

The Integrative Medicine Approach to Colon Cancer

As with all integrative approaches, the conventional approach is considered primary. The integrative approaches can supplement and occasionally guide modifications of the conventional approach in collaboration with the treating medical oncologist. The following discussion focuses only on the integrative aspects. There is ample literature discussing the conventional approaches.

Key Concepts:

- 1) The GI system (along with other organs such as the lung and cervix) is unique in that it is in direct contact with potential carcinogens, as opposed to internal organs such as the pancreas or liver. As these potential carcinogens are usually part of the diet, it's logical to suspect that dietary influences have an enormous role in the development of GI malignancies, including colon cancers. It is estimated that as many as 90% of gastric and colorectal tumors could be prevented by dietary interventions (1).
- 2) Numerous micronutrients present in the diet have been associated with the prevention of colorectal cancer. These include calcium, Vitamin D and folate. Their role in treatment is less clear.
- 3) Different dietary patterns, such as the industrialized, Western diet with excessive fat, red meat, and low fiber are associated with the development of colorectal cancer.
- 4) Numerous tumors have a significant upregulation of COX 2 enzymes, with colorectal malignancies showing the most significant upregulation.
- 5) Mushroom preparations, especially those from *Coriolus Versicolor* (Krestin, PSK, PSP), have been used widely in Asia. These preparations have immunomodulatory activity. Studies comparing conventional treatment with or without these mushroom preparations have suggested a synergistic benefit when these are used along with conventional treatments.

Relationship of diet to prevention and treatment of colorectal cancer

The human body has an external aspect that is in direct contact with the outside environment, and an internal aspect, that is separated from the environment by various boundary tissues. The external aspect includes the obvious organs, such as the skin and the external sensory organs, as well as the less obvious, which include the respiratory system (particularly the proximal part), the bladder, cervix, and the entire gastrointestinal system. These organs are therefore more likely to be directly effected by substances in the

outside environment. This is clearly recognized in oncology, where toxic substances such as those found in cigarettes, are carcinogenic partly due to their direct contact with the respiratory system.

The gastrointestinal system is in direct contact with foods and other orally ingested substances, as well as having direct contact with the huge microbiological population found especially in the large intestine. This population of microorganisms is also directly effected by the nature of the diet. A typical Western diet of low fiber, a paucity of plant based foods, and a relative excess of red meat and dairy will promote a completely different population of GI flora than an Asian or Mediterranean diet (2). These microorganisms will then be part of a complex ecological environment which will lead to production of different substances such as short chain fatty acids and enzymes (3), and the immunological reactions ensuing from the large population of GI immune cells.

It is therefore logical to suspect that the incidence of GI cancers is very dependent on our diet and type of GI flora that our diet promotes. The study of the prevention of GI cancers has thereby been shown to be related to both macro and micronutrients found in our diet. The macronutrients that predispose to the development of colorectal cancers are typical of the Western diet as mentioned above (2) whereas the micronutrients that are protective include especially calcium, vitamin D (4), and folate (5).

Although the role in prevention of these substances is relatively clear, their place in the treatment of already established colorectal cancer isn't known. Nevertheless, the physiological changes that occur with changing to a diet with low amounts of red meat and dairy, increased amounts of plant foods and fiber (and increasing fish), are those which are likely to be of benefit in most malignancies. This type of diet leads to a lower level of inflammation, a decreased amount of proinflammatory cytokines, and an increased level of antioxidants, flavonoids, etc. These are likely to be of benefit in both prevention and treatment, and are discussed in more detail in the sections discussing inflammation, antioxidants, and the general integrative approach to cancer.

The various micronutrients that have been found helpful in prevention may also promote activities probably helpful in treatment. Calcium has been shown to induce apoptosis and lower rates of proliferation (6), whereas vitamin D has the effect of promoting differentiation in cells (6,7). Natural vitamin D and vitamin D analogues, along with different forms of vitamin A, have generated considerable interest regarding their potential use in malignancies. Cells that are differentiated have decreased rates of proliferation, a higher tendency to apoptosis, and fewer mutations. Malignancies tend to be less differentiated, and the level of aggressivity often correlates with the degree of undifferentiation. Folate (8) has important effects regarding methylation, which is often disturbed in malignancies, being associated with stimulation of oncogenes, and has other potential benefits in cardiovascular disease prevention through its effect on homocysteine.

The Role of Inflammation

Upregulation of inflammatory pathways, particularly mediated through COX 1 and 2 enzymes, lipoxygenase enzymes, and signaling substances such as NFkB, has been found in most, if not all malignancies, particularly as the tumors become more aggressive. (see section on inflammation). This is especially true in colorectal malignancies, and has led to studies evaluating COX 2 inhibitors such as celecoxib (9). As in the above discussion of the micronutrients calcium, Vitamin D and folate, the use of substances that lower inflammation is likely to be of benefit in prevention and treatment. The use of herbs such as curcumin and boswellia, as well as high doses of omega-3 fatty acids will have wide ranging beneficial effects on inflammation. Depending on the clinical situation, the use of these substances potentially with or without prescription COX 2 and possibly LOX inhibitors will have a comprehensive

effect on lowering inflammation. As is discussed in the section on inflammation in more detail, the presence of an inflammatory state has the effect of producing growth promoting substances and favoring angiogenesis. Due to the high prevalence of inflammation in colorectal cancers, the therapeutic program should include these anti-inflammatory measures.

Mushroom preparations (for more detail see the section on the use of Mushroom preparations in malignancies)

Mushroom preparations have been used widely in Asian countries as anticancer treatments for a long time. Medicines derived from the *Coriolus Versicolor* mushroom have been specifically studied in patients with colorectal malignancies. Ohwada studied patients with Stage II or III colorectal cancer, comparing a group treated with surgery and chemotherapy versus a group which also received PSK produced from *Coriolus*. After three years they found a mild benefit in disease free survival (68.7 vs. 80.6 $p=0.02$) and overall survival (80.6 vs. 87.3 $p=0.024$) in the PSK group. In stage III patients the three year overall survival was improved (59.3 vs. 80.3 $p=0.02$). The treatment group also showed a decrease in distant metastases (0.05), particularly to the lung (0.01) (10).

Ito studied patients with Dukes C colorectal tumors, comparing 440 patients treated with either 5 FU and PSK or with 5 FU alone. He found a statistical difference in cancer related deaths (37 vs. 49 $p=0.19$) in the treated group (11).

Other studies (12, 13) have supported these positive findings.

Wheat germ extract (Avemar)

Mention should be made of a recent study evaluating a wheat germ extract, Avemar (14). This was an open label trial of patients receiving conventional treatment with (66) or without (104) Avemar for 6 months. Statistical benefit was noted for new recurrences (3 vs 17.3 $p<0.01$), new metastases (7.6 vs. 23.1 $p<0.01$), and deaths (12.1 vs. 31.7 $p<0.01$).

Integrative Approach to the Treatment of Colorectal Malignancies

As in all malignancies, there are different phases of treatment, which will require different integrative approaches. There is the surgical treatment phase, usually followed by chemotherapy. There is then an extended observational phase.

Treatment during the surgical period can address issues related to the catabolic, inflammatory, and immunosuppressive effects of surgery. The catabolic effects involve, among other things, excessive production of reactive oxygen species (ROS). Treatments addressed directly at immune stimulation can include the use of mistletoe and especially, with colorectal malignancies, mushroom preparations (see appropriate sections). These products contain substances such as lectins and high molecular weight polysaccharides and proteoglycans with beta-glucan linkages which have immune stimulating properties. Indirect approaches to the immune system involve the use of high doses of antioxidants to counter excessive production of ROS, anti-inflammatory substances, correcting and protecting against nutritional deficiencies. The use of substances involved in collagen production, such as vitamin C, should be considered. Consideration should also be given towards mind-body approaches (15), as well as therapies such as therapeutic massage. Massage should be considered both because of its stress reducing and general health benefit, but also to help recover from the traumatic effects of surgery.

Integrative treatment during the time when patients are receiving chemotherapy or radiation therapy is complicated and controversial, particularly regarding the use of antioxidants (see section on antioxidants and chemotherapy and/or radiation therapy).

The use of substances which counter inflammation and decrease production of proinflammatory prostaglandins and NFkB is less controversial and significant literature supports their use (see appropriate sections). Again mind-body approaches should be strongly considered (10).

As colorectal malignancies and their treatment have a direct effect on nutrition, particular attention should be paid to avoiding deficiencies and malnutrition.

The general integrative approach to malignancies involves addressing issues that appear to be etiologic for most cancers. These include excessive local inflammation mediated through eicosanoids, resistance to apoptosis, increased angiogenesis, escape from immune mechanisms, a tendency towards a less differentiated state, and excessive production of reactive oxygen species. The rationale for attempting to treat these different processes simultaneously is discussed in more detail in the section discussing the general integrative approach to treatment. The approach to treatment of these individual processes is outlined in the appropriate sections. Countering inflammation, for instance, involves dietary manipulations emphasizing plant and fish foods while discouraging animal and dairy products, the use of natural and pharmaceutical substances such as curcumin and possibly COX 2 inhibitors that block inflammatory pathways involving COX and LOX enzymes, and the use of supplements such as omega-3 fatty acids that decrease the availability of arachidonic acid, a precursor for proinflammatory cytokines. The recent concern about the use of pharmaceutical COX 2 inhibitors needs to be looked at closely. It should be noted that the approach advocated here is directed at numerous inflammatory pathways, rather than only COX 2 enzymes. It is likely that if only one pathway is blocked, the other pathways will be enhanced in a compensatory manner.

Similarly, other approaches can address apoptosis and angiogenesis.

In addition to the general approach, the use of supplemental calcium and vitamin D should be considered. Attention needs to be paid to the avoidance of hypercalcemia with vitamin D supplementation. It should be noted though, that usual recommendations about appropriate doses of vitamin D and optimal serum levels are probably greatly understated. Folate supplements can also be considered as discussed above.

Mushroom preparations, especially those from *Coriolus Versicolor* (PSK and PSP) are recommended, both given during active conventional treatment as well as during the observational periods. The studies cited above suggest a synergistic benefit with conventional surgery and chemotherapy. The use of Avemar appears highly promising.

Evidence-informed clinical protocol

Inflammation

- 1) Antiinflammatory diet – see section on diet and cancer treatment
- 2) Fish oils containing omega-3 fatty acids – dosage ranges typically from 4-20 grams of a typical fish oil supplement, one capsule of which typically contains about 4-500 mg of EPA and DHA. Some

fish oil supplements contain twice the amount of EPA and DHA and dosage should be adjusted accordingly.

- 3) Curcumin – 1500-3000 mg daily.
- 4) Boswellia – 900-1800 mg daily
- 5) COX 2 inhibitors – due to the recent concern of an increase incidence of cardiovascular incidents, especially when high doses are used, these agents should only be used judiciously and in combination with other agents that block the other inflammatory pathways, such as COX 1 and leukotrienes. It should be noted that the herbs discussed above have inhibiting effects on these other pathways.
- 6) Leukotriene inhibitors – consider montelukast 10mg/d use in more aggressive situations, again with the considerations noted about COX 2 inhibition.

Angiogenesis

- 1) Antiinflammatory and antioxidative programs will decrease angiogenesis
- 2) Ammonium tetrathiomolybdate – see general discussion

Immune support

- 1) Mushroom preparations – Coriolus preparations (PSK and PSP) are the most widely studied. Dosages are 1500-3000 mg daily. Other preparations, such as maitake, shitake and mixtures are also commonly used. Genistein Complex Polysaccharide, a fermented combination of genistein and ganoderma, combines in a synergistic manner the benefits of isoflavones and mushrooms (see discussion above).
- 2) Mistletoe preparations – the most commonly used is Iscador, or Iscar. Three different types are commonly used: Quercus (from the oak tree), Mali (from the apple tree), and Pini (from the pine tree). They have a history of specific preparations being used depending on organ involved. Typically, prostate has been treated with the Pini preparation. However, they also have varying concentrations of the most active substances, lectins and viscotoxins, which can govern the choice of preparation. See the appropriate section on immune function for discussion of the choice of preparation.
- 3) Avemar – 9g daily. This is a wheat germ extract. The exact mechanism of action is not known, but immune mechanisms are involved.

Excessive free radical and toxin production

- 1) High potency multivitamin/mineral – numerous good formulations exist. Formula 950 from Primary Encapsulations, which is iron and copper free, is commonly used.
- 2) Pycnogenol – grape leaf and pine needle preparations contain pycnogenol.
- 3) Green tea concentrates, decaffeinated – equivalent of 15-45 cups daily.
- 4) N-acetyl cysteine – 1500 mg daily
- 5) Folic acid – 2-5 g daily
- 6) Calcium – 1000-1500 mg daily. Possibly best form in colon cancer is calcium gluconate

Decreased apoptosis – effected by all of the above

Differentiation agents

- 1) Vitamin A

Short term use – 100,000-300,000 iu/day, not to exceed 1-2 months
Medium term use – 40,000-50,000 iu/day, for up to 1 year
Long term use – 20,000 iu/d, for up to 5 years

- 2) Vitamin D
Vit D2 or Vit D3 – 1,000 – 4,000 iu/day
Calcitriol (1-25OH vit D) - .5mcg/kg weekly
- 3) Consider the use of insulin sensitizing agents, such as glitazones (Actos or Avandia), especially in overweight patients.

Colorectal Cancer Bibliography

1. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), 1997
2. Heber D, Blackburn GL, Go VLW, Holland JF. Nutritional oncology. San Diego: Academic Press, 1999, pp. 491-2.
3. Kim DH. Intestinal bacterial beta-glucuronidase activity of patients with colon cancer. Arch Pharm Res. 24(6): 564-7, 2001.
4. Slattery ML, Neuhausen SL, Hoffman M, Caan B, Curtin K, Ma KN, Samowitz W. Dietary calcium, vitamin D, VDR genotypes and colorectal cancer. Int J Cancer. 111(5):750-6, 2004.
5. Cravo ML, Pinto AG, Chaves P, Cruz JA, Lage P, Nobre Leitao C, Costa Mira F. Effect of folate supplementation on DNA methylation of rectal mucosa in patients with colonic adenomas: correlation with nutrient intake. Clin Nutr. 17(2):45-9, 1998.
6. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. Annals of the New York Academy of Sciences 952:73-87, 2001.
7. Hansen CM, Hamberg KJ, Binderup E, Binderup L. Seocalcitol (EB 1089): a vitamin D analogue of anti-cancer potential. Background, design, synthesis, pre-clinical and clinical evaluation. Curr Pharm Des. 6(7):803-28, 2000.
8. Cravo ML, Pinto AG, Chaves P, Cruz JA, Lage P, Nobre Leitao C, Costa Mira F. Effect of folate supplementation on DNA methylation of rectal mucosa in patients with colonic adenomas: correlation with nutrient intake. Clin Nutr. 17(2):45-9, 1998.
9. Gasparini G, Longo R, Sarmiento R, Morabito A. Inhibitors of cyclo-oxygenase 2: a new class of anticancer agents? The Lancet Oncology. 4(10): 605-15, 2003.
10. Ohwada S, Kawate S, Ikeya T, Yokomori T, Kusaba T, Roppongi T, Takahashi T, Nakamura S, Kawashima Y, Nakajima T, Morishita Y. Adjuvant therapy with protein-bound polysaccharide K and tegafur uracil in patients with stage II or III colorectal cancer: randomized, controlled trial. Gunma Oncology Study Group (GOSG). Dis Colon Rectum. 46(8):1060-8, 2003.

11. Ito K, Nakazato H, Koike A, Takagi H, Saji S, Baba S, Mai M, Sakamoto J and Ohashi Y. Adjuvant therapy with protein-bound polysaccharide K and tegafur uracil in patients with stage II or III colorectal cancer: randomized, controlled trial. *Int J Colorectal Dis.* 19(2):157-64, 2004. Epub 2003 Sep 12.
12. Kudo S, Tanaka J, Kashida H, Tamegai Y, Endo S, Yamano HO. Effectiveness of immunochemotherapy with PSK, a protein-bound polysaccharide, in colorectal cancer and changes of tumor marker. *Oncol Rep.* 9(3):635-8, 2002.
13. Torisu M, Hayashi Y, Ishimitsu T, Fujimura T, Iwasaki K, Katano M, Yamamoto H, Kimura Y, Takesue M, Kondo M, et al. Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. *Cancer Immunol Immunother.* 31(5):261-8, 1990.
14. Jakab F, Shoenfeld Y, Nichelatti BM, Hoffmann A, Kahán Zs, Lapis K, Mayer, Sápy, Szentpétery F, Telekes A, Thurzó L, Vágvölgyi A, Hidvégi M. A medical nutriment has supportive value in the treatment of colorectal cancer. *British Journal of Cancer.* 89(3):465-469, 2003.
15. Rossman ML. *Fighting cancer from within: How to use the power of your mind for healing.* New York: Henry Holt and Company, 2003.