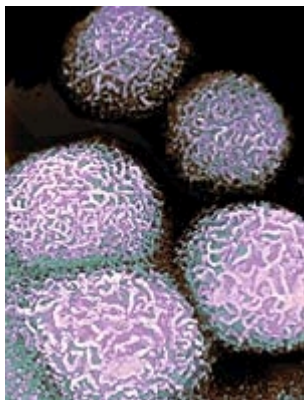


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REPORT**Nutritional Strategies for Conquering Colon Cancer**

By Debra Fulghum Bruce, PhD



A common yet preventable disease, colon cancer is the second leading cause of cancer death in both sexes, accounting for about 10% of all cancer deaths. Colon cancer is the third most common cancer in both men and women, and is also the most hereditary of all cancers: about 10% of adults with colon cancer have a family history of the disease.¹ Although colon cancer is rarely diagnosed in people under the age of 40, its incidence increases significantly between the ages of 40 and 50, and its age-specific incidence rates rise in each decade of life thereafter.²

While today's diagnostic and therapeutic tools are highly advanced, abundant research suggests that certain nutrients may help people avert colon cancer altogether.

Although colon cancer usually strikes after age 40, the disease process begins silently and without warning much earlier in life. Several environmental and genetic factors influence one's susceptibility to colon cancer. According to the American Cancer Society, most colon cancers begin as a polyp (adenoma) or growth on the inside of the rectum and colon. Removing these adenomas early may prevent them from becoming cancerous. Other key risk factors for colon cancer include having an inflammatory bowel disease (Crohn's disease or ulcerative colitis) or diabetes, or having a family member with colon cancer. Unhealthy lifestyle factors, such as lack of exercise and obesity, also raise one's risk for colon cancer, as does the typically Western diet rich in red and processed meats, sweets, and refined carbohydrates.³

The early stages of colon cancer may be marked by symptoms such as abdominal pain, a change in bowel habit, or fatigue and weakness. Anemia and weight loss in the absence of gastrointestinal symptoms can signal colon cancer.⁴ Yet many people with colon cancer have no signs or symptoms of the disease at all.

As with many serious diseases, colon cancer is treatable if detected early, and today's advanced screening exams and imaging techniques allow doctors to make well-informed treatment decisions. Many experts believe that death from colon cancer could be prevented if men and women at average risk for the disease begin screening tests at the age of 50. For people at greater risk due to family history or inflammatory bowel disease, screening should be started earlier.⁵ (The Life Extension Foundation recommends flexible-tube colonoscopy screening to detect early-stage colon cancer beginning at age 40. See "The Colonoscopy Dilemma," *Life Extension*, December 2004.)

New Discoveries, New Targets

In the late 1970s, Dr. William R. Waddell noticed that when he gave sulindac, a drug similar to aspirin, to patients with an inherited disorder that leads to hundreds of colon polyps, almost all the polyps disappeared.⁶ About a decade later, scientists from several laboratories took this clue further and identified two forms of the cyclooxygenase (COX) enzyme, COX-1 and COX-2. They found that COX-2 generates potent, hormone-like substances called prostaglandins that play a role in many physiological functions. One of these substances, prostaglandin E2 (PGE-2), was linked to the development of colon polyps.⁷ When COX-2 is expressed in a tumor, it allows new blood vessels to nourish the tumor, prevents tumor cells from dying, and increases the tumor's ability to grow and spread (metastasize).⁸



Colon cancer treatment using colonoscopy or sigmoidoscopy to remove polyps (inset).

Thanks to the work of Waddell and other scientists, we now know that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are potent suppressors of colon polyps and colorectal cancer itself.⁹

THE CHEMOPREVENTION ARSENAL

While medical intervention is sometimes successful in treating colon cancer, a more powerful strategy for enhancing one's health is to target prevention of the cancer altogether. Chemoprevention, the use of naturally occurring dietary supplements or synthetic agents to reduce the risk of cancer, shows promise for preventing, arresting, and reversing colon cancer development.

As noted earlier, aspirin and other NSAIDs are chemopreventive, as they suppress colon polyps and cancer. Dietary patterns also are controllable risk factors for the development of colon cancer. Folate, calcium, vitamin D, and selenium are among the dietary nutrients that offer protection against colon cancer. Diets rich in polyphenols such as green tea catechins and phytochemicals—including phenolics, flavonoids, and carotenoids from fresh fruits and vegetables—have also been shown to be chemopreventive.¹⁰ A diet high in fiber, particularly from grains, cereals, and fruits, may be associated with a decreased risk of colon cancer.¹¹ Moreover, specialized plant compounds such as resveratrol and curcumin show promise in protecting against colon cancer.^{12,13}

Folic acid. Comprehensive studies have linked a high intake of dietary or supplemental folate and high blood folate levels with a reduced risk of colon cancer. Cumulative data suggest that people who have the highest dietary folate intake have an approximately 40% lower risk of colon cancer compared to those with the lowest folate intake.¹⁴

Folate, or folic acid, is important for DNA synthesis and repair, and plays a key role in recycling the amino acid homocysteine into methionine, which the body uses as a building block in manufacturing new proteins. Moreover, the production of S-adenosyl-L-methionine (SAME), which is crucial for normal DNA methylation and gene expression, depends entirely on folic acid. Some scientists now believe that folate deficiency may increase the risk of malignancy by disturbing these pathways.¹⁵



Many studies support the use of folic acid supplementation in preventing colon cancer. For example, data from Harvard's Health Professionals Follow-up Study, an ongoing study evaluating the link between nutrition and serious illness in 51,529 male professionals, showed a significantly reduced risk of colon cancer in men who used multivitamins with folic acid for more than 10 years compared to those who did not take folic acid.¹⁶

Similarly, in the Harvard Nurses' Health Study, an observational study that followed more than 85,000 nurses from 1976 to 1994, scientists established that women who used multivitamins containing folic acid had a significantly lower chance of developing colorectal cancer. Researchers reported only 15 new cases of colon cancer per 10,000 women aged 55 to 69 years who used folic acid supplements, in contrast to 68 cases of colon cancer per 10,000 in those who did not supplement with folic acid—a risk reduction of over 75%.¹⁷ Folic acid supplementation is especially important for those who drink moderate amounts of alcohol, as alcohol blocks the absorption of folic acid and inactivates circulating folate, increasing the risk of colon cancer.¹⁸

Calcium. A wealth of evidence supports calcium's role in colon cancer prevention. Dr. Harold Newmark, a Rutgers University-based authority on cancer prevention, has called on the FDA to require the addition of calcium and vitamin D to all cereal-grain products. In a recent article in the *American Journal of Clinical Nutrition*, Newmark wrote that the addition of these two nutrients could reduce colon cancer deaths by 20%, saving about 11,000 American lives and over \$1 billion in US health care costs annually.¹⁹ Newmark also noted that the addition of vitamin D and calcium to cereal-grain products would likely reduce the incidence of osteoporotic fractures by 20%.¹⁹

The American College of Gastroenterology has recommended calcium supplementation for the primary or secondary prevention of colon adenomas.²⁰ Harvard School of Public Health researchers have noted that higher total calcium intake is associated with a 27-42% decreased rate of cancer of the distal colon.²¹ Calcium in amounts of more than 700 mg daily appeared to offer minimal benefit in further risk reduction, according to the Harvard scientists.²¹ Calcium supplementation could reduce the number of colon cancer deaths by 16,000 annually, reports the American Cancer Society.

Evidence also suggests that calcium confers the most protection against the advanced polyps that are most strongly associated with invasive colorectal cancer. In the Calcium Polyp Prevention Study, researchers analyzed data from 930 patients (with an average age of 61) who had recently had a colorectal adenoma removed. The subjects took either a 1200-mg daily calcium supplement or placebo, then had follow-up colonoscopies at one and four years after starting supplementation.²² Calcium supplementation yielded an 18% lower risk of hyperplastic polyps and an 11% lower risk of tubular adenoma. Most significant,

however, was a 35% reduction in histologically advanced neoplasms, an advanced form of colorectal lesion.²² The protective effect of calcium supplements was most pronounced among people with a high dietary intake of fiber and a low intake of fat.²⁴ Calcium is thought to protect colon cells by precipitating fatty acids and bile acids that are potentially toxic to the colorectal epithelium.²³



Vitamin D. While most experts acknowledge that calcium alone is chemopreventive against colon cancer, biochemical and biological evidence in cell culture systems suggests that exposure to calcium and vitamin D together may confer even more protection, reducing the tumor-forming properties of colon cancer cells.²³

In late 2003, the *Journal of the National Cancer Institute* published groundbreaking research on vitamin D's role in preventing colon cancer. In this study, researchers concluded that calcium and vitamin D work together to reduce the risk of colorectal cancer. Their four-year study followed 803 patients with a history of surgically removed colon adenoma polyps. Subjects who took 1200 mg of elemental calcium daily experienced a 31% occurrence of polyps compared to a 38%

occurrence in the placebo group.²⁴

Most revealingly, calcium supplements helped to prevent polyps only among participants with high levels of vitamin D levels in their bodies. Additionally, vitamin D levels were linked to reduced polyp recurrence only among those subjects who took calcium supplements. These findings strongly suggest that vitamin D and calcium have a synergistic anti-cancer effect in the bowel and may be far less effective when not used in combination.²⁴

REPORT

Nutritional Strategies for Conquering Colon Cancer

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Fiber. Despite 30 years of study, data on the association between dietary fiber and colon cancer risk are still inconclusive. A much-publicized study by Harvard University scientists in 1999 found no correlation between dietary fiber intake and colorectal cancer risk.²⁵ Other studies, however, suggest that dietary fiber may indeed reduce the risk of colon cancer.²⁶ An American Cancer Society study examined the relationship between colon cancer and the consumption of whole grains, fruits, vegetables, and dietary fiber. They found that men with the highest vegetable intake experienced reduced risk, while men with the lowest intake of vegetables and dietary fiber were at greater risk.²⁷ Since fiber-rich fruits and vegetables are known for their many other health-promoting benefits, it seems prudent to consume them in abundance while scientists continue to unravel dietary fiber's association with colon cancer.



Selenium. An essential trace mineral, selenium is one of the most important cancer-preventive nutrients. Scientists have noted a statistically significant correlation between low soil concentrations of selenium and increased rates of colorectal cancer.²⁸ Scientists believe that selenium-poor soils contribute to low dietary selenium intake by their influence on the nutritional quality of locally grown foods. In studies, selenium compounds have inhibited tumor formation in various animal models, and other research suggests that supplemental selenium may reduce cancer risk in humans.²⁹ Selenium is incorporated in numerous proteins in the body, including glutathione peroxidase, a powerful antioxidant. These selenium-containing proteins appear to offer antioxidant protection from reactive oxygen species that can damage DNA and alter protein function.³⁰

Patients prone to colon adenomas have demonstrated low selenium levels. Supplementation can normalize selenium levels and thus may reduce the incidence of colon cancer.³⁰ Epidemiological studies suggest that selenium reduces the risk of certain cancers, including colon cancer.³¹

Omega-3 fatty acids. Fish oil contains the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Epidemiological studies and animal experiments suggest that both EPA and DHA exert protective effects against colon cancer.³² In patients with colon cancer, EPA and DHA decrease cell proliferation and favorably modulate the balance between colon cell proliferation and apoptosis.³² In a laboratory study of mice, University of Texas researchers found that omega-3 fatty acids block the action of a chemical called protein kinase C beta II, which is thought to promote colon cancer, suggesting a potential role for omega-3 fatty acids in preventing colon cancer.³³

SCREENING TESTS FOR COLON CANCER

Flexible-tube colonoscopy is the most invasive and accurate of colon cancer screening tests. It requires laxative-induced preparation of the colon the day before the procedure and may require sedation during it. The cost ranges from roughly \$600 to \$2,000. Medicare and some health insurance plans now pay for this procedure. Depending on family history of the disease and whether polyps are discovered, the test should be repeated every three to five years. The American College of Gastroenterology now considers this form of colonoscopy to be the "preferred" screening test.⁴³

Sigmoidoscopy requires no sedation, but examines only the lower third of the colon, where most cancers occur. Polyps are biopsied, and adenomatous or cancerous polyps are removed by sigmoidoscopy or flexible-tube colonoscopy. The cost is a few hundred dollars, and the test is repeated every five years. The risk of missing cancer in the upper two thirds of the colon makes sigmoidoscopy only partially effective and therefore not highly recommended.

Barium enema requires no sedation, but if polyps are found, a flexible-tube colonoscopy is necessary for treatment. The cost is a few hundred dollars, and the test should be repeated every five years. This procedure exposes the lower abdominal cavity to radiation that may be associated with increased risk of cancers, and thus is not recommended.

Fecal occult blood test is a routine test conducted in a physician's office that looks for blood in the stool. The cost is around \$25 and the test is repeated annually. This test can be negative in those with colon cancer, as not all polyps bleed all the time.

Virtual colonoscopy is a 15-minute, computer-enhanced screening test (also called CT colonography) that does not

require sedation and uses a computerized technology scanner to provide three-dimensional images of the entire colon. The cost ranges from about \$1,000 to \$2,000, and a flexible-tube colonoscopy is required to remove any polyps found. High-dose radiation exposure, the inability to remove polyps found, and a lower detection rate of polyps and cancerous lesions makes virtual colonoscopy less desirable than flexible-tube colonoscopy.

FUNCTIONAL FOODS

A considerable body of literature suggests that specific compounds in tea, red wine, and tumeric (curcumin) inhibit the COX enzymes, thus reducing prostaglandin-mediated effects on the colon. Because colon tumors have been shown to strongly express the COX-2 protein, and many cancer-preventive NSAIDs suppress the COX enzymes, it is tempting to speculate that these functional food compounds may help to prevent colon cancer by inhibiting one or both forms of the COX enzyme.



Green tea. Green tea is rich in polyphenolic compounds, with catechins as its major component. Studies have shown that catechins possess diverse pharmacological properties that include antioxidant, anti-inflammatory, anticarcinogenic, anti-arteriosclerotic, and antibacterial effects. In the gastrointestinal tract, green tea has been shown to activate intracellular antioxidants, inhibit pro-carcinogen formation, and suppress angiogenesis and cancer cell proliferation.³⁴

The most prominent catechin in green tea is epigallocatechin-3 gallate (EGCG), which modulates numerous molecular targets in

the presence of inflammation and cancer.³⁵ In-vitro cell culture studies show that tea polyphenols potently induce apoptotic cell death and cell cycle arrest in tumor cells but not in their normal cell counterparts.³⁶ Animal studies have revealed that green tea inhibits tumor incidence and multiplicity in the colon and other organ sites.³⁶

A large, population-based, case-controlled study in China found that consuming green tea reduced the risk of cancers of the colon, rectum, and pancreas.³⁷ Tea polyphenols have been found to influence the metabolism of arachidonic acid in human colon mucosa cells and colon tumors by inhibiting the lipoxygenase and cyclooxygenase enzymes. This mechanism may be responsible for some of green tea's protective effects against colon cancer.³⁸

Resveratrol. A red wine poly-phenol, resveratrol is considered cancer chemopreventive because of its antioxidant and antimutagenic effects.¹² Inflammatory bowel disease in humans is known to be a major risk factor for colon cancer. In an animal study, resveratrol reduced the tissue injury caused by experimentally induced colitis, and also alleviated oxidative damage.³⁹ These promising results suggest a role for resveratrol in modulating colon cancer risk, particularly for those at heightened risk because of inflammatory bowel disease.

Curcumin. Extensive research during the past 50 years indicates that curcumin (diferuloylmethan), the yellow pigment in the curry spice turmeric, can prevent and treat cancer. The lower incidences of colon cancer in Asian nations have been attributed to their intake of curcumin, which has been widely used for centuries without toxic effects. This phytonutrient inhibits some COX-2 while also inhibiting the actions of lipoxygenase, another enzyme involved in inflammation. Curcumin also inhibits the promotion and progression stages of carcinogenesis in cell cultures and animal studies.¹³

Scientists have theorized that cancer incidence at different body sites may be related to oxidative damage, which may in turn be modified by plant phytochemicals. When scientists from India's National Institute of Nutrition studied curcumin's protective effect against DNA damage in human cells, they concluded that this non-nutritive dietary constituent possesses antimutagenic properties and appears to be a promising chemopreventive agent.⁴⁰



THE SCIENCE BEHIND "AN APPLE A DAY"

Quercetin, a compound found in fruits and vegetables, may be a primary reason why the adage "an apple a day keeps the doctor away" has endured. Quercetin is a major dietary flavonoid present in high concentrations in apples, onions, tea, and other foods. German researchers recently discovered that a high dietary intake of plant foods helps prevent colorectal cancer in humans, and that flavonoids, as part of such a diet, are considered to contribute to those protective effects.

Quercetin alters the levels of various proteins involved in the growth, differentiation, and apoptosis (destruction) of colon cancer cells. These cells have been identified as molecular targets of quercetin, helping to explain the anti-cancer effects of this flavonoid.⁴⁴



In the past year, researchers at the MD Anderson Cancer Center in Houston, TX, have revealed how various synthetic NSAIDs such as aspirin and ibuprofen, as well as natural compounds such as curcumin and resveratrol, that inhibit tumor cell proliferation. Recently published in the journal *Oncogene*, the study concluded that resveratrol and curcumin were among the most potent anti-inflammatory and antiproliferative agents, while aspirin and ibuprofen were (surprisingly) among the least potent.⁴¹

CONCLUSION

The prevalence of colon cancer is frighteningly high, and the disease will kill some 57,000 Americans this year. You can begin a program of colon cancer prevention today by heeding the myriad studies that endorse the importance of a healthy diet and lifestyle, dietary supplementation, and preventive screening.⁴² The good news is that colon cancer's lethality could be greatly reduced with widespread and regular screening by colonoscopy. A colonoscopy allows for the removal of precancerous polyps before they develop into cancerous lesions. If an early-stage cancerous lesion

is detected, the chance of curing it is very good. If one waits for physical symptoms of colon cancer to manifest, however, the mortality risk is terribly high.

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