Colorectal Cancer

Last Section Update: 08/2021

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Table of Contents

1 Overview

Summary and Quick Facts for Colorectal Cancer

- Colorectal cancer remains the second most common cause of cancer death in the United States, although as many as 70 percent of cases are believed to be preventable through moderate dietary and lifestyle modifications.
- In this protocol, you will learn about several unappreciated risk factors for colorectal cancer and gain insight into genetic and molecular mechanisms that drive the evolution from healthy cells to cancerous cells in the colon. You will also discover evidence-based methods using natural compounds and novel drug strategies to target these risk factors and carcinogenic mechanisms.
- If the cancer is detected while still localized in the colon, it is removed surgically. Adjuvant techniques may be employed post-surgery to improve the chance for sustained disease-free survival.

Colorectal cancer remains the second most common cause of cancer death in the United States, although as much as *70%* of cases thought to be *preventable* through moderate dietary and lifestyle modifications.[1,2]

The colorectal cancer mortality rate has consistently declined in recent decades due largely to enhanced accuracy of early detection techniques, such as colonoscopy. However, the outlook for colon cancer patients rapidly diminishes if the cancer has metastasized to other organs or lymph nodes before detection.

If the cancer is detected while still localized in the colon, it is surgically removed and adjuvant techniques may be employed post-surgery to improve the chance for sustained disease-free survival. Treatment for advanced metastatic colon cancer usually encompasses multi-agent chemotherapy accompanied by palliative radiation.

Unfortunately, conventional standardized chemotherapy regimens may be ineffective for some patients due to genetic resistance against the drugs employed. Further, rarely do mainstream oncologists implement *nutritional therapeutics* or novel drug strategies to target genetic abnormalities associated with colon cancer growth, despite the fact that many peer-reviewed studies highlight the potential value of these agents.

Investigations have shown that several factors such as dietary habits, nutritional status, and *inflammation* influence the genetics involved in colon cancer development and progression, thus revealing multiple targets of interest in the prevention and management of colon cancer.

For example, a review of nine studies found that for every 10 ng/mL *increase* in serum vitamin D, the relative risk of colorectal cancer *decreased* 15%.[3] Another landmark trial revealed that daily *low-dose aspirin* reduced the risk of developing colon cancer by *24%* and the risk of dying from the disease by *35%*.[4]

In recent years, the introduction of advanced cancer analytical technology such as *circulating tumor cell testing* and *chemosensitivity assays* has improved outlook considerably by paving the way towards individually tailored treatments based upon the unique cellular characteristics of each patient's cancer.

In this protocol, you will learn about several *unappreciated* risk factors for colorectal cancer, and gain insight into several genetic and molecular mechanisms that drive the evolution from healthy cells to cancerous cells in the colon. You will also discover evidence-based methods for targeting these risk factors and carcinogenic mechanisms using natural compounds and novel drug strategies. The protocol will also present resources and guidance for thoroughly analyzing the unique biological characteristics of your cancer cells, which is a critical step towards establishing an effective, personalized cancer treatment regimen.

2 About the Colon

The colon is the third-to-last section of the gastrointestinal tract in humans, followed by the rectum and anus. Food is mostly digested by the time it reaches the colon, so the role of this segment of the large bowel is to absorb water, some short chain fatty acids from plant fiber and undigested starch, sodium, and chloride, and compact waste to be eliminated during defecation. Moreover, colonic bacteria play a central role in metabolic detoxification by secreting chemicals that encourage excretion of toxins and pathogens. Beneficial bacteria in the colon (*probiotics*) also ferment dietary fiber and generate compounds, such as *butyrate*, which nourish cells in the colon wall and protect against carcinogenesis.

3 Causes of and Risk Factors for Colon Cancer

Risk factors for colorectal cancer include age (90% is found in those over 50), personal history of polyps or adenomas, family history of colorectal cancer, and diagnosis of inflammatory bowel disease (IBD) (Crohn's or ulcerative colitis). Other risks include a diet high in fat or low in fruits and vegetables, physical inactivity, obesity, smoking and excessive alcohol consumption.[5]

Lifestyle

As mentioned in the introduction of this protocol, as much as 70% of colon cancers are thought to be **preventable** through diet and lifestyle modification.[1]

Factors such as diet, physical activity level, tobacco use, alcohol consumption and sleep patterns are associated with increased risk of colorectal cancers.[6] Obesity and physical inactivity are known to increase biomarkers of inflammatory processes, such as faecal *calprotectin* and serum *C-reactive protein* (CRP); elevated levels of inflammation are linked with higher rates of colorectal cancer. Greater vegetable and fiber intake has been associated with reduced levels of fecal calprotectin, a marker of intestinal inflammation.

A colon cancer treatment or prevention plan should start with foundational lifestyle measures that include physical activity and a diet rich in plant foods; patients should also strive to attain a healthy body weight.

Genetics and Family History

Genetic alterations, both inherited and non-inherited, are responsible for the carcinogenic process in colon cancer. About 75% of colorectal cancers are "sporadic," meaning that they arise in those without any family history of this disease, while the remaining 25% have an inherited predisposition that raises risk.[7]

Two familial disorders raise risk significantly, *familial adenomatous polyposis* (FAP) and *hereditary nonpolyposis colon cancer* (HNPCC, or Lynch syndrome). These inherited disorders are responsible for 1–2% and 3–5% of all colorectal cancers, respectively.

Familial adenomatous polyposis syndrome causes hundreds to thousands of polyps to form before age 30 and often leads to colon cancer at a young age (average age 39 years old). Familial adenomatous polyposis arises from inherited mutations of the adenomatous polyposis coli (APC) gene, a gene mutation that is also present in 60–80% of sporadic colon cancers.

Hereditary nonpolyposis colon cancer does not cause the multitude of polyps, but polyps are much more likely to become cancerous in those with this disorder. Those with hereditary nonpolyposis colon cancer have mutated *mismatch repair genes* (MMR genes), which fail to make necessary corrections to errors in DNA replication, allowing mistakes in the DNA to accumulate and colon cancer to ensue.

Metabolic Syndrome and Inactivity

Higher levels of insulin and glucose in the blood can increase the risk of developing colorectal cancers.[8] An analysis of clinical data from 1966 through 2005 found that a diagnosis of diabetes raised the risk of colon cancer by more than 30% in both men and women.[9]

A recent study, which looked at much of the previous data on diabetes and risk of colon cancer, concluded that diabetes is an independent risk factor for developing colon cancer.[10]

The link between elevated insulin levels and colon cancer may be mediated though the *insulin-like growth factor-1 receptor* (IGF-1R). Insulin activates IGF-1R, which in turn functions to stimulate cellular growth and proliferation. Overexpression of IGF-1R has been observed in colon cancer cells, suggesting an increased sensitivity to the growth-promoting effects of insulin.[2]

Obesity is a risk factor for developing cancers in general, and studies show that reducing weight can reduce inflammation in the colon, thereby reducing risk of colorectal cancers.[11] Adipose tissue (fat tissue) is not simply an inert storage system for excess calories—it actively produces many *adipokines*, or chemical messengers, that circulate throughout the body. One such adipokine, *leptin*, is linked specifically to the increased risk of developing colon cancer.[12]

Regular physical activity, which combats all the components of metabolic syndrome, is associated with a decreased risk for colorectal cancer as well. One study compared those who did not have a sedentary job with those that worked a sedentary job for 10 years or more; the risk of cancer arising in the left (distal) colon was doubled, and the risk of developing rectal cancer increased 44%.[13]

Inflammation

People with chronic inflammatory conditions of the bowel, such as Crohn's disease or ulcerative colitis (UC), have up to a six times greater risk of developing colon cancer than those without the conditions.[14] However, the inflammatory process is involved in the development of colorectal cancer growths even in those without Crohn's or ulcerative colitis.[15,16]

Cyclooxygenase-2 (COX-2) is an enzyme that produces inflammatory end products by converting the omega-6 fatty acid *arachidonic acid* into *prostaglandin E2*, which promotes growth of cancerous cells; COX-2 is often overexpressed in colon cancer. Aspirin blocks COX-2 and has been shown to also lessen the development of colorectal cancers.[17]

5-Lipoxygenase (5-LOX), similarly to COX-2, metabolizes *arachidonic acid* into metabolites that drive development and progression of cancer. In colorectal cancer, 5-LOX expression was shown to correlate with the

density of blood vessel growth within tumors.[18] Moreover, 5-LOX is overexpressed in pre-cancerous polyps, and inhibition of 5-LOX caused a suppression of tumor growth in a murine colorectal cancer model.[19] A compound extracted from *Boswellia serrata*, called 3-O-acetyl-11-keto-ß-boswellic acid (**AKBA**), is a powerful inhibitor of 5-LOX and may modulate the cellular properties of colorectal malignancies.[20,21]

For a complete discussion of the roles of COX-2 and 5-LOX in cancer development and progression, see the "**Cancer Treatment: The Critical Factors**" protocol.

More recently, nuclear factor-kappa B (NF-kB), a pro-inflammatory mediator that influences more than 500 genes involved in proliferation, angiogenesis, immune evasion and metastatic spread, has been the topic of intense research. Not surprisingly, NF-kB is a target for thwarting cancer's growth and many natural agents act on NF-kB to prevent its signaling. The most notable natural agent able to suppress NF-kB signal transmission is *curcumin*.[22] The high intake of curcumin, and resultant inhibition of NF-kB, may be one reason that the incidence of colon cancer in India is so much lower than in the United States or Europe.[23]

Low Vitamin D Levels

More akin to a hormone than a vitamin, vitamin D broadly influences the genome by activating the vitamin D receptor in the cell nucleus. Activation of the vitamin D receptor is estimated to modulate as many as 2,000 genes, many of which are related to inflammation and cellular mutation—initial drivers in all cancers.[24]

As mentioned in the introduction of this protocol, a review of nine studies found that for every 10 ng/mL increase in serum vitamin D, the relative risk of colorectal cancer decreases 15%.[3] These findings are consistent with the conclusion of a large, case-control study across 10 European countries, which also found that as vitamin D blood levels rose, the risk for colorectal cancer declined considerably. Compared with those in the lowest quintile (1/5th) (<10 ng/mL), those in the highest (>40 ng/ml) had a 40% lower risk of developing colorectal cancer.[25]

Individuals with colon cancer appear to have lower levels of vitamin D at the time of diagnosis as well. Serum vitamin D levels were insufficient (less than 29 ng/mL) in 82% of patients with stage IV colon cancer at the time of diagnosis.[26]

Low levels of vitamin D may adversely impact prognosis as well. One large study found an inverse association between serum *25-hydroxyvitamin D* at the time of diagnosis and colon cancer mortality.[27] Individuals with *25-hydroxyvitamin D* levels *over* 32 ng/mL had a 72% reduction in mortality compared to those with blood levels *less than* 20 ng/mL.

Life Extension encourages the maintenance of serum 25-hydroxyvitamin D levels between *50–80 ng/mL* for optimal health. This typically necessitates supplementation with 5,000–8,000 IU of vitamin D daily, but supplemental doses should always be determined by blood test results.

Low Folate and B-vitamin Intake

Homocysteine is an indirect marker for folate, B6 and B12 status. Homocysteine can be high when there is a deficiency in any of these B vitamins. Folate deficiency is associated with greater risk of developing colorectal cancers. In a large pooled analysis of data from 13 prospective studies including over 725,000 subjects, the highest quintile of folate intake was associated with a 15% reduced risk of colon cancer compared to the lowest quintile of intake.[28]

Many Factors Affect Colorectal Cancer Risk

Contributing factors to the development of colorectal cancer have been extensively studied, which has led to increased understanding of modifiable risk factors for colorectal cancer. In a recent review article, the results of 80 meta-analyses of various dietary and pharmacotherapeutic interventions for the prevention of colorectal cancer were compiled and classified by evidence level. According to the review article, which was published in the journal *Gut* in 2020, a moderate level of evidence supported aspirin use for reducing the risk of developing colorectal cancer by 14–29%. The protective effect of aspirin was reported at doses as low as 75 mg/day and increased with higher dosages up to 325 mg/day.

Based on low or very low quality of evidence, the authors also reported benefit with higher levels of intake of the following:

- Non-steroidal anti-inflammatory drugs (NSAIDs): risk reduction of 26% to 43%
- Magnesium: risk reduction of 13% to 22%
- Folic acid: risk reduction of 12% to 15%
- Dairy products: risk reduction of 13% to 19%
- Fiber: risk reduction of 22% to 43%
- Fruits and vegetables: risk reduction of 8% to 52%
- Soy: risk reduction of 8% to 15%

In this review, the authors found no evidence for the benefit of vitamins A, B (excluding folic acid), C, D, and E; antioxidants; beta-carotene; selenium; tea; allium or garlic; coffee or caffeine; fish or omega-3 fatty acids; calcium; and statins. However, these results were based on low or very low quality of evidence for all except beta-carotene and selenium, which had moderate quality of evidence supporting the lack of benefit.

Both meat and alcohol consumption were associated with increased risk of colorectal cancer based on very low quality of evidence. Meat consumption increased the risk of colorectal cancer by 12–21%, while alcohol consumption increased risk by 12–20%. For alcohol use, the risk of colorectal cancer development increased with higher alcohol intake, with up to a 53% increase in risk with heavy drinking of more than four drinks per day.[283]

4 Pathology and Tumorigenesis

Colorectal cancers begin with *epithelial cells* that line the surface of the colon along finger-like projections called *villi*. The spaces between the villi are called *crypts*, and at the base of each crypt are immature stem cells that give rise to ever-renewing cells that migrate up the crypt and toward the tips of the villi. This normal cellular process is strictly governed by a balance of cellular renewal (normal proliferation) and cellular death (apoptosis), as well as elegantly choreographed expression of various genes along the path from immature stem cells to mature epithelial cells.

Early in the course of colon cancer development, however, the normal renewal of cells is disturbed. Cellular maturation (differentiation) is blocked and apoptosis is impaired leading to an accumulation of immature cells in the crypts. This is called an "aberrant crypt" and it is the first step in the carcinogenic process of colorectal cancers.[29,30] These aberrant crypts almost always involve a genetic pathway that both embryos and colon cancer have in common, a pathway called *Wnt*.[31] Many natural agents exert protective action through influencing this Wnt pathway, including components of black tea,[32] green tea[33] and turmeric.[34]

Once the aberrant crypt forms, it may go on to become a polyp, which is a growth along the lining of the colon that can be seen during a colonoscopy exam. Polyps are benign, but they can progress to adenomas, which are considered precancerous. If further mutations occur, an adenoma can then progress to cancer over years or decades. This is the primary reason that screening colonoscopies are recommended, to remove the polyps or adenomas before they have a chance to become cancer.

Genetic Abnormalities in Colorectal Cancer

Several genes and/or genetic processes are frequently malfunctional in colon cancer cells, and therefore have become intriguing targets for treatment interventions. Some dietary compounds have been shown to influence these genes and may modulate colon cancer development and progression.

KRAS

KRAS is a gene that orchestrates cellular receptor sensitivity to a number of growth factors. When KRAS is activated, cellular proliferation is enhanced, while deactivated KRAS slows proliferation. In several types of cancer, including colorectal cancer, KRAS is mutated in such a way that causes it to be chronically activated, leading to unabated cellular proliferation. Mutations in KRAS are present in up to 40% of colorectal cancers.[2]

While drugs that *directly* target KRAS are not yet available, the mutational status of this gene helps determine the likelihood that certain anticancer agents will be effective. For example, the anti-EGFR antibodies cetuximab and panitumumab may be ineffective if activating mutations in KRAS are present.[35]

Several natural compounds have been shown to target the KRAS pathway, including:

- **Perillyl alcohol**, a substance extracted from citrus fruits[36,37]
- **Curcumin**[38]
- **Fish oil**[39]
- **Tea polyphenols**[40]

EGFR

Epidermal growth factor receptor (EGFR) is a protein expressed on the surface of epithelial cells that variably regulates a number of pathways involved in cellular growth and proliferation. The KRAS pathway is among those that EGFR effects.

Overexpression of EGFR is observed in approximately 65–70% of colon cancers, and is associated with an advanced disease stage.[2]

Activation of EGFR stimulates KRAS-induced signal transduction leading to proliferation. However, in KRAS mutant (upregulation; overexpression) cancer cells, binding of EGFR is not necessary to activate KRAS. Therefore, medications sometimes used to treat colon cancer, called anti-EGFR antibodies, are only effective in patients not harboring a KRAS mutation.[41] For example, *cetuximab* is a monoclonal antibody against EGFR indicated for metastatic colorectal cancer in patients *not* carrying a KRAS mutation.

Natural compounds shown to modulate EGFR include:

- **Genistein** (an isoflavone from soy)[42]
- **Curcumin**[43]
- **American ginseng**[44]

Note: Targeting EGFR directly may not be beneficial in a colorectal cancer patient overexpressing KRAS (constitutional activation). However, the aforementioned nutrients may also influence transcription downstream of EGFR and KRAS; thus, they may be capable of inducing cell cycle arrest in KRAS mutant or wild type cancer cells. For example, curcumin was shown to act synergistically with dasatinib to reduce KRAS mutant colon cancer cell viability through alternative pathways[38]; the other nutrients likely target additional pathways as well.

Microsatellite Instability (MSI) and Mismatch Repair Mutations

The human genome contains thousands of short, repeated base pair sequences called *microsatellites*, which vary in length from person to person, but are all the same length in an individual. DNA damage induced by factors such as oxidative stress and chemical carcinogens can cause dysfunction of genes responsible for ensuring that the microsatellites remain of consistent length; these genes are called *mismatch repair genes*. Mismatch repair gene mutations lead to microsatellite instability (MSI)—the lengthening or shortening of microsatellites. This causes dysfunction in the region of the genome containing the unstable microsatellites. If this occurs in a tumor suppressor region, the consequence can be uncontrolled cell growth, the hallmark of cancer.

Microsatellite instability is found in about 15% of colorectal cancers.[45]

Ironically, MSI (versus stable microsatellites) is associated with a better prognosis in colorectal cancer,[41] likely for the same reasons that it leads to cancer in the first place—the cells are unable to repair major DNA damage and thus more readily succumb to apoptosis.

- **Tea polyphenols** have been shown to inhibit the proliferation of MSI colon cancer cells[46,47];
- Cells with disrupted MMR function are highly sensitive to the apoptotic effects of **curcumin**.[48]

5 Screening for Colorectal Cancer

Colonoscopy

Colonoscopy is an endoscopic process using a lens that allows a physician to visualize the mucosa from the rectum to the start of the colon (ileo-cecal junction). Removal of adenomatous polyps during colonoscopy has been proven to lower the risk of colorectal cancer.[49,50]

Screening colonoscopies are recommended beginning at age 50, but those with any risk factors and/or a family history should consider screening at an earlier age.

How a colonoscopy is performed and by whom may influence whether or not adenomas or cancers are detected. During a 15-month period, analysis of 7,882 colonoscopies performed by 12 experienced gastroenterologists found that the time it took to withdraw the colonoscope influenced detection rates. Gastroenterologists who took less than 6 minutes to withdraw the scope were much less likely to detect cancer than those who withdrew the scope more slowly (up to over 16 minutes.). Even advanced cancers were more likely to be missed when the scope was withdrawn more quickly.[51]

The time of day the colonoscopy is performed may also influence its reliability. In a chart review of a total of 2,087 colonoscopies at Metro Health Medical Center in Cleveland, Ohio, those done in the afternoon had a significantly higher failure rate compared to those done in the morning.[52] The "failure" of a colonoscopy means that the scope could not reach the start of the colon (the cecum). This incomplete look at the colon often necessitates repeating the scoping procedure or undergoing further imaging, such as a CT scan.

The rate of incomplete colonoscopies may be influenced by who performs the procedure. In a study designed specifically to look at factors that lead to incomplete colonoscopies, the elderly, females, and those that have had prior abdominal or pelvic surgeries are more likely to have an incomplete colonoscopic evaluation. In this same study, the researchers found that having the colonoscopy done in an office rather than hospital setting tripled the risk of new or missed colon cancer in men and doubled it in women.[53]

Computer Tomographic Colonoscopy

Computer tomographic colonoscopy (CTC) is sometimes referred to as a "virtual colonoscopy." It involves the use of CT imaging the colon. Preparation for CTC is much like a traditional colonoscopy with the use of laxatives to create an empty bowel. Carbon dioxide or air is infused through the rectum to create a smoother surface to assess. CTC's are useful for larger polyps but may not pick up smaller or flattened polyps as well as traditional colonoscopy. If any polyps or suspicious areas are seen on CTC, the patient must then undergo a colonoscopy to visually assess and/or remove the polyps.

CTC is limited in some extent relative to a traditional colonoscopy in that if a polyp is detected, it cannot be removed during the procedure. This is a disadvantage as the patient will then need to undergo a traditional colonoscopy following the CTC to remove the polyp. Another disadvantage of virtual colonoscopies is the high levels of radiation needed to perform the procedure.

Fecal Occult Blood Test

Fecal occult blood test (FOBT) Occult blood in the stool can be detected with a simple test and is recommended as routine screening for colorectal cancers. Long before blood can be seen by the naked eye, minute quantities may signify the presence of cancer. The association of a positive FOBT with actual colorectal cancer, however, is fairly low, only 10%.[54] This is because occult blood more often comes from benign conditions, such as minor hemorrhoids; a FOBT may even detect bleeding associated with the upper gastrointestinal tract.

The FOBT is about 70% sensitive to the detection of colorectal cancer, while a colonoscopy performed by an experienced gastroenterologist is roughly 95% sensitive.[55,56]

Indirect Tests for Colon Cancer and Emerging Techniques

Colon Cancer Specific Antigens (CCSAs): A blood-based means of detecting colon cancer may be right around the corner. CCSAs are nuclear matrix proteins that are unique to colon cancer cells. When circulating, these CCSAs serve as a "fingerprint" indicating that either colon cancer or a premalignant adenoma is likely present.[57] Circulating levels of several of the CCSAs, including CCSA-2, CCSA-3 and CCSA-4 have all been independently

shown to be both sensitive and specific to colon cancer or premalignant adenomas.[58,59] While this test is not commercially available yet, ongoing research is looking at optimizing combinations of the different CCSAs to predict the likelihood of colon cancer with great accuracy. In the future, this blood test may be used to gauge the urgency for colonoscopy screening.

Calprotectin in the stool has been used as a marker for IBD, and is a useful tool in determining the possibility of adenoma or colorectal cancer.[60,61] Fecal calprotectin is a product of granulocyte formation, a hallmark of chronic inflammation, and as such is not specific to the cancerous process but indicates that inflammation is present. In one study, of the patients referred for colonoscopy due to abdominal symptoms, elevated calprotectin was found in 85% of those with colorectal cancer, 81% of those with IBD and only 37% of those with normal findings.[62]

Molecular markers in the stool. Since precancerous adenomas and colon cancer arise in the lining of the colon, the cells involved are shed with the stool on passing. With advances in technology and molecular biology, examining the stool for unique DNA changes that signify cancer is an area of interest.

The next generation of stool testing for colon cancer involves the *stool DNA* (sDNA) test, which was able to detect 64% of precancerous adenomas greater than 1 cm and 85% of colon cancers, and the *fecal immunochemical test* (FIT).[63] A patented stool DNA test called PreGen-Plus is approximately 65% sensitive to the detection of colorectal cancers,[64] but the high cost of this test may limit its utility for many consumers.

These non-invasive tests remain less sensitive than a colonoscopy, and have advantages and disadvantages that should be discussed with a healthcare provider.[49]

6 Prognosis

Following diagnosis, oncologists and pathologists must analyze the extent to which the cancer has progressed and determine whether it has metastasized to other organs. This process, called "staging," is crucial in guiding treatment.

Cancer confined to the mucosa of the colon wall is classified as *stage I* and is easily removable by surgery in the great majority of cases. When the cancer has penetrated deeper into the muscle layers of the colon, or has just perforated the colon wall, it is classified as *stage II*. Stage II colon cancer also carries a fairly good prognosis. *Stage III* is defined by detection of cancer in nearby lymph nodes, tissues or organs. *Stage IV* colorectal cancer defines metastasis to one or more distant organs, such as the lungs.

The outlook diminishes as stages advance; surgery is usually no longer a curative option for cancer not contained within the colon or isolated to nearby tissue (colon cancer with isolated liver or lung metastasis can rarely be treated effectively with surgery). Five-year survival rates for stage I colon cancer are very good, at about 90%, while the median survival plummets to just six months in advanced stage IV cancer.[65]

A valuable innovation in cancer prognostic technology is *circulating tumor cell* testing. Circulating Tumor Cell testing involves the detection of cancer cells in the bloodstream. These circulating tumor cells are the "seeds" that break away from the primary site of cancer and spread to other parts of the body. Understanding circulating tumor cells is critically important since it is the spread of cancer to other parts of the body—and not the primary cancer—that is very often responsible for the death of a person with cancer. For a detailed discussion of circulating tumor cell testing, please refer to section three of the "**Cancer Treatment: The Critical Factors**" protocol.

7 Conventional Treatment of Colorectal Cancer

Colorectal cancer treatment is adjusted in accordance with the characteristics of each patient's cancer. Surgery is a mainstay for treatment of stage I and most stage II cancers, while stage III and IV cancers are treated with chemotherapy and radiation. Advanced cancers are treated with an aim of reducing symptoms and improving quality of life, as they cannot be cured in most cases.

Surgery

Surgery is the most common local treatment and usually the first-line treatment for patients diagnosed with

localized colorectal cancer. Overall survival rates vary between 55% and 75%, with most recurrences of cancer seen within the first two years of follow-up. For patients whose cancer has not spread to the lymph nodes, survival with surgery alone varies from 75% to 90%. Surgery can also be performed for cancer metastases confined to the liver or lung whenever possible. Surgical removal of metastatic lesions results in long-term survival in a significant number of patients.[66]

In some cases, the patient will require a colostomy, which is an opening into the colon from outside the body that provides an exit for fecal waste. A colostomy may be temporary or, if the surgery is very extensive, may be permanent. Total colonic resection is sometimes performed as a prophylactic measure for patients with familial polyposis and multiple colon polyps.

Nutritional supplementation and dietary modification should be considered before, during, and after surgery (for more information, refer to the "**Cancer Surgery**" protocol).

Radiofrequency Ablation

Radiofrequency ablation (RFA) uses radiofrequency energy produced by an electrode that creates temperatures above 60°C (about 140°F) within the tumor, resulting in cancer cell death. RFA is used as an alternative to surgery in patients with inoperable colorectal liver metastases.[67,68] Although RFA is unlikely to cure patients, it has a definite role in palliative therapy/relieving symptoms.[69]

Radiation Therapy

Radiation therapy (also known as radiotherapy) uses targeted, high-energy ionizing X-rays to destroy cancer cells. It is usually used after surgery to eliminate any remaining microscopic cancer cells in the vicinity. However, it may be used prior to surgery to reduce the tumor volume, which enables the removal of tumors previously considered inoperable. Intraoperative radiation therapy (IORT) has the advantage of maximally irradiating the tumor bed while reducing damage to surrounding, normal organ tissue from the field of radiation.

For more information regarding radiation therapy and prevention of its well-known side effects, refer to the chapter "**Cancer Radiation Therapy**" protocol.

Adjuvant Therapy

The goal of adjuvant therapy is to eliminate any cancer cells that may have escaped the localized treatment. Adjuvant means "in addition to," and adjuvant therapy is used in combination with surgery and radiation. Several types of adjuvant treatments are usually used for early-stage colorectal cancer. These include chemotherapy, radiotherapy, immunotherapy, nutritional supplementation, and dietary intervention.

Chemotherapy. Chemotherapy uses drugs that can be taken orally or injected intravenously to kill cancer cells. Chemotherapy usually begins four to six weeks after the final surgery, though some oncologists may initiate chemotherapy sooner post-surgery. Typical chemotherapy for colon cancer consists of a combination of drugs that have been found to be the most effective, such as *FOLFOX 4* (oxaliplatin, 5-fluorouracil (5-FU), and leucovorin) or *FOLFIRI* (folinic acid, 5-FU, and irinotecan), followed by *FOLFOX6* (folinic acid, 5-FU, and oxaliplatin).[70]

For many tumors, the potential for eradication using chemotherapy is slight.[71] However, chemotherapy using oxaliplatin may make metastatic colorectal cancer patients eligible for liver cancer removal.[72] Nevertheless, chemotherapy drugs have many side effects that can damage or destroy some healthy tissues as well; for information on natural compounds that may help to reduce such adverse effects, refer to the "**Chemotherapy**" protocol.

Chemoresistance is a major hurdle in the treatment of all cancers. This phenomenon occurs when genetic abnormalities make cancer cells resistant to chemotherapeutic drugs. Fortunately, some natural agents may combat chemoresistance.

Studies show that *curcumin* can inhibit the development of chemoresistance to FOLFOX through effects on insulin-like growth factor 1 receptor (IGF-1R) and/or endothelial growth factor receptor (EGFR).[73] When curcumin was used in combination with the targeted drug dasatinib, colon cancer cells' resistance to FOLFOX was eliminated.[38] Curcumin has also been shown to sensitize colorectal cancer cells to the lethal effects of radiation therapy.[74]

Anti-Angiogenic Therapies

Anti-angiogenic therapies stop tumors from forming new blood vessels (eg, by inhibiting VEGF activity) and therefore impede tumor growth. A targeted anti-angiogenic agent, bevacizumab (Avastin), which is a humanized monoclonal antibody targeting circulating VEGF, prolonged survival of metastatic colorectal cancer patients who had inoperable tumors.[75] Interestingly, in patients with metastatic colorectal cancer, the addition of Avastin to irinotecan, fluorouracil, and leucovorin improves survival regardless of the level of VEGF expression.[76] However, side effects from Avastin can be severe and improvements in survival seldom result in cures for advance cases.

8 Novel and Emergent Modalities in Colon Cancer Prevention and Management

COX-2 Inhibitor Drugs

Aspirin. In 2016, the US Preventive Services Task Force (USPSTF), an independent panel of national experts in disease prevention, recommended that adults 50–59 years old who are at risk for cardiovascular disease take low-dose aspirin to prevent both colorectal cancer and cardiovascular disease. The USPSTF also recommended considering low-dose aspirin for those aged 60 to 69 years who are at risk for cardiovascular disease. In both age ranges, the USPSTF noted that adults should be willing to take aspirin for at least 10 years to see benefit.[278] These recommendations are based on extensive data from clinical trials.

A large retrospective look at data over a 20-year period showed that low-dose aspirin use (75–300 mg) for longer than five years reduced the risk of colon cancer by 24%, and was most effective at reducing risk of right-sided (proximal) colon cancer—by about 70%.[4] For people at increased risk of hereditary colorectal cancer, 600 mg aspirin daily for an average of 25 months decreased the risk of cancer diagnosis by 37%.[279] One study also showed taking aspirin after diagnosis of colorectal cancer decreased the risk of death by 16%.[280] In most studies, the beneficial effect of aspirin is greater in those who have taken it for longer periods of time.[278]

Aspirin's anticancer properties stem in part from its capacity to inhibit the action of *cyclooxygenase-2* (COX-2), an enzyme that plays a central role in the onset and progression of most cancers, and is overexpressed in 50% of adenomas and 80% of colorectal cancers.[77-79,280] Higher levels of COX-2 expression have been linked with better responses to aspirin therapy in patients with colorectal cancer.[280] Aspirin also beneficially modulates activity of the protein complex *nuclear factor-kappa B* (NF-κB), a transcription factor that contributes to the growth of a variety of cancers, including colorectal cancers.[80]

Celecoxib. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that inhibits COX-2. In one study, 1,561 individuals with a history of adenomas were recruited to take either celecoxib (400 mg/day) or placebo. Follow-up colonoscopies at three years found that the risk of developing advanced adenomas was halved in the celecoxib group.[81] One preclinical study suggested a synergistic effect when celecoxib is taken with a diet containing fish oil.[82] However, while celecoxib can lessen adenoma formation, it is also well documented to raise the risk of cardiovascular events,[83,84] leaving a risk/benefit equation that should be carefully considered.

Etodolac. Etodolac (Lodine) is a NSAID that inhibits COX-2. In animal studies, combining etodolac with β-adrenergic blockers (β-blockers), such as propranolol (Inderal), decreased the risk of cancer recurrence after surgery.[281] Simultaneous inhibition of β-adrenergic signaling (a pathway involved in the "fight-or-flight" response) and COX-2 may decrease circulating levels of inflammatory factors and stress hormones, which are both upregulated during surgery. For patients with cancer, upregulation of these pathways can increase the risk of metastasis. In a randomized placebo-controlled trial of 34 patients with colorectal cancer, 17 patients received a combination of etodolac and propranolol while 18 received placebo. Etodolac (400 mg twice daily) and propranolol (extended-release formulation dosed at 20 to 80 mg twice daily) were started five days before surgery and continued for a total of 20 days. Compared with placebo, etodolac and propranolol resulted in significantly lower levels of some biomarkers associated with tumor growth and the development of metastases in patient blood samples. Furthermore, within three years after surgery, cancer recurred in only 13% of patients who received etodolac and propranolol, while cancer recurred in 33% of patients who received placebo.[282]

Note: additional information about inhibiting the COX-2 enzyme can be found in step five of the "**Cancer Treatment: The Critical Factors**" protocol.

Metformin

Metformin is an oral antidiabetic drug that works by suppressing the production of glucose in the liver and boosting insulin sensitivity in peripheral tissues. Metformin is currently considered the treatment of choice for type 2 diabetes.

As with other malignancies, colorectal cancer risk is increased in diabetics, and there is a growing body of evidence that advanced glycation end products (AGEs), which are a consequence of elevated blood glucose, and insulin-receptor signaling are involved in the initiation and propagation of these common tumors.[85,86]

Moreover, colorectal cancers are among those malignancies most closely associated with obesity. Obese individuals are deficient in the *protective* hormone adiponectin, which activates tumor-suppressing AMPK. Metformin, by independently activating AMPK, may circumvent this deficiency and help to reduce its impact on colorectal cancer risk.[87] Naturally, these findings have piqued interest in investigating the potential role of metformin against colorectal cancer.

In 2011, researchers conducted a comprehensive review of observational data on the use of metformin and the risk of colorectal cancer in diabetic patients.[88] This review encompassed five studies including nearly 110,000 subjects. Compared to all other antidiabetic treatments, the use of metformin was associated with a 37% lower risk of colorectal cancer.

While this review provides compelling data in support of the protective role of metformin against colorectal cancer, it should be noted that the trials included were observational in nature; the protective effects of metformin must still be substantiated in clinical intervention trials.

Nonetheless, *Life Extension* suggests colorectal cancer patients, especially those who are overweight or have a fasting glucose level of greater than *85 mg/dL*, ask their healthcare provider if metformin would be a positive addition to their regimen.

Cimetidine

Cimetidine (Tagamet) reduces the production of stomach acid by binding with H2 receptors on the acid-secreting cells of the stomach lining. These receptors normally bind with histamine to produce stomach acid, which helps to break down food. By competing with histamine to bind with H2 receptors, cimetidine reduces the stomach's production of acid. This mechanism of action accounts for cimetidine's use in managing gastroesophageal reflux disease (GERD), a condition marked by an excess of stomach acid. Before stronger antiemetic drugs became available, cimetidine was prescribed to treat nausea associated with chemotherapy. As far back as 1988, scientists observed that colon cancer patients who had been treated with cimetidine had a notably better response to cancer therapy than those who did not receive cimetidine.[89]

Cimetidine functions via several different pathways to inhibit growth of tumors. It inhibits proliferation of cells, blocks new blood vessel growth, and interferes with cell to cell adhesion, a necessary process in the spread of cancer.[90] It also has positive effects on immune function.

In a 1994 study, just seven days of cimetidine treatment (400 mg twice daily for five days preoperative and intravenously for two days post-operative) in colorectal cancer patients decreased their three-year mortality rate from 41% to 7%. In addition, tumors in the cimetidine-treated patients had a notably higher rate of infiltration by lymphocytes, a type of white blood cell.[91] These tumor-infiltrating lymphocytes, part of the body's immune response to the tumor, serve as a good prognostic indicator.

Since cimetidine is a histamine receptor *antagonist*—that is, an agent that binds with a cell receptor without eliciting a biological response—it may help circumvent immunosuppression caused by increased histamine levels in a tumor's microenvironment.[92] While histamine appears to stimulate the growth and proliferation of certain types of cancer cells, inhibiting histamine's action may be only one mechanism by which cimetidine fights cancer.

Cimetidine inhibits cancer cell adhesion by blocking the expression of an adhesive molecule—called E-selectin—on the surface of endothelial cells that line blood vessels.[93] Cancers cells latch onto E-selectin in order to adhere to the lining of blood vessels.[94] By preventing the expression of E-selectin on endothelial cell surfaces, cimetidine significantly limits the ability of cancer cell adherence to the blood vessel walls.

Administering cimetidine may enable the immune system to mount a more effective response, possibly minimizing the risk of growth and spread from surgical resection of the tumor. Recent studies suggest that

cimetidine enhances local tumor response through the production of Interleukin-18 (IL-18) by immune cells (monocytes).[95] IL-18 blocks new blood vessel growth and encourages apoptosis of cancer cells.

A report in the *British Journal of Cancer* examined findings of a collaborative colon cancer study conducted by 15 institutions in Japan. First, all participants had surgery to remove the primary colorectal tumor, followed by intravenous chemotherapy treatment. They were then divided into two groups: one group received 800 mg of oral cimetidine and 200 mg of fluorouracil (a cancer-fighting medication) daily for one year, while a control group received fluorouracil only. The patients were followed for 10 years. Cimetidine greatly improved the 10-year survival rate: 85% of the cimetidine-treated patients survived 10 years, compared to only 50% of the control group.[96] Cimetidine produced the greatest survival-enhancing benefits in those whose cancer cells showed markers associated with the tendency to metastasize.

Several other studies have corroborated cimetidine's benefits in colorectal cancer. For instance, in a Japanese study in 2006, colorectal cancer patients who received cimetidine following surgical removal of recurrent cancer had an improved prognosis compared to those treated with surgery alone.[97]

Safety Note: Although cimetidine is available without a prescription, it is important to talk with a doctor before adding cimetidine to your treatment program. Cimetidine can interact with several commonly prescribed medications, such as digoxin (Lanoxin), theophylline (Theobid or Theo-Dur), phenytoin (Dilantin), warfarin (Coumadin), lidocaine (Xylocaine), propranolol, and antidepressants. These drug interactions can result in increased risk of side effects and altered efficacy of the medications.

Statins

Studies on statins' influence on colorectal cancer risk and mortality have produced inconsistent results.[284-290] Differing dosage regimens and treatment durations; types of statins; tumor-specific factors (eg, genetics and site, pre-existing conditions including inflammatory bowel disease, diabetes, and cardiovascular disease); and whether statin usage commenced before or after the cancer diagnosis are among the factors that appear to influence these effects.[286,289,291,292]

One example of statins' potential benefit in colorectal cancer patients comes from a retrospective cohort study that included nearly 12,000 patients who underwent surgical resection for rectal cancer. This study found that statin use within the year before surgery was significantly associated with a reduced risk of 90-day all-cause mortality (0.7% with statins vs. 5.5% without statins). Statin use was also associated with lower mortality from cardiovascular and respiratory events, as well as sepsis and multiorgan failure.[293]

Given the uncertainty related to the effect of statins on colorectal cancer risk and outcomes, in 2021 the American Gastroenterological Association advised physicians against using statins to prevent colorectal cancer in those at average risk, and similarly advised that statins should not be used to reduce mortality in colorectal cancer patients.[294]

Antihypertensive Drugs

A meta-analysis of 25 studies involving 1.95 million people suggests a positive association between hypertension and risk of colorectal cancer, with male patients at a higher risk than female patients.[296] Observational evidence suggests that use of certain blood-pressure-lowering medications is associated with reduced risk of colorectal cancer incidence and mortality. In one large, non-interventional, retrospective analysis of data from nearly 14,000 people aged 65 or older who had been diagnosed with colorectal cancer, beginning a regimen of ACE-inhibitors, beta-blockers, and thiazide diuretics after colorectal cancer diagnosis was associated with reduced cancer-specific mortality. Patients taking antihypertensive drugs prior to cancer diagnosis, and those with stage 0 or stage IV tumors, were excluded from the study. Moreover, more consistent use (ie, better adherence) of these blood pressure medications was associated with reduced mortality as well.[297] And in a meta-analysis of 16 observational studies involving over 2.8 million participants, use of ACE-inhibitors, angiotensin II receptor blockers (ARBs), or both was associated with reduced colorectal cancer risk and mortality.[298] However, not all observational studies have found these links: beta-blocker use was not associated with a reduced risk of colorectal cancer in some earlier observational studies.[299,300]

Beta-blockers have been associated with improved outcomes in colorectal cancer patients undergoing treatment

with bevacizumab and in those undergoing surgery.[301-303] In one randomized placebo-controlled trial in 34 patients undergoing colorectal cancer surgery, perioperative treatment with the beta-blocker propranolol and the COX2 inhibitor etodolac for 20 days (beginning five days before surgery) resulted in improvement of tumor biomarkers, including reduced malignant and metastatic potential.[282] ACE-inhibitors and ARBs may also improve outcomes of patients treated with bevacizumab[304]; however, a clinical study of 100 participants found ACE-inhibitor therapy had no effect on outcomes of patients who underwent liver resection for colorectal liver metastases.[305] Further interventional clinical trials are needed to help clarify antihypertensive drugs' potential role in colorectal cancer treatment and prevention.

In addition to the observational and interventional data described above, preclinical research has identified some mechanisms by which certain antihypertensive drugs may affect cancer biology, providing biological plausibility for a possible benefit. For instance, ACE-inhibitors and ARBs may affect solid tumor growth and angiogenesis via inhibition of the renin-angiotensin system, which has been implicated in the formation and metastasis of solid tumors.[306] The beta-blocker propranolol has been shown to enhance apoptosis, decrease energy production, reduce metastatic potential, and suppress growth of colorectal cancer cells.[307,308]

Vaccines and Immunotherapies

An enlightened medical approach to cancer treatment involves the use of cancer vaccines. The concept is the same as using vaccines for infectious diseases, except that tumor vaccines target cancer cells instead of a virus. Another distinguishing feature of tumor vaccines is that while viral vaccines are created from a generic virus, tumor vaccines can be *autologous*, that is, they can be produced using a person's own cancer cells that have been removed during surgery. This is a critical distinction since there can be considerable genetic differences between cancers. This highly individualized cancer vaccine greatly amplifies the ability of the immune system to identify and target any residual cancer cells present in the body. Cancer vaccines provide the immune system with the specific identifying markers of the cancer that can then be used to mount a successful attack against metastatic cancer cells.

Autologous cancer vaccines have been studied extensively, with the most encouraging results noted in randomized, controlled clinical trials including more than 1,300 colorectal cancer patients in which tumor vaccines were given after surgery. These trials reported reduced recurrence rates and improved survival.[98] Unlike chemotherapy, which can cause severe side effects and toxicity, cancer vaccines offer the hope of a "gentler" type of therapy with improved long-term safety.[99]

In a landmark study reported in 2003, 567 individuals with colon cancer were randomized to receive surgery alone, or surgery combined with vaccines derived from their own cancer cells. The median survival for the cancer vaccine group was over seven years, compared to the median survival of 4.5 years for the group receiving surgery alone. The five-year survival was 66.5% in the cancer vaccine group, which dwarfed the 45.6% five-year survival for the group receiving surgery alone.[100] This glaring difference in five-year survival clearly displays the power of individually-tailored cancer vaccines to greatly focus a person's own immunity to target and attack residual metastatic cancer cells.

Monoclonal antibody therapies currently employed in colorectal cancer therapy include bevacizumab, which targets VEGF, and panitumumab and cetuximab, which target EGFR.

For a detailed discussion of cancer vaccines, please review the "**Cancer Immunotherapy**" protocol.

Personalizing Your Cancer Treatment Regimen

All cancers, including colon cancer, can have unique genetic characteristics from person to person. Gene expression profiles can highlight minute differences in the character of a cancer, and help identify which anticancer drugs will be most effective.

In one study, a 50-gene array conducted on resected colon cancers (stage I or II patients) determined that those with more "aggressive" patterns may be ideal candidates for interventions with specific preventative agents such as COX-2 inhibiting agents.[101] Such testing may be able to determine with great precision which natural or prescriptive agent to choose based on the molecular characteristics of the cancer. Specifically, tests for KRAS mutational status, EGFR expression, microsatellite instability, and other relevant tests are available currently.

Cancers have traditionally been treated as follows: if one therapy proves ineffective, then try another until a successful therapy is found or all options are exhausted. Evaluating the molecular biology of the tumor cell population helps to eliminate the need for this trial-and-error method by providing individualized information to help determine the optimal therapy before initiating treatment. This can save the patient time and money and most importantly, it may provide a better opportunity for "first strike" eradication.

Life Extension recognizes the value that advanced cancer testing delivers to cancer patients and suggests that every cancer patient test their cancers as extensively as possible. For more information on testing the unique biological characteristics of your cancer, refer to steps one and two of the "**Cancer Treatment: The Critical Factors**" protocol.

9 Dietary and Lifestyle Considerations for Colon Cancer

There is a 25-fold difference in geographical areas in incidence of colorectal cancers, within North America, Australia, New Zealand, Western Europe, and select areas of Eastern Europe having the highest rates.[102] People who migrate from low rate areas to high rate areas see an increase in development of colorectal cancers, indicating that the cultural environment and dietary habits contribute significantly to risk.[103]

Diet

In general, Western diets contain too much red meat and not enough fruits and vegetables compared to Non-Western diets. Fruits and vegetables, in addition to the vitamins, minerals and fiber they provide, contain thousands of other compounds (phytochemicals) that have anticancer effects. One class of phytochemicals that lessen cancer risk are the *phenolic* compounds, including hesperidin, anthocyanins, quercetin, rutin, epigallocatechin-3-gallate (EGCG), and resveratrol, among others.[104-107]

Many cultures outside the United States also use a more diverse and greater proportion of herbs and spices in their cooking. Many spices have anti-inflammatory effects and daily consumption of a variety of spices may contribute to the lower rates of colorectal cancers in non-Western cultures.[108,109] Perhaps the most well studied spice with a potent anti-inflammatory action is turmeric, whose active ingredient is curcumin. Curcumin, through its modifying action of NF-kB, affects hundreds of molecules involved in proliferation, survival, migration and new blood vessel development.

While there is some controversy over the precise components of the diet that influence colorectal risk, there is no real debate that whole foods, with the nutrients and fibers intact, provide protection against colorectal cancers. A recent look at data from a study using the Dietary Approaches to Stop Hypertension (DASH) diet, which is high in whole grains, fruit, and vegetables; moderate amounts of low-fat dairy; and lower amounts of red or processed meats, desserts, and sweetened beverages, found the DASH diet reduced the risk of colon cancer by nearly 20% and rectal cancers by 27%.[110]

Unfortunately, intake of sugar-sweetened beverages has increased substantially, with adolescents and adults under age 50 having the highest intake. In the prospective Nurses' Health Study II from 1991–2015, intake of sugar-sweetened beverages during adolescence and young adulthood was investigated for its connection to early-onset colorectal cancer incidence in women. Out of over 95,000 participants, 109 cases of early-onset colorectal cancer were reported. Consuming sugar-sweetened beverages was associated with a significantly increased risk: women who reported consuming more than 2 servings of sugar-sweetened beverages per day during adulthood had more than double the risk of early-onset colorectal cancer than those who reported consuming less than 1 serving per week. With each serving per day increase, the risk increased by 16%. Consuming sugar-sweetened beverages during adolescence also conferred greater risk—each serving per day increase was associated with a 32% higher risk of early-onset colorectal cancer. Importantly, replacing 1 serving per day of sugary beverages with a serving of milk, coffee, or artificially sweetened beverages *reduced* risk of early-onset colorectal cancer by 17–36%, depending on the replacement drink. Replacing sugary beverages with water or tea was associated with a non-significant reduction of risk.[295]

A healthy diet not only reduces risk, but appears to favorably affect outcomes once colon cancer has been diagnosed as well. A study of patients with stage III colon cancer divided their dietary habits into two dietary

patterns. The “Prudent” pattern was characterized by high intakes of fruits and vegetables, poultry, and fish; and the “Western” pattern was characterized by high intakes of meat, fat, refined grains, and dessert. Those with Prudent diet had less recurrence of their colon cancer and were more likely to still be alive at the 5-year point.[111]

Boosting Vitamin C’s Benefits with Intermittent Fasting

While vitamin C remains a promising cancer adjuvant, its clinical application awaits further high-quality controlled trials of pharmacologically-dosed vitamin C in specific types of cancer. A 2020 mouse study may offer a solution to improving the efficacy of vitamin C: combining it with a fasting-mimicking diet (FMD). A FMD—one that is plant-based, calorie-restricted, low-sugar, low-protein, and high-fat—was shown to increase the effectiveness of pharmacologically-dosed vitamin C treatment in a mouse model of KRAS-mutated colorectal cancer. While both the FMD and vitamin C delayed tumor progression when used alone, the combination of the two was even more effective. Interestingly, the combinations of FMD or high-dose vitamin C with the common chemotherapeutic drug oxaliplatin were all equally effective. However, the combination of FMD, vitamin C, and oxaliplatin was the most effective at delaying tumor growth and improving survival, indicating potential synergism between traditional drugs and these non-toxic adjuvants.[277]

Exercise

Population studies show that those who exercise have a reduction in the risk of developing many cancers, including breast, prostate, lung, pancreatic and colon cancer.[112] A study in the *Journal of the American Medical Association* showed that overweight survivors of cancer who took part in nutritional improvement, exercise and modest weight loss had less functional decline than non-participants.[113]

Exercise may protect against the development of cancers by reducing the likelihood of obesity and/or diabetes, but there are other, more direct effects as well. Fat, or adipose tissue, releases chemical messengers called *adipokines*. These adipokines increase inflammation and create glucose dysregulation and other metabolic disturbances. Recently, *myokines* from muscle have also been discovered. These myokines, which are made when muscles contract, appear to have a cross-talk with the adipokines, and the net effect is that myokines lead to improved glucose utilization and less fat deposition.[114] Therefore, usage of muscle and reduction of adipose through exercise results in a reduction of inflammation overall.

Maintaining normal weight protects against many cancers[115] and may be one reason that diet and exercise are linked so strongly to the reduction of risk of colorectal cancer.[116]

10 Nutrients

Multivitamin

Many nutrient deficiencies can increase risk of cancer, and biochemical variations in each person’s ability to utilize nutrients from food may lead to some harboring a nutrient deficiency despite eating well.[117] Multivitamin supplements vary in forms and formulations of the nutrients they contain. All multivitamins contain folate, which is often cited as the nutrient responsible for conferring protection from colon cancer. Since several other nutrients have also been shown to lower risk, it is possible that there is synergy between nutrients that lead to protection.

Several studies indicate that multivitamin use is linked with a lower risk of colon and rectal cancers.[118-120] Recently, a large pooled analysis of 13 clinical studies showed multivitamin use was associated with a 12% lower risk of colon cancer versus non-use.[121] Moreover, an animal model revealed that experimental rats given a multivitamin in their drinking water were 84% less likely to developed chemical-induced aberrant crypt foci in their colons compared to their counterparts who received the chemical carcinogen without multivitamins.[122]

In addition, a 3-year clinical trial looked at a mixture of beta-carotene 15 mg, vitamin C 150 mg, vitamin E 75 mg, selenium 101 mcg, and calcium carbonate (1.6 grams daily) versus placebo and found that the supplement group had significantly less adenoma formation.[123]

Vitamin D

The World Cancer Research Fund conducted a systematic review of studies on colorectal cancer and vitamin D intake and 25-hydroxyvitamin D status. They confirmed that higher vitamin D intake and 25-hydroxyvitamin D

status were associated with reduced colon cancer risk.[124]

The active form of vitamin D, 1,25-dihydroxycholicalciferol has been shown to directly increase the expression of tumor suppressor *cystatin D* in colon cancer.[125] This is of interest because both normal and malignant colon epithelial cells have the enzyme required to transform circulating 25-hydroxycholicalciferol to the active 1,25-dihydroxycholicalciferol, which is then used intracellularly to thwart the growth of the colon cancer.[126]

In one study, 1,179 post-menopausal women were randomized to receive calcium (1,500 mg/day), calcium with vitamin D (1,500 mg and 1,100 IU) or placebo. After four years, the incidence of cancers was less in women receiving the calcium plus vitamin D, but not the calcium alone or placebo.[127] These results were in keeping with earlier data in women (46–70 years old) showing that higher vitamin D status was associated with less risk of developing colon cancer.[128]

Precancerous lesions, or adenomas, are more likely to develop in those with lower circulating levels of vitamin D. A review of 12 studies of vitamin D consumption and seven studies of circulating vitamin D found that high versus low dietary intake of vitamin D reduced the risk of adenoma development by 11% and high versus low circulating levels of vitamin D reduced the risk by 30%.[129]

Higher circulating levels of 25-hydroxycholicalciferol [25(OH)D] are protective against colorectal cancer. For example, pooled data from the Physician's Health Study combined with eight prospective trials showed the risk of developing colorectal cancer was lower for those with higher 25(OH)D status.[130]

Vitamin E

Vitamin E is a family of eight naturally occurring compounds, four tocopherols and four tocotrienols. All forms of vitamin E are antioxidants, able to neutralize free radicals directly as well as recycle other antioxidants. Over the decades, studies have been predominantly on alpha-tocopherol, although more recent evidence suggests *gamma tocopherol* is the more active cancer preventative agent, particularly for colon cancer.[131-133] Importantly, gamma tocopherol was more effective at inhibiting COX-2 than alpha-tocopherol, which may result in improved protection from colon cancer.[134]

Oxidized compounds reach the epithelial cells of the colon and rectum both from dietary sources and from normal bacterial metabolism in the colon. Alpha and gamma tocopherol have been shown to mitigate the oxidative damage, thus lowering the carcinogenic potential of these compounds.[135] In an animal model, a mixture of tocopherols high in gamma tocopherol lessened colon cancer development through antioxidant, anti-inflammatory and other anti-carcinogenic mechanisms.[136]

Several clinical studies suggest a benefit attributable to vitamin E. In one study, intake of supplements containing alpha-tocopherol (>200 IU/d) significantly reduced the risk of colon cancer development compared to no vitamin E intake.[118] In two other studies, those with the highest intakes of vitamin E had reduced risk of developing colorectal cancer as well.[137,138]

Tocotrienols may have their own unique anticancer mechanisms. Tocotrienols were found to increase apoptosis in colon cancer cells through modulation of the balance between pro- and anti-apoptotic mediators.[139,140]

Calcium

Higher calcium intake appears to lower the risk of developing colorectal cancer.[141,142] Calcium may protect the mucosa of the colon and rectum through binding carcinogenic bile acids,[143] or through encouraging proper maturation (differentiation) of colorectal cells. Supplemental calcium, as well as vitamin D, was shown to induce favorable cellular changes in colonic cells of patients with adenomas.[144]

A study of 92 men and women with a history of adenoma compared the effects of calcium and vitamin D alone and together on the normal cellular turnover of the colonic epithelium. Both calcium and vitamin D, alone and together, enhanced apoptosis of normal epithelial cells.[145] Interestingly, one study showed that up to five years after stopping the calcium supplementation, there was still less adenoma formation.[146] Another study showed that Vitamin D and calcium taken as a supplement was associated with reduced risk, but this benefit was not found from dietary sources alone, indicating that supplementation may be necessary to attain benefit.[147] Two studies in men with previous adenomas showed a risk reduction of 36% for future adenomas with supplemental calcium (1,200 mg/day for four years in one study, 2,000 mg/day for three years in the other).[148]

Selenium

Selenium deficiency has been linked to formation of many cancers, including colorectal cancer.[149] Selenium is incorporated into proteins within cells, called "selenoproteins," involved with protecting the cells from free radical accumulation that can lead to DNA damage. Some of these proteins include glutathione peroxidases (GPx), thioredoxin reductases (TrxR), and selenoprotein P (SePP). People that form adenomas are more likely to be deficient in selenium as well as the selenoproteins that protect DNA from damage. Repletion of selenium through supplementation restored both deficiencies, presumably leading to protection from further adenoma formation.[150]

There have been a number of studies showing that selenium is lower in those with adenomas or colorectal cancer compared to controls.[151-153] Selenium may afford even more protection in current smokers and those that have quit less than 10 years previously.[154]

Selenium supplementation at the time of cancer surgery can increase local immune function, an effect which may reduce recurrence.[155] There may also be synergistic effects of selenium with other nutrients such as folate.[156]

A clinical trial of 200 mcg of selenium versus placebo found that the incidence of colorectal cancer was significantly less in those taking selenium.[157]

Selenium may also synergize with some cancer treatment drugs.[158] In a phase I clinical trial using high doses of *selenomethionine*alongside the chemotherapy drug irinotecan, the authors remarked "unexpected responses and disease stabilization were noted in a highly refractory population."[159]

Selenium in high amounts can be toxic and evidence suggests doses in the 200–400 mcg range are most beneficial.[160]

Folate

Folic acid is necessary for the synthesis of both *S*-adenosylmethionine (SAMe) and deoxythymidine monophosphate (dTMP). dTMP and SAMe are needed in the synthesis and function of DNA, respectively. Therefore, a deficiency of folic acid may disrupt proper DNA synthesis or function. A pooled analysis of 13 studies involving over 725,000 participants, found a 2% risk reduction for every 100 mcg/day increase of total folic acid intake.[28] In a large population study, those taking the highest amount of folate from diet and supplements (>900 mcg/day) had a 30% reduced risk of developing colon cancer versus those with the lowest consumption (<200 mcg/day).[161]

Alcohol consumption increases the risk of colon cancers, and evidence suggests this may be potentiated by polymorphisms in genes that produce enzymes involved in folate metabolism.[162] Maintaining adequate levels of folate, and its co-nutrient methionine, may offer protection from colon adenoma development, particularly in those consuming alcohol or those with genetic polymorphisms in folate metabolism.[163]

Green Coffee and Chlorogenic Acids

Greater coffee consumption has been linked with a lower rate of a variety of cancers, including colon cancer.[164,165]

Coffee contains powerful antioxidant compounds, called *chlorogenic acids*, which have been shown to exert several potentially chemopreventive effects, including favorably modulating glucose metabolism, and quelling inflammation.[166,167] In fact, a recent study found that chlorogenic acids were able to interfere with a variety of cellular processes that drive colon cancer metastasis, including NF-kB signaling.[168]

However, the roasting process used to prepare conventional coffee beverages destroys the majority of these beneficial chlorogenic acids. Therefore, drinking coffee is an inefficient means of obtaining these bioactive compounds.

Recent scientific innovation has led to the availability *green coffee bean extract* standardized to 50% chlorogenic acids. Supplementation with green coffee bean extract is a viable option for obtaining robust quantities of bioactive chlorogenic acids.

Garlic

Consumption of garlic has been linked with lower colon cancer risk.[169] Garlic has been shown to reduce the carcinogenic potential of compounds such as nitrosamines, as well as exert anti-proliferative effects.[170,171] Components that may be responsible for the cancer protective effects of garlic include organosulfur compounds

and flavonoids.

There are many mechanisms that can explain how garlic reduces carcinogenesis in the colon and rectum.

- Inhibition of cell growth and proliferation directly
- Inhibition of new blood vessel growth
- Increased cell death (apoptosis)
- Increased detoxification of carcinogens
- Suppression of carcinogen activating enzymes
- Inhibition of cyclooxygenase-2 (thereby inhibition of inflammation)
- Antioxidant action, squelching free radicals in the bowel[172]

One clinical trial showed that supplementing with aged garlic extract reduced the formation of pre-cancerous adenomas in patients with a history of adenomas.[173]

Ginger

Like garlic, ginger has been a mainstay of traditional medicine for more than 2,500 years. Ginger's multiple chemopreventive benefits have been reported in a wide range of experimental models.[174] Key compounds in ginger and its extracts limit the oxidative damage to cells caused by free radicals. They also lower levels of signaling molecules called cytokines, specifically those that provoke an inflammatory response. This dual mode of action may inhibit initiation of carcinogenesis and limit expansion of existing malignancies.[175,176] Some ginger components also increase the activity of vital enzymes that detoxify carcinogens present in the body.[177,178]

Indian researchers provided direct evidence of ginger's chemopreventive power in rats with chemically induced colon cancers in two recent studies.[179,180] After injection with a potent carcinogen, animals were either supplemented with ginger or given normal diets. In both studies the incidence of cancers and the number of individual tumors was significantly reduced in the supplemented groups. The first study also detected lower levels of oxidative agents and higher levels of natural antioxidants in supplemented animals, while the second study further showed a decrease in the activity of bacterial enzymes that release intestinal toxins and damage the colon's natural protective mucous layer.

In recent clinical trial, 30 healthy subjects consumed 2 grams of ginger or a placebo each day for 28 days. Colon biopsies were taken at baseline and at day 28 and assessed for levels of inflammatory markers. The subjects that received ginger displayed significantly lower levels of PGE-2 and 5-HETE, two inflammatory fatty acid metabolites, in their tissue samples than those who received a placebo.[181] These findings are encouraging due to the role of inflammation in driving colon cancer growth.

Modified Citrus Pectin

Modified Citrus Pectin (MCP) is a type of soluble dietary fiber derived from citrus fruits that has been modified by pH and heat to form smaller units of absorbable galactose residues that are able to bind to cancer cells. Specifically, MCP binds to *galectin-3,* a protein expressed by cancer cells that is involved in cell to cell adhesion, survival and spread to distant organs (metastasis).[182,183] Nullifying the effects of galectin-3 by finding agents to bind to it is one means of inhibiting these pro-cancerous mechanisms.[184,185] MCP has been shown to effectively bind galectin-3 and inhibit growth and metastasis of various cancers,[186] including colon cancer.[187]

Interfering with galectin-3 and preventing metastasis is particularly important in colorectal cancer, where spread to the liver means a much worse prognosis than limited or local disease. Galectin-3 levels appear to be increased in colon cancer, and are associated with advanced disease stage,[188,189] confirming that galectin-3 is an important molecule in the growth and spread of colon cancers.

Additional discussion on the role of MCP in combatting cancer metastasis can be found in the Life Extension Magazine article entitled " **Fighting Cancer Metastasis and Heavy Metal Toxicities With Modified Citrus Pectin**".

Curcumin

Curcumin is derived from the spice turmeric (*Curcuma longa*), an ancient spice used throughout Asia. Cultures in which diets high in turmeric are consumed have much lower rates of colon cancer than Western cultures.[108] Curcumin is a powerful anti-inflammatory compound that acts on NF-kB, a proinflammatory mediator that influences hundreds of genes involved in the growth and spread of cancer. In addition, curcumin regulates tumor suppressor pathways and triggers mitochondrial-mediated death in cancer cells.[190,191]

Despite aggressive surgical care and chemotherapy, nearly 50% of people with colorectal cancers develop recurrent tumors.[192] This may be due in part to the survival of dangerous colon cancer stem cells that resist conventional chemotherapy and act as "seeds" for subsequent cancers.[193] There is evidence that combining curcumin with FOLFOX, the first line chemotherapy drug combination of 5-fluorouricil, leucovorin and oxaliplatin, eliminates the persistent pool of colon cancer stem cells,[194] and potentiates the lethality of FOLFOX on cancer cells.[195]

Finally, curcumin interferes with tumor invasiveness and blocks molecules that would otherwise open pathways to penetration of tissue.[1] It also helps to starve tumors of their vital blood supply and it can oppose many of the processes that permit metastases to spread.[196] These multi-targeted actions are central to curcumin's capacity to block multiple forms of cancer before they manifest.[197]

Curcumin also creates a gastrointestinal environment more favorable to optimal colon health by reducing levels of so-called secondary bile acids, natural secretions that contribute to colon cancer risk.[198] That has a direct effect, inhibiting proliferation of cancer cells and further reducing their production.[199]

A novel feature of curcumin is its ability to bind to and activate vitamin D receptors (VDR) in colon cells.[200] Binding to VDR elicits a host of anti-proliferative and anti-inflammatory actions.

Curcumin given to patients undergoing treatment for colon cancer led to weight gain, decreased circulating inflammatory mediator tumor necrosis factor (TNF)-alpha, and increased apoptosis.[201]

Omega-3 Fatty Acids

There is a substantial amount of experimental, population-based studies and clinical trials showing that risk of colorectal cancer is reduced with higher intakes of omega-3 fatty acids.[202-208]

EPA (2 grams/d for three months) reduced crypt cell proliferation and promoted proper apoptosis of colonic epithelial cells in patients with a history of colonic adenomas.[209] Separately, a large population study of physicians found that those who consumed fish oil supplements during a 10-year period had a 35% reduction in the risk of developing colon cancer.[210]

Omega-3 fatty acids may prevent colorectal cancer through supporting normal turnover of the epithelial cells by encouraging apoptosis.[206] Fish oils reduce the pro-tumor effects of many molecules involved in the growth and spread of colon cancer, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-derived endothelial cell growth factor (PDECGF), cyclo-oxygenase 2 (COX-2), prostaglandin-E2 (PGE2), nitric oxide, NF-kB, matrix metalloproteinases and beta-catenin.[211]

DHA, an omega-3 fatty acid found in fish oil, disrupts cell signaling in colon cancer and is synergistic with butyrate in inducing apoptosis.[212,213]

Fish oil (2.5 grams/day) normalized abnormal rectal proliferation patterns in patients with a history of adenomas, and this is thought to be through lessening the availability of the inflammatory omega-6 fatty acid arachidonic acid and modifying vitamin E availability.[214,215]

Chemotherapies induce cell death by inducing DNA damage in quickly dividing cells, tipping the death/survival pathways toward cellular self-destruction (apoptosis). Experiments have shown EPA and DHA can make cancer cells more vulnerable to damage from chemotherapy and radiation, thus encouraging the cells to turn on cell death pathways in lieu of repair pathways.[216-218] Eventual resistance of colon cancer cells to the cytotoxic effects of chemotherapy may also be lessened with EPA/DHA.[219]

Polysaccharide K (PSK)

PSK is a mushroom polysaccharide complex used more commonly in other countries such as Japan and Australia for immune support in cancer care. Pure PSK cannot be obtained in the United States, but the mushroom *Trametes*

versicolor (formerly called *Coriolus versicolor*) is high in this polysaccharide and is often substituted. Many mushrooms have some immune enhancing properties, but PSK can also suppress activation of NF-kB, therefore reducing the expression of hundreds of pro-cancerous genes.[220]

A review of three clinical trials in patients who had surgery and chemotherapy for their colon cancer showed that overall survival was improved by 29% with the addition of PSK.[221]

A group of colon cancer patients were randomized to receive chemotherapy alone or chemotherapy plus PSK, which was taken for two years. The group receiving PSK had an exceptional 10-year survival of 82%. The group receiving chemotherapy alone had a 10-year survival of only 51%.[222] In a similar trial reported in the *British Journal of Cancer* in 2004, colon cancer patients received chemotherapy alone or combined with PSK (3 grams per day) for two years. In the group with stage 3 colon cancer, the five-year survival was 75% in the PSK group. This compared to a five-year survival of only 46% in the group receiving chemotherapy alone.[223]

Sulforaphane

Sulforaphane is a compound that is found in cruciferous vegetables, like broccoli and kale. It improves the elimination of toxic substances by the liver. It also may have a more direct role in thwarting the growth of cancers, including colorectal cancer, through re-activation of tumor suppressor genes that were formerly silenced.[224,225]

Sulforaphane inhibited the formation of colon tumors in an animal model.[226] It is also able to induce apoptosis in colon cancer cells with impaired apoptosis capability.[227]

Sulforaphane appears to protect normal colon cells while encouraging self-destruction of colon cancer cells.[228] When added to oxaliplatin, sulforaphane improved the ability of the drug to kill colon cancer cells.[229]

In one study, sulforaphane was synergistic with indole-3-carbinol, another compound from cruciferous vegetables. Together the compounds resulted in greater toxicity to colon cancer cells than either compound alone.[230]

Resveratrol

Resveratrol is a polyphenol found in grapes, peanuts and mulberries. Resveratrol suppresses colitis and colitis associated colon cancer in mice.[231] Grape powder and resveratrol inhibited the carcinogenic Wnt pathway in normal colonic mucosa.[232,233] Resveratrol also inhibits the COX-2 enzyme, suppressing inflammation.[234] Resveratrol may synergize with butyrate in the colon as well.[235]

Resveratrol has been shown to lessen aberrant crypt formation[236,237] and adenoma formation[238] as well as induce apoptosis of colon cancer cells.[239,240]

A small study of twenty patients scheduled for colon resection to remove malignancy showed that a dose of 0.5–1.0 grams/day for eight days prior to surgery resulted in adequate levels of resveratrol in the tumors to have biological effects. This was particularly true for tumors on the right (proximal) side.[241]

Resveratrol may also increase the sensitivity of colon cancer cells to the killing effects of chemotherapy.[242]

Green Tea Extract

Green tea contains potent antioxidants known as catechins, the most well studied of which is epigallocatechin-3-gallate (EGCG), which has been found to inhibit carcinogenesis in various cancers, including colorectal cancers.[243-245]

Green tea extract is well established to have anticancer actions on growth, survival, angiogenesis and metastatic processes of cancer cells[246,247] and favorable effects on immune function.[248] Green tea has also been shown to reduce the carcinogenicity of nitrosamines, carcinogenic compounds from cooked meats.[249]

A meta-analysis of consumption of green tea across populations found that those consuming the highest levels of green tea had an 18% lower risk of developing colorectal cancer compared to those consuming the lowest amounts.[250] In a clinical study, green tea extract (equivalent of >10 cups/day, or about 150 mg EGCG) lessened adenoma formation, both number and severity, in those with a prior history of adenomas.[251]

Milk Thistle

Milk thistle (*Silybum marianum*) contains silibinin and silymarin, flavonoid compounds shown to have numerous anticancer effects. Milk thistle is generally used to improve the break down and elimination of chemicals and

toxins, so it is not surprising that silymarin was able to prevent chemically induced colon cancer in mice.[252] In another animal study, silymarin, along with quercetin, curcumin, rutin, all independently reduced aberrant crypt formation, an early process in colon cancer formation.[253] Silymarin also inhibits angiogenesis,[254] a necessary process for tumor growth.

Silibinin has been shown to inhibit colorectal carcinogenesis directly.[255] Silibinin blocks proliferation, reduces new blood vessel growth and induces cell death (apoptosis) of colorectal cancer cells.[256-259] It may achieve some of these anti-tumor effects through disruption of signaling pathways within cancer cells as well as by blocking activation of NF-kB.[260]

Quercetin

Quercetin belongs to a class of potent antioxidants called flavonoids. These are what give apples their color. Onions, garlic, tea, red grapes, berries, broccoli, and leafy greens are also rich sources of quercetin.

It's well known to nutritional scientists as a potent free radical-scavenger.[261] Quercetin also happens to possess a singular cancer-fighting feature: it can prevent cancer caused by chemicals. Its unique molecular structure enables it to *block* receptors on the cell surface that interact with carcinogenic chemical compounds. This makes it a perfect anticancer agent for the colon, where carcinogenic chemicals tend to accumulate.[261]

Researchers in Greece have also discovered that quercetin dramatically suppresses one particular cancer-causing gene in colon cells. This makes quercetin supplementation an ideal form of early prevention for individuals with a family history of colon cancer.[262]

Dutch scientists uncovered even more evidence of its cancer-preventive power at the genetic level. In an animal study, quercetin reduced "cancer gene" activity and *increased* "tumor-suppressor gene" activity in colon cells after 11 weeks.[263]

In yet another promising animal study, scientists in South Carolina were able to halt the development of aberrant crypts. Cancer-prone rats fed a diet high in quercetin[34] underwent a four-fold reduction in the number of aberrant crypts compared to a control group. Similar research has yielded additional evidence of quercetin's capacity to reduce emerging aberrant crypts—a vital first step in preventing colon cancer from developing at all.[264]

In 2006, scientists at the Cleveland Clinic evaluated patients suffering from familial adenomatous polyposis. They discovered that a combination of curcumin and quercetin could cause these growths to diminish substantially. The researchers supplemented the patients with 480 mg of curcumin and 20 mg of quercetin orally, three times a day, for six months. Every single patient experienced a remarkable decrease in polyp numbers and size, with average reductions of 60% and 51%, respectively.[265]

N-Acetylcysteine (NAC)

NAC is a slightly modified version of the sulfur-containing amino acid cysteine.

When taken internally, NAC replenishes intracellular levels of the natural antioxidant glutathione (GSH), helping to restore cells' ability to avoid damage from reactive oxygen species. NAC suppresses the NF-kB, which in turn prevents activation of multiple inflammatory mediators.[266,267] NAC also regulates the gene for COX-2, the enzyme that produces pain- and inflammation-inducing prostaglandins in a wide array of chronic conditions.[268]

NAC (800 mg/day) lessened the rate of proliferation of the cells in the colonic crypts in patients with a history of adenomatous polyps.[269] This is in keeping with a study that showed that those with a history of polyps had a 40% reduction in recurrence of their polyps using 600 mg of NAC daily.[270]

Whey Protein

Sarcopenia, the loss of lean body and skeletal muscle mass, is a real concern for cancer patients undergoing chemotherapy. Sarcopenia is often a predictive factor of chemotherapy outcome,[271,272] and is associated with chemotherapy toxicity and worse survival.[273] Cancer patients are frequently at risk of malnutrition and sarcopenia, and whey protein supplements have been suggested to prevent this, as whey protein can help build lean muscle mass.[274] Preclinical studies have also shown whey protein to have some anticancer properties.[275]

In a randomized study published in 2019, preliminary findings indicate whey protein improved nutritional status and prevented toxicity in colorectal cancer patients undergoing chemotherapy.[276] Forty-seven participants received

either highly purified whey protein or placebo for six months while undergoing chemotherapy. Their physical and nutritional health was assessed before starting chemotherapy and again at three and six months. In addition to reducing the incidence of sarcopenia by 30%, versus 6% with placebo, whey protein also reduced the toxicity of treatment. In fact, 94% of participants in the treatment group, versus 29% in the placebo group, did not experience any hematological and gastrointestinal toxicities. While these results are only preliminary, they indicate whey protein could prove to be an important therapeutic adjuvant to chemotherapy.

NOTE: This protocol should not be used in isolation. Individuals with colorectal cancer should also review the content in other Life Extension cancer protocols, including:

- **Cancer Treatment: The Critical Factors**
- **Cancer Adjuvant Therapy**
- **Cancer Radiation Therapy**
- **Cancer Surgery**
- **Cancer Immunotherapy**
- **Chemotherapy**

Update History

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References