer. □

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