

Colorectal Cancer

Cancer of the colon and rectum (colorectal cancer) affects nearly 160,000 Americans each year, causing approximately 62,070 deaths annually. Colorectal cancer ranks fourth worldwide in cancer occurrence and deaths (Shibuya K et al 2002), though it has a better prognosis than do most cancers. In the general population, the risk of developing colorectal cancer is approximately 19 percent, and it is estimated that 2 percent to 5 percent of sporadic polyps will develop into an invasive cancer (Markowitz AJ et al 1997). Therefore, early detection of colorectal cancer dramatically increases survival (Weir HK et al 2003). For example, 90 percent of patients who receive treatment before the cancer has spread are alive after five years, compared to only 10 percent who survive if the cancer is widespread and treated conventionally (Dashwood RH 1999).

RATE OF OCCURRENCE

The lifetime risk of developing colorectal cancer is 4.6 percent for men and 3.2 percent for women (Chu KC et al 1994). Its occurrence is higher in developed countries and in African-Americans versus Caucasians. The peak age of onset of colorectal cancer in the United States is 65 (Khan A et al 2002).

ABOUT THE COLON AND RECTUM

Together, the colon and rectum make up the large intestine, which is located in the abdomen and pelvis, and the term “colorectal cancer” refers to cancers of both areas. The function of the colon is storage, concentration, and propulsion of undigested material toward the rectum and anus for the purpose of defecation (i.e., a bowel movement).

A colorectal carcinoma is a malignant (cancerous) new growth that arises from cells in the bowel lining. Carcinomas tend to invade nearby tissue and spread (metastasize) to distant organs such as the liver, lungs, bone, and brain. Adenocarcinoma of the colon and rectum develops in the glands of the intestine’s inner lining (mucosa) and accounts for 95 percent of colorectal cancer cases.

WHAT CAUSES COLORECTAL CANCER?

Colorectal cancer develops through a process involving genetic change in the epithelial cells of the colon lining. The main factors that initiate colorectal cancer are consumption of cooked red meat (due to heterocyclic amines) (Gerhardsson de V et al 1991; Reddy S et al 1987), high intake of refined carbohydrates (Franceschi S et al 2001), poor vitamin and mineral intake, alcohol consumption, smoking, bile acids, fecal mutagens (DNA-damaging agents), fecal pH, and compromised detoxification enzymes (Winawer SJ et al 1992). An example of one important detoxification enzyme is N-acetyltransferase, which catalyzes the formation of DNA-damaging products from heterocyclic amines that form in cooked meats. Differences in the activity of this enzyme classify individuals as slow or fast acetylators. The level of red meat consumption in fast but not slow acetylators is associated with risk for colorectal cancer development (Welfare MR et al 1997).

RISK FACTORS

Individuals at high risk of developing colorectal cancer can be identified by their age (older than 40), genetic factors such as familial polyposis syndromes, hereditary nonpolyposis colon cancer (Boutron MC et al 1995; Grossman S et al 1988), or a personal or family history of colon carcinoma or polyps (Collett JA et al 1999; Foutch PG et al 1991). Other predisposing conditions include inflammatory bowel disease (particularly ulcerative colitis), Crohn’s disease (Karlen P et al 1999), pelvic irradiation (Neugut AI et al 1991), high fasting glucose level, high insulin level, and diabetes mellitus (Ma J et al 1999; Schoen RE et al 1999). Other risk factors include poor diet (Evans RC et al 2002; Martinez ME et al 1999; Russo A et al 1998), lifestyle, lack of exercise (Giovannucci E et al 1996a), tobacco (Lieberman DA et al 2003; Giovannucci E et al 1996b) and alcohol use (Nagata C et al 1999; Giovannucci E et al 1998, 2003), overeating, and nonsteroidal anti-inflammatory drug (NSAID) use.

CONTROLLABLE RISK FACTORS

Dietary factors. In industrialized Western societies, both polyps and colon cancer occur more frequently due in part to diets low in fruits, vegetables, vegetable protein, and fiber (Satia-Aboutaj J et al 2003). Fecal mutagens are produced by certain diets such as those containing overcooked or burnt meat or fish. Increased intake of fiber, on the other hand, shortens the intestinal transit time, which in turn reduces the exposure of the colorectal lining to mutagens within the stool (Johansson G et al 1997).

Fat intake. A diet high in saturated animal fat, particularly dairy products and red meat (Jones et al R 2003), increases colorectal

cancer risk (Pierre F et al 2003; Stadler J et al 1988). The digestion of fats requires the activity of normal bile acids that irritate and damage cells lining the colon. Consequently, bile acids activate factors associated with abnormal growth of these cells, resulting in an increased risk of colorectal cancer (Glinghammar B et al 1999; Suzuki K et al 1986). The ratio between the secondary bile acid deoxycholic acid and cholic acid may be an indicator of colorectal cancer risk (Kamano T et al 1999). Ingesting a sensible amount of calories and maintaining a desirable weight also play important roles in preventing colorectal cancer (Mason JB 2002).

Red meat intake. The heterocyclic amines when meat is cooked at high temperatures (e.g., by frying) are strongly associated with death from colorectal cancer (Bingham SA et al 1996; Armstrong B et al 1975). People who eat fried, well-cooked red meat more than once weekly are 2.2 times more likely to develop colorectal adenomas than are those who eat lightly browned red meat once a week or less frequently. Dietary beef induces, and dietary rye bran prevents, formation of intestinal polyps (Mutanen M et al 2000).

Folate. Low folate intake, especially when combined with alcohol consumption and a low-protein diet, increases colorectal cancer risk (Kato I et al 1999). Dietary folate influences DNA methylation, synthesis, and repair. Abnormalities in these DNA processes enhance cancer development, particularly in rapidly growing tissues such as the colorectal mucosa (Lengauer C et al 1997; Feinberg AP et al 1983). Higher folate intake from either dietary sources or supplements may protect against the initiation of colorectal cancer (Giovannucci E 2002, 1998).

Selenium. Low levels of selenium correlate with the presence of adenomas (benign tumors), whereas increased levels of selenium are associated with reduced risk of adenomas. Intervention trials have found a beneficial effect of selenium supplementation (Russo MW et al 1997).

Iron. Iron exposure is associated with the development of colorectal polyps (Bird CL et al 1996). Curcumin acts as an iron chelator (i.e., it binds excess iron) and is one of the more successful cancer-preventive compounds investigated in recent years (Jiao Y et al 2006b).

Genetic Risk Factors

Familial adenomatous polyposis (FAP) is a rare syndrome in prone individuals, involving early onset of multiple polyps and virtually 100% risk of colorectal cancer development (Bussey HJ 1990). This condition is characterized by the presence of 500 to 2500 colon polyps, with a minimum of 100 needed for diagnosis of FAP. The polyps are not present at birth but develop over time.

Polyps of the colon or rectum may be single or multiple growths (adenomas) and are almost always benign (non-cancerous), but can also become pre-cancerous. Polyps usually produce no symptoms, but may cause rectal bleeding, which in turn may cause anemia. Polyps larger than 1 centimeter, or with atypical cells (hyperplastic), have an increased risk of progressing to colon cancer (Liljegren A et al 2003; O'Brien MJ et al 1990).

The cumulative risk of cancer developing in a polyp (if it is not removed) is 2.5 percent at 5 years, 8 percent at 10 years, and 24 percent at 20 years. If removed, the relative risk of developing colon cancer is 2.3 percent (Donovan JM et al 1998; Winawer SJ et al 1993).

Hereditary nonpolyposis colon cancer (HNPCC) accounts for approximately 1 percent to 6 percent of colorectal cancers (Marra G et al 1995). Individuals are at risk of HNPCC when there is a strong family history of colorectal cancer at an early age (averaging 46 years) (Peltomaki P et al 1997). Ninety percent of patients with HNPCC have tumors that show a measurable trait called microsatellite instability (Akiyama Y et al 1997).

SYMPTOMS

Colorectal cancer can cause symptoms such as blood in the stool, changes in normal bowel habits (constipation and/or diarrhea), narrowing of the stool, abdominal pain and distension, anemia, weight loss, and constant fatigue. Individuals who have symptoms should undergo a total colon examination (barium enema or colonoscopy) to look for tumors.

SCREENING

Screening involves testing asymptomatic individuals to determine whether they have benign polyps or early-stage, surgically curable colorectal cancers.

Colonoscopy has become the established method of evaluating and treating diseases of the large intestine, including diagnosing pre-cancerous growths (polyps) or colon cancer. A colonoscopy uses a flexible tube to examine the entire colon (large intestine) and anal region. Asymptomatic individuals with no history of colorectal cancer should begin colonoscopy screening at 40 years of age and repeat it every five years. If polyps are detected, a colonoscopy should be performed every three years.

If abnormalities are detected during a colonoscopy procedure, such as a polyp or colonic masses, they may be completely removed by small instruments passed through the colonoscope. If bleeding is found in the colon, the physician can pass a laser or electrical probe or inject special medications through the scope to stop the bleeding.

Virtual colonoscopy uses computer-generated images of the colon constructed from data obtained during an abdominal CT (computed tomography) scan. Virtual colonoscopy is not as accurate as a flexible tube colonoscopy, and if suspicious lesions are found, a full colonoscopy should be performed anyway to remove and biopsy the lesion. Virtual colonoscopies also expose the patient to high amounts of radiation. Thus, flexible tube colonoscopy is recommended over virtual colonoscopy.

Screening of High-Risk Groups Includes:

Familial adenomatous polyposis (FAP): Start during adolescence, then colonoscopy after age 24 every 2 years until age 34, then every 3 years until age 44, then revert to general population screening.

Hereditary nonpolyposis colon cancer (HNPCC): Colonoscopy every 1 to 3 years, starting at age 25.

Family or personal history of colorectal cancer or adenomatous polyps: Beginning at age 40; individuals who have a relative with early-onset disease should start 3 to 10 years prior to the age of onset of their relative's disease.

Inflammatory bowel disease: Colonoscopy after 8 years of disease in cases of pan-colitis or after 15 years with colitis (Provenzale D et al 1995).

Colorectal cancer follow-up: Individuals in whom colorectal cancer has been surgically removed should undergo a complete examination of the colon within 1 year after resection. If the results are normal, the individual can undergo evaluation in 3 years (Winawer SJ et al 1990).

Genetic tests that identify mutated DNA (e.g., adenomatous polyposis coli (APC) gene) in stool samples may significantly improve identification of patients with potentially pre-malignant colon polyps (Doxey BW et al. 2005); Traverso G et al 2002).

What You Have Learned So Far

- Most colorectal cancers arise from malignant transformation of a benign polyp.
- Colorectal cancer is initiated by heterocyclic amines from overcooked red meat, poor vitamin and mineral intake, fecal mutagens, and compromised detoxification enzymes.
- Some types of colorectal cancer (5 percent) are inherited, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC).
- Early detection of colorectal cancer dramatically increases the effectiveness of treatment and likelihood of survival.
- A flexible tube colonoscopy should be used to screen for pre-cancerous lesions and colon cancer beginning at age 40, and should be repeated every five years thereafter. If polyps are found, then a colonoscopy should be repeated every three years.
- Symptoms such as rectal bleeding, bowel problems, abdominal pain and bloating, or iron-deficiency anemia warrant a total examination of the colon.
- Risk factors for colorectal cancer include poor diet and lifestyle, older age, predisposing conditions such as inflammatory bowel disease (ulcerative colitis), Crohn's disease, and pelvic irradiation.

DIAGNOSING COLORECTAL CANCER

When diagnosing cancer, blood and pieces of tumor tissue are tested to determine the tumor's growth rate and aggressiveness. In the 10 percent to 15 percent of patients who present with advanced (metastatic) disease, signs and symptoms are usually present. Colorectal cancer can spread locally or distantly via the lymphatic system, leading to enlarged lymph nodes. The cancer usually spreads to the liver, which is detected by an ultrasound (high-frequency sound waves). However, the cancer can also spread to the vertebrae, pelvis, and spine (Giess CS et al 1998), which can be determined by an x-ray or radionuclear bone scan.

Endoscopic ultrasonography, 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET), and a PET/CT hybrid system are the best ways to determine the staging (progression of) colorectal cancer prior to surgery (Dietlein M et al 2003; Kantorova I et al 2003; Kalantzis CH et al 2002).

CANCER STAGING

The stage of the cancer (stage 0, I, II, III, or IV, or 0 to 4), or the extent to which cancer has spread from its original site to other

parts of the body, is usually determined after surgical treatment and laboratory analysis of the tissue sample removed during surgery. Stage 0 has the best prognosis or outcome, whereas stage IV (4) is the most advanced and thus has a poor prognosis.

The Tumor, Node, Metastasis (TNM) Staging System of Colorectal Cancer

TNM definitions (from the American Joint Committee on Cancer (AJCC) 1977): T = Tumor, N = Node, M = Metastasis (Yarbro JW et al 1999).

T: Primary tumor

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ, intraepithelial or invasion of the lamina propria*

T1: Tumor invades submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues

T4: Tumor directly invades other organs or structures and/or perforates visceral peritoneum**

*Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

**Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa (e.g., invasion of the sigmoid colon by a carcinoma of the cecum).

Regional lymph nodes (N) – at least 12 lymph nodes should be analyzed

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in 1 to 3 regional lymph nodes

N2: Metastasis in 4 or more regional lymph nodes

Distant metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0 T2, N0, M0
Stage II	T3, N0, M0 T4, N0, M0
Stage III	Any T, N1, M0 Any T, N2, M0
Stage IV	Any T, Any N, M1

TUMOR MARKERS

Tumor markers are substances produced by the tumor itself or by the body in response to the presence of cancer, and can be detected in higher-than-normal amounts in the blood of colorectal cancer patients.

Serum tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), alpha-fetoprotein (AFP), and tissue polypeptide-specific antigen (TPS), may be helpful in the early diagnosis of colorectal cancer, in the initial assessment of the extent of the disease (aggressiveness, metastases), and in monitoring tumor growth or regression during treatment (Nakagoe T et al 2003; Yachida S et al 2003; Krauss H et al 2002; Lawicki S et al 2002; Griesenberg D et al 1999). The measurement of CA 125 in patients with normal CEA levels is useful in managing colorectal carcinoma (Mavligit GM et al 2000). Blood tests (complete blood count, or CBC) should be performed to evaluate the presence of anemia or liver dysfunction, both of which can be consequences of the patient's underlying cancer.

CEA is the most reliable colorectal tumor marker. If a patient's CEA level is raised prior to surgery and does not decrease to normal levels following surgery, it is an indication that the cancer may recur (Belluco C et al 2000). For patients with stage II or III colorectal cancer who may be candidates for liver resection, and for stage IV advanced cancer patients, CEA levels should be measured every two to three months for at least three years after diagnosis (Duffy MJ et al 2003; Palmqvist R et al 2003). Patients with a CEA level of greater than 5.0 nanograms/ml before surgery have an almost fourfold higher relative risk of recurrence (Carriquiry LA et al 1999).

Prognostic Markers

Factors that affect survival of colorectal cancer patients include age and gender, tumor type and grade, cancer stage, presence of symptoms (versus asymptomatic), presence of obstruction or perforation, low Bcl-2 levels, p53 and ras gene mutations, low cancer-cell death rate, and vascular endothelial growth factor (VEGF) levels (Stoeltzing O et al 2003; Kos M et al 2002). VEGF levels may be useful in predicting whether cancer will recur in patients who do not have cancer in their lymph nodes (Hanrahan V et al 2003; Broll R et al 1998; Takahashi Y et al 1997).

Serum p53 antibodies. Approximately half of all colorectal cancers do not have a normal p53 tumor-suppressor gene; on the contrary, they have p53 gene mutations that are associated with poorer survival (Pricolo VE et al 1997). When a mutation in the p53 gene occurs, p53 loses its ability to block cancer growth. More important, mutation of p53 renders cancer cells more resistant to current cancer treatments due to lack of p53-mediated cancer cell death (He TC et al. 1999b; Jalving M et al. 2005i; Sun Y 2006). High levels of p53 protein produce antibodies, which can be measured by a blood test (Takeda A et al 1999).

Curcumin reduces the activity of mutant p53 in cancer cells, which may underlie its cancer-preventive action. Curcumin treatment causes p53-independent cell death in colon cancer cells (Jaiswal AS et al 2002). The anti-cancer activities of genistein depend on the presence of p53 (Wilson LC et al 2003).

Ras gene mutations occur in 21 percent to 60 percent of primary colorectal cancers (Wang JY et al 2003) and contribute to tumor initiation and progression (Pretlow TP et al. 2005); thus, they may be of clinical value in the prognosis of colorectal cancer (Castagnola P et al. 2005); Okulczyk B et al 2003). K-ras mutations increase gastrin gene levels in colon cancer cells, which stimulate cell growth in some colorectal cancers (Hori H et al 2003). Furthermore, K-ras gene increases VEGF levels and thus may increase tumor angiogenesis (Zhong SS et al 2003).

Unfortunately, clinical trials using drugs that target Ras—such as tipifarnib, a farnesyl transferase inhibitor (FTI)—have been disappointing even in patients whose tumors harbor Ras mutations (Mesa RA 2006; Rao S et al. 2004). However, Ras gene activity can be slowed by:

- Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil ((Collett ED et al. 2001; Singh J et al. 1998)
- d-Limonene and perillyl alcohol from citrus fruits and essential oils (Broitman SA et al. 1995; Gelb MH et al. 1995)
- Epigallocatechin gallate (EGCG) from green tea extract (Lyn-Cook BD et al. 1999)
- Black tea polyphenol (BTP) from black tea extract (Lyn-Cook BD et al. 1999)
- Diallyl disulfide, from garlic (Singh SV 2001).

Deleted in colorectal cancer gene (DCC), a gene frequently deleted in colon cancer, is associated with a worse prognosis in certain patients with colorectal adenocarcinoma (Vogelstein B et al 1988).

Determining Whether Cancer Has Spread

Removal and examination of at least 12 lymph nodes during surgery can determine whether colorectal cancer has spread to nearby lymph nodes. For the first two years after surgery, the patient should have the following procedures performed every three months to assess for possible recurrence: determination of tumor markers; fecal occult blood test (FOBT); ultrasound of the upper abdomen and CT of the lower abdomen; and total colonoscopy every six months (Griesenberg D et al 1999; Stangl R et al 1994).

If the cancer spreads, surgical removal is the only treatment that can ensure long-term survival and cure in some patients. New treatment modalities, including blocking off the liver (portal) vein (embolization), chemotherapy, and local eradication with cryotherapy or radiofrequency ablation, may help to increase the number of patients suitable for surgical resection of their hepatic metastases, and may prolong survival in cases not suitable for surgery.

CONVENTIONAL TREATMENT OF COLORECTAL CANCER

The course of treatment for colorectal cancer is largely determined by the stage of the cancer. Possible treatments include surgery, chemotherapy, radiation therapy, radiofrequency ablation (RFA), vaccines, and immunotherapy. Nutritional supplementation and dietary modification may be considered in addition to any of these conventional therapies.

Local Treatments

Surgery is the most common local treatment and usually the first treatment for patients diagnosed with colorectal cancer. Overall survival rates vary between 55 percent and 75 percent, 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 percent to 90 percent. Surgery must 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 (Zeng Z et al 1992).

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 colon resection is performed for patients with familial polyposis and multiple colon polyps.

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

Radiofrequency ablation (RFA) uses radiofrequency energy produced by an electrode that creates temperatures above 60° C within the tumor, resulting in cancer cell death. RFA is used as an alternative to surgery in patients with inoperable colorectal liver metastases (Otsuka S et al 2003; Pawlik TM et al 2003). Although RFA is unlikely to cure patients, it has a definite role in relieving symptoms (Lau TN et al 2003).

Radiation therapy (also known as radiotherapy) uses targeted, high-energy x-rays to prevent cancer cells from growing and dividing. 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 eliminating surrounding normal organs 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.

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 (see the chapter Complementary Alternative Cancer Therapies). Several types of adjuvant treatments are usually used for early-stage colorectal cancer. These include chemotherapy, immunotherapy, nutritional supplementation, and dietary intervention.

Chemotherapy uses drugs that can be taken orally in tablet or capsule form or injected intravenously to kill cancer cells. Chemotherapy usually begins four to six weeks after the final surgery and is given as a combination of drugs (sometimes two to three 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, FU, and irinotecan) followed by FOLFOX6 (folinic acid, FU, and oxaliplatin) (Tournigand C et al 2004). For many tumors, the potential for eradication using chemotherapy is slight (Hahnfeldt P et al 2003). However, chemotherapy using oxaliplatin may make metastatic colorectal cancer patients eligible for liver cancer removal (Zaniboni A et al. 2005). Nevertheless, chemotherapy drugs have many side effects that can damage or destroy healthy normal tissues throughout the body; for information on nutritional supplements that help to reduce such adverse effects, refer to the chapter Cancer Chemotherapy.

Immunotherapy. Colorectal carcinoma can be detected by the immune system and thus can be targeted by immunotherapy (Dalerba P et al 2003) and vaccine therapy. For more information, refer to the chapter Cancer Vaccines and Immunotherapy.

Anti-angiogenic therapies stop tumors from forming new blood vessels (e.g., by inhibiting VEGF activity) and therefore impede tumor growth. A targeted anti-angiogenic agent, bevacizumab (Avastin®), which is a humanized monoclonal antibody targeting the circulating VEGF (O'Neil BH et al 2003), prolonged survival of metastatic colorectal cancer patients who had inoperable tumors. Avastin® is now an FDA-approved drug to treat colon cancer. Interestingly, in patients with metastatic colorectal cancer, the addition of Avastin® to irinotecan, fluorouracil, and leucovorin improves survival regardless of the level of VEGF (Jubb AM et al. 2006).

Innovative Drug Strategies

Cimetidine (Tagamet®) is an over-the-counter ulcer medication that has beneficial effects in treating colorectal cancer and improving survival. Cimetidine prevents cancer growth and spread by several different mechanisms, including enhancing the immune response via stimulation of natural killer (NK) cells and interleukin-2 (IL-2) production, preventing histamine activity and thus immunosuppression, and reducing cancer-cell adhesion molecule expression (Tang NH et al 2004; Kubota T et al 2002; Kobayashi K et al 2000).

Colorectal cancers secrete histamine in high concentrations, enough to be locally immunosuppressive (Reynolds JL et al 1997; Melmon KL et al 1972). Histamine's suppression of the immune response (immunosuppression) prevents the body from mounting a

desirable attack against the tumor (Rocklin RE et al 1979). Cimetidine helps restore natural killer cells (Bai D et al 1999) and thus prevents this immune suppression (Adams et al 1993,1994a,b; Hansbrough JF et al 1986), resulting in prolonged survival of patients who undergo colorectal cancer surgery (Matsumoto S et al 2002).

In just seven days of treatment with 800 mg of cimetidine twice daily (Kelly MD et al 1999)—five days prior to surgery and two days post-surgery—the three-year mortality rate decreased from 41 percent to 7 percent in colorectal cancer patients (Tavani A et al 1998; Uchida A et al 1993). Furthermore, cimetidine improves survival in patients with noncurative surgery for stage IV colorectal cancer (Yoshimatsu K et al 2003). Indeed, cimetidine used in conjunction with chemotherapy can significantly improve survival rates. Patients with aggressive colon cancer had a remarkable 84.6 percent 10-year survival rate when treated with cimetidine (800 mg per day) together with 200 mg per day of 5-fluorouracil (5-FU) for one year starting two weeks after surgery, compared to a 49.8 percent 10-year survival rate for patients who were not treated with cimetidine as an adjuvant therapy (Matsumoto S et al 2002). Patients who had tumors with high expression of the Lewis antigen and were treated with cimetidine had a 10-year cumulative survival rate of 95.5 percent compared to 35.1 percent for those who had tumors with low expression of the Lewis antigens (Matsumoto S et al 2002).

The FDA, however, has not approved cimetidine for use in cancer treatment, which means that colorectal cancer patients should discuss the off-label use of cimetidine with their treating physician. While cimetidine can be purchased over the counter, it may be covered by insurance if prescribed by a physician.

PREVENTING COLORECTAL CANCER

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the few agents known to prevent the development of colorectal cancer (Chan TA 2006). Aspirin or NSAID use results in an impressive reduction in the risk of developing colorectal cancer (Janne PA et al. 2000). In two randomized, placebo-controlled trials, aspirin decreased the risk of polyp recurrence, considered a precursor to cancer (Baron JA et al. 2003; Sandler RS et al. 2003); Moran EM 2002; Nakatsugi S et al 1997). Other trials have shown that NSAIDs such as sulindac (Clinoril®) and celecoxib (Celebrex®) decrease the frequency of colorectal adenomas in patients with familial adenomatous polyposis (Jalving M et al. 2005h).

How Do NSAIDs Exert Their Anti-cancer Effects?

NSAIDs inhibit cyclooxygenase (COX) enzymes and prostaglandin synthases, which is at least partly responsible for their anti-cancer effects. Colon cancers have excessive levels of COX-2, which increases production of PGE2 in colon tumors (Sheehan KM et al 1999), promoting tumor progression (Eberhart CE et al. 1994; Jalving M et al. 2005f; Jalving M et al. 2005g; Oshima M et al. 1996) Rigas B et al 1993). NSAID treatment of cancer cells leads to inhibition of COX enzymes and consequent reduction of levels of prostaglandin E2 (PGE2), which in turn suppresses tumor development (Chan TA et al. 1998b; Jalving M et al. 2005e; Tsujii M et al. 1998). PGE2 regulates cancer cell proliferation by modulating the β -catenin-axin signaling pathway, which is essential for the development of colorectal cancer (Castellone MD et al. 2005; Jalving M et al. 2005d). PGE2 also regulates cancer cell death (apoptosis) by transactivating the nuclear receptor NR4A2 (Holla VR et al. 2006; Jalving M et al. 2005c).

However, COX-independent mechanisms are also involved, as NSAIDs such as sulindac sulfone suppress proliferation, prevent tumor growth, and cause the death of cells that do not express COX enzymes (Hanif R et al. 1996; Jalving M et al. 2005b; Stoner GD et al. 1999). NSAIDs also act via prostaglandin-independent pathways involving ceramide, nuclear factor- κ B (NF- κ B), or peroxisome proliferator-activated receptors (PPARs) (Chan TA et al. 1998a; He TC et al. 1999a; Jalving M et al. 2005a; Yamamoto Y et al. 1999).

A 9.4-year epidemiological study showed that COX-2 activation was related to more advanced tumor stage, tumor size, and lymph node metastasis, as well as diminished survival rates among colorectal cancer patients (Sheehan KM et al 1999). With regular use of aspirin (a nonspecific COX-2 inhibitor, but also an anticoagulant), the risk of dying from the disease decreased (Thun MJ et al 1991).

Thus, COX inhibitors have a pivotal role in the prevention and adjuvant treatment of colon cancer. However, the benefits observed with taking prescription COX-2 inhibitors such as Celebrex® (100-200 mg taken every 12 hours) for prolonged periods are accompanied by side effects (Tsujii M et al 1998). Therefore, nutritional supplements that naturally suppress COX-2 such as curcumin (3600 mg/day) could be considered (Gescher A 2004); others include bioflavonoids (250 to 1800 mg/day) and silymarin (420 mg/day) (Pares A et al 1998; Boari C et al 1981).

Intervention for Those at High Risk

Interventions that can prevent the development of colorectal cancer include screening for adenomas, removal of polyps by endoscopic polypectomy, excision of the large bowel (in FAP) (Munkholm P 2003; Watson P et al 1998), and regular NSAID use (Reeves MJ et al 1996; Giardiello FM et al 1993), in addition to the following dietary interventions:

Fiber from bran and cellulose is effective in reducing the risk of colorectal cancer development (Gonzalez CA 2006b); Greenwald P et al 1986). In those with low intake of dietary fiber, doubling of total fiber intake could reduce the risk of colorectal cancer by 40 percent (Bingham S 2006). Fruit fiber consumption, as opposed to vegetable fiber, reduces the risk of colorectal adenomas (Platz EA et al 1997). High-fiber foods include legumes, beans, seeds, nuts, wild rice, and oatmeal.

Calcium reduces the growth rate of rectal and colon epithelial cells both directly and by binding bile acids and fatty acids in the stool, resulting in compounds that are less likely to adversely affect the colon (Rozen P et al 1989). Calcium's beneficial effects may occur only in individuals who have a low level of fat intake (Cats A et al 1995). Oral calcium supplementation reduces benign tumor (adenoma) formation by 19 percent (Baron JA et al 1999) and slightly reduces cell proliferation in the rectum (Cats A et al 1995). Foods such as broccoli, kale, Chinese cabbage, milk, cheese, and yogurt are good sources of calcium.

Curcumin is currently being investigated in human clinical trials for the prevention and treatment of colorectal cancer (Jiao Y et al. 2006a). Curcumin may be effective in preventing the development of colon cancer related to Apc mutations (Corpet DE et al 2003; Pierre F 2003; Reddy BS et al 1994, 2002). The suggested daily dose is 1.6 grams (Perkins S et al 2002). Curcumin is extracted from turmeric root and is used as a spice in cooking.

Multivitamin use reduces the risk of benign tumor (adenoma) formation in high-risk individuals (Whelan RL et al 1999). Vitamins C, E, and A reduce the risk of developing colorectal cancer (Howe GR et al 1992; Newberne PM et al 1990).

NUTRITIONAL THERAPIES FOR COLORECTAL CANCER

PSK (polysaccharide K) extracted from the mushroom *Coriolus versicolor* is a unique polysaccharide that has been used as a chemo-immunotherapy agent to treat cancer in Asia for over 30 years (Fisher M et al. 2002).

Several randomized clinical trials have demonstrated that PSK has great potential as an adjuvant colorectal cancer therapeutic. In one such trial, PSK was effective in prolonging survival in colorectal cancer patients who underwent curative surgery. Patients took PSK (3 grams daily) for one year from the second week after surgery, along with rectal suppositories of the chemotherapy drug FT-207 (750 mg twice a day); now known as tegafur, or tegafur alone. The five-year survival rate was 88.6 percent in the tegafur-only group and 93.0 percent in the PSK-plus-tegafur group (Takashima S et al 1988).

In another randomized study of stage II or III colorectal cancer patients who were treated with either UFT (tegafur/uracil) alone or the combination of UFT and PSK, PSK prevented lung metastases, decreased the risk of recurrence by 43.6 percent, and increased the five-year disease-free survival rate (to 73.0 percent versus 58.8 percent). The five-year survival rate was 82 percent in the PSK group and 72 percent in the control group (Ohwada S et al. 2004).

PSK's multifold anti-cancer activity includes its ability to improve the immune response through natural killer and lymphocyte-activated killer (LAK) cell activation (Matsunaga K et al. 1986), its potential to inhibit cancer spread through several different mechanisms (Kobayashi H et al. 1995), and its effects on cancer cell differentiation or normalization (Kanazawa M et al. 2004).

Fermented wheat germ extract (Avemar®), registered in Hungary since 2002 as a "medical nutriment" standardized to methoxy-substituted benzoquinones, is effective in the supportive therapy of colorectal cancer patients undergoing surgery or chemotherapy (Farkas E 2005a; Jakab F et al. 2000). Specifically, it significantly improves the incidence of metastasis and overall and progression-free survival of colorectal cancer patients when continuously supplemented (9 grams once daily) for more than six months, with no toxicity (Jakab F et al 2003; Illmer C et al. 2005). When used in combination with chemotherapy, Avemar® reduces the occurrence of febrile neutropenia, or the low count of specialized white blood cells (Garami M et al. 2004).

One of Avemar®'s anti-cancer mechanisms is a highly cancer cell-specific activation of caspase-3-mediated cleavage of poly-(ADP-ribose)-polymerase (PARP) (Farkas E 2005b). Avemar® also has metastasis-inhibiting effects (Hidvegi M et al. 1998b; Hidvegi M et al. 1999; Szende B et al. 1998) and works synergistically with 5-fluorouracil (5-FU) and dacarbazine (DTIC) under experimental conditions (Hidvegi M et al. 1998a).

Aged garlic extract (AGE). A preliminary, double-blind, randomized clinical trial using high-dose aged garlic extract (2.4 ml/day) as an active treatment and low-dose AGE (0.16 ml/day) as a control was performed on 51 patients diagnosed with pre-cancerous lesions of the large bowel (adenomas). The number of adenomas increased linearly in the control group from the beginning, but AGE significantly suppressed both the size and number of colon adenomas in patients after 12 months of high-dose treatment. AGE seems to suppress the progression of colorectal adenomas through its effects on their growth and proliferation (Tanaka S et al. 2004; Tanaka S et al. 2006).

In another double-blind, randomized trial of advanced-cancer patients, AGE was administered for six months, resulting in a significant increase in natural killer cell number and activity, without adverse effects (Ishikawa H et al. 2006).

The mechanisms by which garlic prevents colorectal cancer growth and spread include immunomodulatory and antioxidant effects, as well as suppression of cell motility and invasion by inhibition of angiogenesis, through the suppression of endothelial cell motility, proliferation, and tube formation (Matsuura N et al. 2006).

Wheat grass (*Triticum aestivum*) juice is extracted from the pulp of wheat grass and has been used to treat various gastrointestinal disorders. Wheat grass therapy is associated with significant reductions in overall disease activity and the severity of rectal bleeding, without side effects (Ben-Arye E et al 2002).

Wheat grass is reported to contain all the amino acids (except tryptophan), minerals and trace minerals, essential fatty acids, vitamins A and C, iron, B vitamins, vitamin K, and chlorophyll. Chlorophyll is thought to be an immune system booster and antioxidant (Mata JE et al 2004; Robey RW et al 2004; Tajmir-Riahi HA et al 2004). Indeed, wheat grass contains superoxide dismutase (SOD) and displays antioxidant activity (Kulkarni SD et al. 2006).

Modified citrus pectin (MCP) is a polysaccharide found in the peel and pulp of citrus fruits. MCP is rich in galactoside residues that bind galectin-3 on tumor cells, which in turn interferes with tumor cells binding to healthy cells as they circulate (Glinskii OV et al. 2005).

Cancer spread (via metastasis) is one of the most life-threatening aspects of cancer. The lack of effective anti-metastatic therapies has prompted research on modified citrus pectin's effectiveness in blocking colorectal cancer spread. MCP slows cancer growth by 70 percent and spontaneous liver/lung metastasis in mice injected with human colon cancer cells, presumably via its interfering effects on galectin-3 (Nangia-Makker P et al 2002; Hayashi A et al 2000; (Pienta KJ et al. 1995).

MCP produces a healthy bile acid profile (Ide T et al. 1990) and protects against chemically induced colon cancer via carcinogen binding in the colon (Smith-Barbaro P et al. 1981). Furthermore, as a fermentable, soluble fiber, MCP produces high butyrate levels, which in turn inhibit colon cancer development (vivi-Green C et al. 2000).

Curcumin (*Curcuma longa* Linn or diferuloylmethane) is extracted from the spice turmeric. Curcuma extract at doses of up to 2.2 grams daily (equivalent to 180 mg of curcumin) was given for up to four months to 15 advanced colorectal cancer patients who did not respond to standard chemotherapy treatment. Five patients had disease stabilization for two to four months of treatment (Sharma WP et al 2001) without any dose-limiting toxicity. Results from another study of colorectal cancer patients suggest that a daily dose of 3.6 grams of curcumin achieves pharmacologically effective levels in the colorectum (Garcea G et al. 2005).

Curcumin's anti-cancer mechanism of action is complex and multifactorial. It includes preventing colorectal cancer cell division (Leyon PV et al 2003) and the growth of new tumor blood vessels (Gao C et al 2003; Gururaj AE et al 2002), killing cancer cells via apoptosis (Chauhan DP 2002; Moragoda L et al 2001), reducing levels of enzymes involved in cancer progression, migration, and invasion, such as cyclooxygenase 1 and 2, lipoxygenase, and nitric oxide synthase (Su CC et al. 2006) Skrzypczak-Jankun E et al 2003; Cuendet M et al 2003; Brouet I et al 1995), and exerting antioxidant, anti-inflammatory, and anti-metastatic activities (Aggarwal BB et al 2003; Kos M et al 2002).

Green tea has been shown to prevent cancer in preclinical studies (Fujiki H et al. 1998). Its primary anti-cancer component is epigallocatechin gallate (EGCG). Seven patients with familial polyposis who underwent surgical removal of the colon were treated with green tea extract and chemotherapy suppositories (5-fluorouracil) after surgery. No rectal cancer developed in any of the patients and some polyps degenerated in the remaining rectum (Ichikawa et al 1998).

Green tea prevents cancer growth and spread through several different mechanisms, including reducing levels of pro-inflammatory mediators such as prostaglandin E2 (PGE2), COX-2, and lipoxygenase (Peng G et al. 2006); Salucci M et al 2002; Hong J et al 2001; August DA et al 1999), causing mitochondrial damage and direct tumor cell death (Chen C et al 2003), interfering with interactions between tumor cells and normal cells (Mueller-Klieser W et al 2002), and preventing cancer spread by blocking new tumor blood vessel development (Jung YD et al 2001a,b).

A phase I trial of oral green tea extract in patients with solid tumors determined that a dose equivalent to seven to eight cups (120 ml) of Japanese green tea three times daily can be taken safely for at least six months. Side effects of green tea are mild and related to the stimulating effect of caffeine (Pisters KM et al 2001).

Omega-3 fatty acids. EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) supplementation prior to colorectal cancer surgery improves the immune response and decreases the infection rate, improving patients' outcome (Braga M et al 2002). In advanced cancer patients, EPA at doses of 18 grams is well tolerated and improves survival (Barber MD et al 2001; Burns CP et al 1999). Diets rich in omega-3 fatty acids decrease both the initiation and promotion of colon cancer (Kontogiannea M et al 2000). EPA prevents tumor cells from binding to healthy cells, as in blood vessels (Kontogiannea M et al 2000), and thus inhibits the development of liver metastasis (in animals) (Iwamoto S et al 1998). An omega-6 to omega-3 ratio of 2.5:1 reduced rectal cell proliferation in patients with colorectal cancer (Simopoulos AP 2002).

Omega-3 fatty acids (EPA and DHA) are found in oily, cold-water fish such as salmon, mackerel, herring, bluefin tuna, sardines, and trout. Vegan sources of omega-3 fatty acids come from dietary alpha-linoleic acid conversion and include ground flaxseed, soybeans, pumpkin seeds, and walnuts (Davis BC et al 2003; Vegan Society 2003; Mantzioris E et al 1994)

The EPIC study performed in 23 centers in 10 European countries found that high fish consumption had a protective effect against colorectal cancer (Gonzalez CA 2006a). Dietary fish oil supplementation in patients with adenomatous polyps reduces rectal cell proliferation, a marker of cancer risk (Bartram HP et al 1995). In a double-blind study of 60 patients with sporadic adenomas, low-dose fish oil supplementation (2.5 grams, 5.1 grams, or 7.7 grams per day for 30 days) had normalizing effects on the abnormal rectal proliferation patterns associated with increased colon cancer risk (Anti M et al 1994).

Large doses of fish oil prevent tumor growth through a free radical-mediated mechanism, while more moderate doses hinder

inflammation, angiogenesis, and Ras protein activity (Grimm H et al 2002; Collett ED et al 2001; McCarty MF 1996). Mild gastrointestinal symptoms such as belching, bloating, gas, diarrhea, and a fish-oil aftertaste occur in some patients (Bruera E et al 2003; Gogos CA et al 1998).

Selenium is an essential trace element found in vegetables, cereals, grains, and nuts. Selenium reduces the incidence of colorectal cancer (Finley JW 2006), at least in part by increasing antioxidant levels that protect against cancer initiation (Peters U et al. 2006b); Wallace K et al 2003; Fleet JC 1997).

High selenium levels are associated with restoration of glutathione peroxidase levels (Ip C et al 1991), proper functioning of immune system cells, and a reduced occurrence of colorectal adenomas (Connelly-Frost A et al. 2006; Peters U et al. 2006a); Ferencik M et al 2003). By contrast, selenium deficiency increases susceptibility to colorectal cancer (Davis CD et al 2003; Kowal M et al 2003) and is associated with high levels of the tumor marker CA 19-9 (Lasch K et al 1999). Patients prone to colon adenomas and those with colon cancer have significantly lower selenium levels (less than 70 micrograms per liter ($\mu\text{g/L}$)) (Fernandez-Banares F et al 2002; Milde D et al 2001; Psathakis D et al 1998).

In a double-blind, placebo-controlled trial, patients with colon adenomas presented with low serum levels of selenium before treatment, but supplemental selenium normalized their selenium levels (Al-Taie OH et al 2003). Reduced activity of this selenium-dependent enzyme is associated with increased risk and poor prognosis in colorectal cancer patients (Milde D et al 2001). In a double-blind, three-year intervention study of polyp-bearing patients, selenium (101 mcg) protected against the formation of new adenomas (Hofstad B et al 1998). A phase III clinical trial is investigating selenium to see how well it works in preventing the recurrence of polyps in patients with adenomatous colorectal polyps (for more information, visit www.clinicaltrials.gov).

Brazil nuts, plant foods, tuna, cod, and eggs contain high levels of selenium.

Folic acid and folate are forms of a B vitamin and are naturally found in dark green, leafy vegetables such as spinach, blackeye and Great Northern beans, brewer's yeast, and liver. Bacteria in the human colon are also capable of producing folate, and certain dietary fibers such as citrus pectin enhance this effect (in rats) (Thoma C et al 2003). Low folate status is associated with colorectal cancer (Pufulete M et al 2003; Cravo M et al 1994).

Clinical studies show that the higher the level of blood folate and dietary folate intake (Zhang SM et al. 2006), the lower the risk of developing colorectal cancer (Martinez ME et al. 2006); Giovannucci E 2002).

In a study of patients with recurrent adenomatous polyps at high risk for colon cancer development, folate supplementation (2 mg of folic acid per day for three months) decreased colon cell division, thus reducing colon cancer development (Khosraviani K et al 2002). Supplementation with folic acid (5 mg/day for three months) led to a 35 percent decrease in ornithine decarboxylase activity, a key enzyme enhanced in cancer growth (Bukin YUV et al 2001).

In one study, healthy women taking folic acid supplements for at least 15 years showed an astounding 75 percent reduction in colon cancer occurrence (Giovannucci E et al 1998). In another study examining the effect of folate supplementation on cancer risk in ulcerative colitis patients, folate supplementation was associated with a 62 percent lower incidence of cancer compared to individuals who did not receive folate supplementation (Lashner BA et al 1989,1997).

Folate's cancer-preventive mechanisms include improving DNA methylation status (Cravo ML et al 1998), stabilizing tumor suppressor gene(s) such as DCC, adenomatous polyposis coli (APC), and p53, and preventing further increases in cell growth (Nagothu KK et al 2003).

The chemotherapy drugs pemetrexed (Alimta®) and oxaliplatin (Eloxatin®), in combination with folic acid and vitamin B12 supplementation, have anti-cancer activity in advanced colorectal cancer patients (Atkins JN et al. 2005). Folic acid and vitamin B12 markedly decrease the frequency of bone marrow toxicities of pemetrexed (Louvet C et al. 2004).

Cancer prevention with folic acid is currently under investigation at the National Institutes of Health (for more information, visit www.clinicaltrials.gov).

Calcium. In a randomized, controlled trial of 15 patients who had the right side of their colons removed, 1000 mg of elemental calcium per day for two months had a protective effect against colorectal cancer development (van Gorkom BA et al 2002). In adenoma patients, daily calcium carbonate supplementation (1.5 grams of elemental calcium) for one year significantly curbed abnormal rectal cell growth (Rozen P et al 2001).

In individuals at high risk for colon cancer, calcium supplementation (2.0 to 3.6 grams/day for three to four months) reduces the abnormal growth of colon cells, partly by decreasing the level of diacylglycerol, or DAG (Steinbach G et al 1994; Wargovich MJ et al 1992), and partly by producing a healthier bile acid profile (Terry P et al 2002; Lupton JR et al 1996).

Calcium impedes colon cancer development (Lamprecht SA et al 2001) and reduces the risk of colorectal adenoma recurrence by 45 percent (Grau MV et al 2003).

Vitamin A. The risk of developing colorectal adenomas is reduced in those with high vitamin A levels (Breuer-Katschinski B et al 2001; Rumi G et al 1999). By contrast, patients with polyps exhibit significantly lower serum levels of vitamin A. Retinol, retinoic acid, and beta-carotene block protein kinase C (PKC) activity, which when active increases tumor activity in the colon (Kahl-Rainer P et al 1994). When combined, vitamins A and D3 prevent new tumor blood vessel growth, or angiogenesis (Majewski S et al 1996).

Vitamin A comes from green and yellow leafy vegetables, fish liver oils, liver, eggs, and milk.

Caution: Monthly blood tests are necessary to ensure vitamin A toxicity does not occur.

Vitamin D. Increased vitamin D intake reduces colon cancer risk (Garland CF et al 1999). Vitamin D3 brings about normalization (differentiation) of colon cancer cells (Martinez ME et al 1996) and slows liver cancer growth (Martinez ME et al 2002; Alvarez-Dolado M et al 1999; Majewski S et al 1996).

Exposure to sunlight provides most people with their vitamin D requirement; however, elderly people with cancer have a reduced ability to produce vitamin D in their skin and should consider vitamin D supplementation. Foods that contain vitamin D include fish liver oil, fatty fish, and milk; vegan sources include foods fortified with vitamin D derived from torula yeast.

Caution: When taking doses of vitamin D3 in excess of 2000 IU a day, kidney and liver function and serum calcium metabolism should be monitored via a complete blood count (CBC) test.

Vitamin E. Men with a high vitamin E intake are 65 percent less likely to develop colorectal adenomas compared to men with low vitamin E intake (Tseng M et al 1996). For those with advanced-stage colorectal cancer (Dukes' C and D), a daily dose of 750 mg of vitamin E (beginning two weeks prior to chemotherapy or radiation treatment) increases immune function—specifically, increased CD4:CD8 ratios and enhanced capacity of T-cells to produce the T helper-1 cytokines, interleukin 2, and interferon-gamma (Malmberg KJ et al 2002).

Vitamin E succinate (d-alpha tocopheryl succinate) is a potent, highly specific anti-cancer agent of considerable therapeutic potential (Neuzil J 2003; Weber T et al 2002). It reduces colon cancer growth in mice by 80 percent (Neuzil J et al 2001).

Vitamin E is found in wheat germ, avocado, corn, soybeans, sunflower seeds, cod liver, and nuts. It helps prevent colorectal cancer, probably by decreasing the formation of mutagens arising from the oxidation of fecal lipids, as well as by decreasing oxidative stress in the colorectal epithelial cells (Campbell S et al 2003).

Resveratrol, a natural polyphenol found in peanuts, seeds, mulberries, grape skin, and red wine (Latruffe N et al 2002), has colon cancer-preventive activity in experimental studies (Aziz MH et al 2003; Stierum R et al 2001). Resveratrol directly interferes with colon cancer cell growth and causes cancer death by damaging the mitochondria (Liang YC et al 2003; Delmas D et al 2002; Mahyar-Roemer M et al 2002; Schneider Y et al 2000) of cells in vitro. Phase I and II clinical trials are studying the effects of resveratrol treatment in colorectal cancer patients (for more information, visit www.clinicaltrials.gov).

For More Information...

Colorectal cancer patients may wish to read the following chapters and design a program addressing the full range of their cancer concerns:

- Cancer Surgery
- Cancer Chemotherapy
- Cancer Radiation Therapy
- Cancer Vaccines and Immunotherapy
- Complementary Alternative Cancer Therapies
- Anemia, Leukopenia, and Thrombocytopenia.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Colorectal cancer patients should consult their physician before supplementing with any nutrient while under conventional medical treatment. In addition, patients should enlist the assistance of their physician to ensure the implementation of blood tests and diagnostic procedures that are essential for monitoring the effectiveness of any adjuvant therapy for colorectal cancer.

The following summary of an adjuvant/supportive approach to conventional colorectal cancer treatment should be discussed with your physician prior to consideration of implementation:

The Life Extension Foundation suggests:

- **Aged garlic extract (Kyolic®)**—1800 milligrams (mg) daily
- **Alpha tocopherol**—400 to 1200 mg of d-alpha tocopheryl succinate daily
- **Gamma tocopherol**—minimum of 200 mg daily
- **Avemar®**—9 grams (g) daily
- **Calcium**—1000 to 3600 mg daily
- **Curcumin**—Up to 3.2 g daily
- **Fiber**—4 to 12 g daily before meals
- **Fish oils**—2800 mg of EPA and 2000 mg of DHA daily
- **Folic acid**—800 micrograms (mcg) daily
- **Green tea**—725 mg three times daily, or 10 cups of Japanese green tea
- **Modified citrus pectin**—15 g daily in three divided doses
- **Silymarin**—900 mg daily
- **Multivitamin**—containing bioflavonoids daily
- **Perillyl alcohol**—250 mg, four times daily
- **PSK (polysaccharide K)**—3 g daily
- **Resveratrol**—20 to 100 mg daily
- **Selenium**—200 to 400 mcg daily
- **Vitamin A**—10,000 to 30,000 international units (IU) daily; reduce dosage at six months
- **Vitamin C**—500 to 5000 mg daily
- **Vitamin D3**—2000 IU daily
- **Wheat grass juice extract**—100 cubic centimeter (cc) or 1 scoop daily

INNOVATIVE DRUG STRATEGIES

Cimetidine—800 mg nightly for 12 continuous months.

Celebrex®—100 to 200 mg every 12 hours.

PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at www.LifeExtension.com.

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at www.LifeExtension.com

Colorectal Cancer Safety Caveats

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

Curcumin

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Fiber

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

Milk Thistle

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

Pectin

- Do not take pectin if you have a gastrointestinal obstruction.
- Pectin can cause gastrointestinal symptoms such as flatulence, cramps, gas, and diarrhea.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.

- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin D

- Do not take vitamin D if you have hypercalcemia.
- Consult your doctor before taking vitamin D if you are taking digoxin or any cardiac glycoside.
- Only take large doses of vitamin D (2000 international units or 50 micrograms or more daily) if prescribed by your doctor.
- See your doctor frequently if you take vitamin D and thiazides or if you take large doses of vitamin D. You may develop hypercalcemia.
- Chronic large doses (95 micrograms or 3800 international units or more daily) of vitamin D can cause hypercalcemia.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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