Nutritional Oncology

Edited by D. Heber, G. L. Blackburn, V. L. W. Go, J. F. Holland, E. Giovannucci, S. K. Clinton, A. S. Block, and D. W. Nixon

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This book begins with brief introduction by the senior editors, in which they present the book's major premise: "Nutritional oncology recognizes that cancer is a chronic disease of the genome that may be influenced at many stages in its natural history by nutritional factors that could impact both the prevention and treatment of cancer." Accordingly, their purpose is "to provide the theoretical and research basis for nutritional oncology . . . [and] offer practical information on nutrition assessment and nutritional regimens."

To accomplish this goal, the editors recruited the expertise of 78 researchers. The 46 chapters vary widely in length, from 3 to 25 pages, and total more than 600 pages. Disappointingly to the reader not fully versed in the new discipline of nutritional oncology, 20 chapters lack a summary or concluding section, and in about half of the chapters that have such a section it is limited to a single, brief paragraph. In too many instances, the reader is left to grope for guidance in integrating the chapter's information. The usefulness of this book suffers from this failing, which unfortunately is so typical of technical medical books.

The chapters are organized into five sections: Biological Principles of Nutritional Oncology; Nutrition and the Etiology of Cancer; Diet, Nutrition and Cancer Prevention; Nutrition Assessment and Therapy of the Cancer Patient; and Clinical Trials in Nutritional Oncology. Those chapters likely to be of greatest interest to readers are discussed below.

BIOLOGICAL PRINCIPLES OF NUTRITIONAL ONCOLOGY

The first chapter in this section, "Fundamentals of Nutrition: Application to Cancer Research," written by D. Kritchevsky, provides a rather superficial introduction to the subject and arguably could have been omitted. In contrast, the following chapter, "Cancer-Related Genes," by S. D. Hursting et al., provides a useful and very helpful glossary of terms to assist the "genetically challenged" reader.

A chapter on "Invasion and Metastasis" by K. L. Erickson and N. E. Hubbard provides an introduction to the role of angiogenesis and proteases in facilitation of the spread of cancer. According to Erickson and Hubbard, ω-3 fatty acids appear to exert an inhibitory effect on metastasis, which can be induced by dietary ingestion of these fatty acids. In contrast, ω-6 fatty acids appear to encourage metastasis. For example, γ-linolenic acid, an ω-6 fatty acid, has been reported to increase cell-to-cell adhesion of several types of cancer cells in vitro. Unfortunately, no specific advice on using dietary fatty acid ratios to inhibit metastasis of existing cancers is given.

In "Immunobiology of Melanoma," M. H. Ravindranth and D. L. Morton suggest that dietary supplementation with vitamin E, zinc, and ω-3 fatty acids can enhance the production and activity of cytotoxic T cells and antibody-producing B cells. In contrast, dietary tyrosine and phenylalanine appear to stimulate tumor progression. For example, dietary restriction of these amino acids significantly reduced tumor growth in mice.

NUTRITION AND THE ETIOLOGY OF CANCER

In his chapter on the "Epidemiologic Basis for Nutritional Influences on the Cancer Cell," E. Giovannuci repeats the common observation that nutritional differences influence the variation in the rate of cancer worldwide. For example, breast and prostate cancers are largely diseases of the Western world, and their incidence is linked to the widespread availability of energy-dense, highly processed refined foods. As noted by Giovannuci, food-processing technologies deplete fiber and raise the glycemic index of foods, a combination that promotes insulin secretion when such foods are eaten. He also cites evidence that insulin may act as a growth promoter for tumors after early initiation events have occurred. Giovannuci also is concerned about the strong association of milk, dairy products, and meat consumption with the risk for developing prostate cancer. In developing countries, upper gastrointestinal tract cancers are common and are associated with certain dietary practices and methods of food preservation that expose the mucosa to irritants and carcinogens. Giovannuci points out that a low intake of folate is associated with colon cancer in those on a "Western diet" but not in those consuming a diet typical of developing countries. Thus, it appears to Giovannuci that factors other than folate deficiency are involved in the etiology of colon cancer, and it is possible that interaction among these is responsible for initiation of disease. Giovannuci concludes that the induction of xenobiotic detoxification by multiple plant-based nutrients in plant-based diets may provide chemoprotection to the colon.

In "Molecular Epidemiology and the Genetic Susceptibility to Cancer," N. Probst-Hensch and S. A. Ingles discuss phase I and phase II detoxification enzymes and their potential roles in cancer etiology. Phase I cytochrome P450 enzyme activities vary between individuals due to genetic polymorphism and may change in the same individual over time in response to changes in the dietary induction or inhibition of enzyme expression or enzyme activity. The ability to detoxify the substrates of phase I enzymes (steroids, fatty acids, eicosanoids, and exogenous xenobiotics) increases in direct proportion to phase I enzyme activities. Similarly, the rates of phase II detoxification reactions (acetylation, glucuronidation, methylation, sulfation, and conjugation with glutathione and amino acids) depends on the activities of the series of phase II enzymes. Cruciferous vegetables (broccoli, cauliflower, brussel sprouts, cabbage) are rich in phytochemical inducers of phase II enzymes. Sulforaphane is especially potent. However, some cruciferous vegetables also can induce phase I enzymes in excess. Imbalance of phase I and phase II enzyme activities in favor of phase I enzyme can result in activation of carcinogens more rapidly than phase II activities can conjugate and detoxify them. Nutritional schemes to maximize phase I and phase II capacities concurrently are desirable (but not described in this chapter).

In "Nutritional Modulation of the Carcinogenic Process," S. D. Hursting et al. point out the necessity of stopping the process of carcinogenesis as early as possible by inhibiting the enzymes responsible for carcinogen activation, by facilitating the scavenging of DNA-reactive electrophiles, by altering the activity of detoxification enzymes, and by enhancing DNA repair processes. However, the interconnections among diet, nutritional modulation, and carcinogenesis are not presented in sufficient detail to allow the development of useful preventive or treatment protocols.

In "Nutritional Epidemiology," E. Giovannucci briefly overviews the evidence that has been obtained from a few of the many available observational studies and randomized controlled interventional trials

that have linked diet and cancer. He emphasizes that randomized controlled intervention trials are the only studies that can demonstrate definitively "cause and effect" because observational studies cannot exclude the effects of potentially confounding variables. However, even the results of randomized controlled intervention trials must be interpreted intelligently. Giovannucci points out that, for example, the results of the α-tocopherol β-carotene study that found that vitamin E supplementation significantly reduced the incidence of prostate cancer in Finnish men may not be relevant to men whose selenium intake is adequate. In Finland, selenium intake is especially low, and vitamin E may be protective against prostate cancer only under those circumstances. Conversely, an independent protective effect of vitamin E may not be demonstrable among men also receiving supplemental selenium.

Disorders that occur as a result of cancer therapies are discussed by A. S. Block in "Dietary Assessment Tools: Nutritional Assessment of the Cancer Patient." Chemotherapy with cytotoxic drugs may result in nausea, vomiting, diarrhea, anorexia, stomatitis, mucositis, pain on swallowing, and cardiac, kidney, and liver toxicities. A dozen drugs are listed that interfere with nutrient use and impair nutrition status. In addition to the side effects of chemotherapy, radiation therapy may result in stenosis, loss of taste, dental decay, oral infections, absorption problems, fatigue, strictures, and fistulas. Surgery can cause gastrointestinal disorders such as dumping syndrome, rapid transit time, malabsorption, blind loop syndrome, and intestinal obstruction. Immunotherapy has severe effects on the immune system of the gastrointestinal tract. Curiously, Block omits discussion of the adverse effects of chemotherapy on the immune system and the detrimental effects of immunotherapy on nutrition status.

In a chapter on "Energy Balance, Anthropometry and Cancer," R. Ballard-Barbash discusses obesity and central adiposity as risk factors for cancer. In overweight, postmenopausal women, there is increased risk of cancers of the breast, endometrium, colon, rectum, kidney, and gallbladder. Heavier women also have a poorer prognosis and decreased survival and are more likely to develop recurrent disease, especially with hormone receptor-positive cancers. Paradoxically, tall women have double the risk for breast and colon cancers.

S. A. Smith-Warner and E. Giovannuci, in "Fruit and Vegetable Intake and Cancer," report that the available data strongly indicate a protective effect of high produce intake. They emphasize that three-fourths of all published epidemiologic studies have reported a significant inverse association between fruit and vegetable intake and risk for a variety of cancers. These include cancer of the mouth, pharynx, esophagus, lung, stomach, colon, and rectum. Smith-Warner and Giovannuci postulate that components of fruits and vegetables inhibit activation of procarcinogens, enhance detoxification of carcinogens, and prevent carcinogens from interacting with critical target sites. Consumption of citrus fruits, cruciferous vegetables, green and yellow vegetables, and fruits and vegetables high in vitamins A and C are associated with the greatest risk reduction. It is possible that the consumption of *Allium* species (such as garlic and onion) specifically may reduce risk of stomach cancer and that tomatoes may reduce risk of prostate cancer.

In "Dietary Fiber, Carbohydrates and Cancer," M. E. Martinez et al. promote a simple message: complex carbohydrates from whole grains and avoidance of dietary fat and sugar protect against pancreatic, breast, and colon cancers.

J.-R. Zhou and G. L. Blackburn list possible mechanisms of antimetastisis in "Dietary Lipid Modulation of Immune Responses in Tumorigenesis." According to Zhou and Blackburn, the most important of these mechanisms are modulation of adhesion molecules and proteolytic enzyme activation, both of which are mediated through eicosanoids. Because eicosanoids can be regulated by dietary means, controlling the type of lipid consumed provides a mechanism by which tumorigenesis can be controlled. Specifically, ω-3 fatty acid intake should be increased and intake of animal and vegetable fats should be minimized.

In "Selenium and Cancer," G. F. Combs, Jr., and L. C. Clark suggest that intakes of 50 to 70 μg/d of selenium from selenite, selenoamino acids, or selenium-enriched yeast would be sufficient to achieve maximal levels of expression of enzymes with antioxidant function, such as the glutathione peroxidases. However, larger amounts (200 to 300 μg/d) may be needed to inhibit tumorigenesis and to reduce cancer risk. Clearly, this amount of selenium can be obtained only through the use of dietary supplements.

"Vitamin D and Calcium in Colorectal and Prostate Cancer," by E. A. Platz and E. Giovannuci, contains a summary of the current understanding of the roles that the active form of vitamin D, 1,25-$(OH)_2$ cholecalciferol, is likely to play in cancer prevention. It appears that, by directing cells to differentiate, 1,25-$(OH)_2$ cholecalciferol and several non-physiologic vitamin D metabolites may directly inhibit tumorigenesis even after tumor initiation. Even though they contain vitamin D, milk and dairy products increase plasma calcium and phosphorus concentrations, thereby inhibiting the conversion of vitamin D to its active metabolite, 1,25-$(OH)_2$ cholecalciferol. Worse, milk and dairy products also have a high fat content, which potentiates risk for prostate and colorectal tumors. It appears that, in practice, the importance of calcium as a chemopreventive agent outweighs that of vitamin D. The highest risk for colorectal cancer coincides with daily calcium intakes below 500 to 600 mg. However, nature will seek a balance; daily calcium intakes greater than 1 g may increase risk of prostate cancer.

T. Ogino et al., in "Oxidant Stress and Host Oxidant Defense Mechanisms," discuss the role of reactive oxygen species (ROS) in cancer causation. Among the properties of ROS described by these contributors are the modification of DNA by causing mutations and strand beaks, lipids by triggering aldehyde formation and low-density lipoprotein oxidation, and proteins by altering enzyme functions and signal transduction pathways. In some pathologic conditions, such as acute or relapsing inflammation or ischemic reperfusion injury, there is a transient overproduction of ROS. Under these conditions, oxidative stress occurs. ROS-induced oxidative stress is strongly implicated in the pathogenesis of symptoms associated with radiation, chronic inflammation, and metal overload. Dietary supplementation with antioxidants (such as vitamin E, vitamin C, α-lipoic acid, and *N*-acetyl cysteine) may ameliorate oxidative stress by reducing the toxic effect of ROS.

In "Nutrition and Tobacco-Related Cancer," K. El-Bayoumy and D. Hoffman discuss several phytochemicals that have been reported to inhibit tumor formation in animals exposed to tobacco smoke. These include indole-3-carbinol from cruciferous vegetables, epigallocatechin from tea, *d*-limonene from citrus fruits, ellagic acid from berries, alliin from garlic, and myo-inositol from various plants. However, El-Bayoumy and Hoffman overlooked published clinical studies showing that supplemental folate and vitamin B12 reverse the lesions of bronchial dysplasia, a well-recognized precursor of lung cancer.

DIET, NUTRITION, AND CANCER PREVENTION

P. Greenwald et al. defend the much-maligned antioxidant β-carotene in "The Challenge of Cancer Prevention and Control: Diet, Nutrition, and Cancer Prevention." They assert that reports that this nutrient promotes the development of lung cancer in Finnish men may have resulted from reliance on a particularly poor experimental design. For example, the median follow-up of only 6 y may have been too short a period to reverse or overcome pre-existing risk factors for lung cancer. Most obviously, heavy smokers in these studies may have developed the initial stages of lung cancer before enrollment. The subjects had smoked an average of 30 cigarettes

daily for several decades and, in addition, were overweight. It can readily be argued that the Finnish experimentation was treatment and not prevention oriented. It is worth emphasizing that failure to successfully treat existing lesions is not the same as failure to prevent lesion initiation. Moreover, it is axiomatic that antioxidants work in combination in the body, and it is erroneous to hypothesize that one agent in isolation could be effectively chemopreventive in the face of continued exposure to the extremely potent set of four dozen different carcinogens in cigarette smoke, all acting through different carcinogenic mechanisms. Further, Finland is notorious for its selenium-deficient soil. Supplemental selenium, or at least measured selenium intake, should have been included in the study protocol. It is interesting to note that, despite the negative spin the investigators put on their findings, those subjects who had higher serum β-carotene concentrations at the beginning of the study developed fewer lung cancers during the study, regardless of whether they did or did not receive supplemental β-carotene. This controversy does serve as a reminder that, although β-carotene may serve as a marker for intake of vegetables and fruit, primary reliance for chemoprevention should be placed on increasing plant foods in the diet.

In "Cancer Chemoprevention: Subject Cohorts with Early Neoplasia, Agents, and Intermediate Marker Endpoints in Clinical Trials Evaluated by Computer-Assisted Tomography," C. W. Boone and G. J. Kelloff list and discuss nine categories of chemopreventive agents: tannins (gallic acids, ellagic acids, and catechin), phenylpropanoids (curcumin), flavonoids (apigenin and quercetin), terpenes (limonene, dehydroepiandrosterone, and lycopene), nitrogen-containing compounds or alkaloids (indole-3-carbinol), sulfur-containing compounds (*N*-acetylcysteine, sulforaphane, and phenylisothionate), ω-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid), vitamins (retinoids, folate, vitamin D, and vitamin E), and minerals (calcium and selenium). Boone and Kelloff emphasize that all such agents are found in plant foods, thus reinforcing the need to increase the extent to which animal foods are replaced by fruits and vegetables.

In an aside, Boone and Kelloff describe the multiphase chemoprevention program at the National Cancer Institute (NCI). The goal of the first phase is to acquire knowledge concerning the characteristics and mechanism of action of intraepithelial neoplasia. The goal of the second phase is to develop chemopreventive agents by applying the mechanistic knowledge gained during phase 1. Finally, subjects with intraepithelial neoplasia are recruited, and clinical trials are conducted to test the agents identified during phase 2. Because logistic and economic obstacles using clinical trials with detectable cancers as endpoints preclude the possibility of completion, intermediate endpoint markers must be developed. Studies using these markers may then include fewer subjects and be of shorter duration (usually less than 1 y). In this case, change in existing disease is used to reflect efficacy or its absence. The major flaw with this protocol is that only one agent is tested at a time, even though the NCI recognizes that there are multiple mechanisms of cancer induction. In addition, the use of regression of existing intraepithelial neoplasia as an indicator of *chemoprevention* is illogical; this program actually only screens for *chemotherapeutic* agents and learns nothing about chemoprevention.

J. M. Ashley and G. Harrison discuss the findings of the 1997 joint World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) review of the world literature and evidence linking diet and cancer in "Dietary Supplements, Medical Foods, and Functional Foods." The evidence that vitamin C and carotenoids reduce risk for stomach and lung cancers was judged to indicate that such an effect was "probable." From the strength of the available evidence, it was determined that it is "possible" that carotenoids reduce risk for cancers of the stomach, esophagus, colon, rectum, breast, and cervix; that vitamin C reduces risk for cancer of the mouth, pharynx, esophagus, lung, pancreas, and cervix; that vitamin E reduces risk for cancer of the lung and cervix; and that selenium reduces risk for lung cancer. Insufficient evidence was found to conclude that vitamin D reduces risk for cancer of the colon and rectum. Ashley and Harrison also examine the therapeutic potential of plant products that are popular among cancer patients, including *Astragalus*, cat's claw, Essiac, Hoxsey formula, Iscador, Kombucha tea, milk thistle, Pau D'Arco, and shiitake mushrooms. They also consider botanical products that are used to alleviate side effects of cancer therapy. For example, ginger reduces the nausea of chemotherapy but may be contraindicated in thrombocytopenia. For most botanical products, biological activity depends on the timing and method of harvesting and on the specific plant parts used. There is considerable variability in marketed products. Standardization is voluntary, and among the many responsible manufacturers there are a few dishonest purveyors of herbal products who dilute the active constituents beyond any potential for effectiveness. The safety of botanical products also is an issue because natural sources of such products are not all totally innocuous, contrary to popular belief. Although there are several plant compounds known to have biological activity, the AICR/WCRF review was unable to link any botanical product with reduced risk of cancer. However, the available suggestive evidence indicates that there is good reason to expect that future research will produce evidence of chemoprotective efficacy for at least a few botanical products.

H. Mo et al. discuss how isoprenoids work synergistically to suppress 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in "Targeting the Action of Isoprenoids and Related Phytochemicals to Tumors." According to their evaluation of the scientific literature, tumor tissue is the most sensitive to isoprenoids. In animal studies, dietary-relevant intakes of the isoprenoids *d*-limonene, perillyl alcohol, and the *d*-tocotrienols suppressed the growth of chemically induced and transplanted tumors. Consistent with a theme that threads throughout this book, fruit, vegetables, and cereal grains are recommended as rich dietary sources of the isoprenoids.

J. Pinto and R. S. Rivlin discuss "Garlic and Other Allium Vegetables in Cancer Prevention" in their chapter. As summarized by Pinto and Rivlin, at least 20 constituents of garlic have exhibited chemoprotective and therapeutic activities in vitro and in animal studies. These compounds act by impeding the generation of carcinogens from precursor compounds or by preventing carcinogens from reacting with vulnerable cellular targets, thereby delaying or reversing the expression of malignancy by modifying carcinogenic signal transduction. For example, garlic constituents can favorably accelerate phase I metabolism and can selectively induce phase II conjugation systems. Allylsulfides from garlic can modify the activity of cytochrome P450 and thus prevent the chemical induction of tumors. Allylmethyltrisulfide enhances glutathione S-transferase activity, thereby reducing the response of tissues to specific carcinogens. Other garlic extracts, including "aged garlic extract," increase glutathione peroxidase activity and increase the intracellular ratio of reduced glutathione to oxidized glutathione. As this ratio increases, so does the capacity of glutathione to detoxify carcinogens, act as an intracellular antioxidant, and regulate DNA synthesis and microtubule assembly.

The topic of "Nutrition and Chemoprevention of Head, Neck, and Lung Cancers" is discussed by J. L. Schwartz. According to Schwartz, intake of carotenoids from foods is inversely related to risk of upper aerodigestive cancers in 11 different countries. For example, tomatoes, high in lycopene, a non-provitamin A carotenoid, reduce the risk for head and neck cancers. Dietary supplementation with β-carotene and retinol has reduced precancerous oral leukoplakia and the number of micronucleated cells within the oral cavity. Individuals with the highest plasma iron and zinc concentrations are least likely to develop cancers of the larynx and esophagus. One mechanism by which chemopreventive nutrients may act within the head, neck, and lung is to induce programmed cell death (apoptosis) by increasing the expression of the genes for the

p53 protein and related proteins while decreasing the expression of the proto-oncogene *ras*. β-Carotene appears to act as a pro-oxidant in cancer cells within the head and neck, reducing the intracellular activities of antioxidant enzymes and concentrations of non-protein sulfhydryls. After exposure to β-carotene, unquenched ROS within cancer cells disrupt the mitochondrial membrane and impair organelle integrity, thereby initiating cell necrosis or apoptosis.

In "Breast Cancer," D. W. Nixon and K. Rodgers advise women who are at increased risk of breast cancer to limit fat intake to 15% to 20% of total calories, increase fiber intake to 25 to 30 g/d, eat a diet high in whole vegetables and fruits, limit red meat consumption to two or three 3-oz servings a week, limit alcoholic beverages to three to four drinks weekly, and exercise regularly. Although Nixon and Rodgers stop short of recommending supplementation with essential fatty acids, they note that low levels of α-linolenic acid in breast adipose tissue from breast cancer patients has been correlated with an increased risk of metastatic breast disease.

In "Prostate Cancer," W. Aronson et al. point out that, because prostate cancer is frequently slow growing, the potential impact of nutritional intervention may spare patients from undergoing a variety of toxic treatments and therefore improve the quality of their life. The nine-fold lower prostate cancer mortality in Japanese men compared with American men may be attributed in part to the high soy protein content of the Japanese diet. Genistein, an isoflavone in soy, inhibits growth of prostate cancer cell lines, is a potent inhibitor of epidermal growth factor, and is an angiogenesis inhibitor in vitro. Genistein may act by attenuating tyrosine protein kinases, inhibiting phosphatidylinositol turnover, or otherwise interfering with signal transduction pathways that regulate cell growth. Some studies suggest that inhibition of cell adhesion may be the mechanism through which genistein inhibits tumor growth. Other components of soy also may be chemoprotective against prostate cancer. For example, the Bowman-Birk protease inhibitor suppresses chemically induced carcinogenesis in colon, liver, lung, and oral cancer in vitro assays. Aronson et al. emphasize that selenium supplementation (200 μg/d) has reduced the incidence of prostate cancer. Prostate cancer mortality rates also are inversely proportional to ultraviolet radiation exposure; such exposure generates vitamin D that, when converted to 1,25-$(OH)_2$ cholecalciferol, may inhibit the growth and invasiveness of human prostate cancer cells. Lycopenes (carotenoids responsible for the red color of tomatoes) are associated with a decreased risk of developing prostate cancer and inhibit human prostate cancer cells in tissue culture.

In "Nutrition and Bladder Cancer," S. K. Clinton et al. suggest that manipulation of nutrient intake may improve bacille Calmette-Guerin immune therapy for bladder cancer. In a study that has yet to be replicated, a supplement containing the recommended daily allowances of nutrients was compared with a combination of that supplement plus an additional 40 000 IU of vitamin A, 100 mg of vitamin B6, 2 g of vitamin C, 400 IU of vitamin D, and 90 mg of zinc daily. Recurrence rates for bladder cancer were reduced by half in the group receiving the additional supplemental nutrients. These contributors suggest that the mechanism of action of the supplemental nutrients may be the modulation of the immune response to bacille Calmette-Guerin. Micronutrients may not need to be supplied as dietary supplements; diets rich in vegetables have conveyed some protection against bladder cancer in many studies.

In "Nutrient-Gene Interaction and Prevention of Colorectal, Liver, and Pancreatic Cancer," D. M. Harris et al. report the conclusions of a joint panel of the WCRF and AICR concerning prevention strategies for pancreatic cancer. The panel suggested that diets high in cholesterol, meat, and calories probably increase risk of pancreatic cancer, whereas diets high in vegetables, fruits, and fiber probably decrease risk of pancreatic cancer.

NUTRITION ASSESSMENT AND THERAPY OF THE CANCER PATIENT

J. F. Holland's chapter, "Principles of Cancer Therapy," addresses the issue of nutrition support of cancer therapy. Glutamine and branched-chain amino acids added to parenteral amino acid mixtures sustain nitrogen balance better than formulations without these compounds. There is consensus that supplemental nutrition is advantageous in bringing nutritionally borderline patients to surgery and through healing. Also, head and neck cancers have been treated more successfully when enteral feeding was provided. However, Holland asserts that supplemental nutrition should not be given to patients with advanced cancer because it does not reverse the dying process and life should not be extended with no therapeutic strategy in mind.

J. A. Tayek discusses the micronutrient and macronutrient status of cancer patients in "Nutritional and Biochemical Aspects of the Cancer Patient." Between one-fifth and one-half of all hospitalized patients have reduced serum folate concentrations. In addition, patients with leukoplakia have reduced plasma concentrations of retinol, β-carotene, and vitamin C. Patients who die of cancer and infections have a one-fifth to one-third incidence of severe hepatic vitamin A deficiency. In hospitalized cancer patients, low serum zinc and magnesium concentrations are not uncommon; zinc supplementation may promote normal immune responses and improve wound healing. When patients with cancer were given multivitamin/mineral supplementation (including 80 mg of vitamin C, 15 000 IU of vitamin A, and 14 mg of zinc) daily for 1 y, there was a 50% reduction in the number of days of infection-related complications.

S. Chan and G. L. Blackburn, in "Total Parenteral Nutrition in Cancer Patients," assess the advantages and disadvantages of this technique. Total parenteral nutrition (TPN) is invaluable and lifesaving for patients with chronic severe gastrointestinal insufficiency such as short bowel syndrome or radiation enteritis. However, routine use of TPN in the well-nourished or mildly malnourished cancer patient is not beneficial. TPN is beneficial as an adjuvant to chemotherapy only when there are prolonged periods of gastrointestinal toxicity that severely limit oral intake and intestinal absorption of nutrients. TPN is not associated with improved survival in chemotherapy or in radiation therapy. Glutamine-enriched TPN may decrease the recurrence of systemic infection, improve nitrogen balance, and promote protein synthesis without stimulating tumor growth. However, glutamine is not contained in most TPN formulations because of its instability. Whenever possible, enteral nutrition is preferable to TPN because enteral nutrition costs less, is safer and more convenient, and maintains gastrointestinal function.

CLINICAL TRIALS IN NUTRITIONAL ONCOLOGY

D. W. Nixon and K. Rodgers, in "The Multicenter Trial and the Cooperative Group in Nutritional Oncology Research," summarize the results of three, very large, multisite clinical trials. The highest-quality study involved approximately 29 000 subjects living in a part of China with a high basal rate of esophageal and stomach cancers. A factorial design allowed evaluation of combinations of retinol, zinc, riboflavin, niacin, vitamin C, molybdenum, β-carotene, vitamin E, and selenium. The combination of β-carotene, vitamin E, and selenium was associated with a significantly lower overall cancer mortality, and the combination of retinol and zinc reduced gastric cancer by 62%. Several trials that were "in progress" when this chapter was written are attempting to evaluate calcium supplementation in colorectal adenoma, vitamin E and selenium in prostatic intraepithelial neoplasia, and retinoids in smokers with bronchial dysplasia. It is unfortunate that these studies rely primarily on one or two agents because the combined effect of several agents is more likely to be effective (see Jaakkola et al., Anticancer Res 1992;12:599).

The final chapter, "Future Directions in Cancer and Nutrition Research: Gene–Nutrient Interaction and the Xenobiotic Hypothesis," summarizes several themes that were repeated throughout the book and sets the course for future research in nutritional oncology. According to the authors of this chapter, D. Heber and V. L. W. Go, the epidemiologic literature implicates nutrition as a major factor in the development of common forms of cancer. They describe a "unifying xenobiotic hypothesis," so called because it encompasses the relationships among the genetic polymorphisms of the enzymes that metabolize ligands and effectors, oxidative stress, nutrients, hormone metabolism, and carcinogenesis. According to this hypothesis, the biodiversity of the food supply has been reduced considerably within the past 200 y, and more recently the diet has been altered further by overuse of fats and sugars at the expense of vegetables, fruits, and whole grains. A consequence of this is obesity in genetically susceptible individuals, accompanied by increased secretion of peptide and steroid hormones capable of promoting cancer growth. Oxidative stress also contributes to the carcinogenic process and interacts synergistically with exposure to a wide variety of environmental carcinogens. Opposing the tendency toward xenobiotic-driven carcinogenesis are detoxification enzymes. Phase I enzymes add a functional group, such as the hydroxyl moiety, to a xenobiotic; this reactive group can be acted on ("detoxified") subsequently by phase II enzymes. Together, the phase I and phase II enzymes, alternatively referred to as effector ligand-metabolizing enzymes, usually result in the conversion of relatively hydrophobic xenobiotics to hydrophilic intermediates that can be readily excreted.

There are three ways in which dietary components can interfere with carcinogenesis. First, they can block the metabolic activation of enzymes involved in conjugation or oxidation reactions that generate highly reactive intermediates. Second, they can increase the rates of metabolic detoxification reactions. Third, they can provide alternative targets for electrophilic metabolites. For example, phytonutrients increase the levels of glutathione, glutathione transferase, and glucuronic transferase, thereby facilitating the conversion of reactive electrophiles and oxidants into harmless metabolites that can be excreted. If the "xenobiotic hypothesis" of carcinogenesis is correct, cancer prevention should emphasize the consumption of phytonutrient-rich plant-based diets. Further, known or suspected dietary carcinogens should be avoided, including aflatoxins (from moldy foods), heterocyclic amines (from meats cooked at high temperature), *N*-nitroso compounds (from spoiled foods and the metabolism of nitrates and nitrites), and polycylic aromatic hydrocarbons (from cooked foods and dark beer). Heber and Go conclude by declaring: "The current dogma that cancer is the result of genetic changes and is not influenced by nutrition must be changed."

Sponsored by the Cancer Treatment Research Foundation, this volume represents the most ambitious and extensive attempt to focus attention on a new subdiscipline in medical oncology, i.e., nutritional oncology. It is, however, disappointingly inadequate in its execution. Many promising additions to the armamentarium of the nutritional oncologist are not mentioned. These include calcium glucarate, sterols and sterolins, β-glucans, bromelains, coenzyme Q-10, inositol hexaphosphate, conjugated linoleic acid, PC-SPES, thymosin, resveratrol, *Chlorella* extract, whey protein concentrate, alkylglycerols, shark cartilage, aloe extracts, and the mushrooms cordyceps, maitake D-fraction, lentinan, and schizophyllan.

Moreover, the contributors failed to consider provocative studies such as a report by Jaakkola et al. (Anticancer Res 1992;12: 599) in which pharmacologic doses of micronutrients and essential fatty acids prolonged the survival of patients with small-cell lung cancer given conventional therapy. In that study, it is noteworthy that three-fourths of the patients still alive at the end of the study had started nutritional intervention and conventional therapy together, whereas four-fifths of the deceased had begun nutritional therapy only after a course of conventional therapy had been completed.

In another study (Carter et al., J Am Coll Nutr 1993;12:209), the mean survival of patients with metastatic stage D-2 prostate cancer who adopted a macrobiotic diet was 177 mo versus 91 mo for patients who did not adopt the diet. Similarly, the mean survival of 23 patients with pancreatic cancer who adopted a macrobiotic diet was three times the average obtained from the National Tumor Registry. Despite methodologic shortcomings, such favorable reports concerning poorly survivable cancers deserve greater attention.

Despite its obvious importance to the practice of nutritional oncology, insufficient attention was given the use of nutrients to mitigate the side effects of conventional therapy. For example, the concurrent use of supplemental antioxidants can offset the cardiotoxic effects of doxorubicin (adriamycin).

Despite these shortcomings, this volume provides a synthesis of decades of research into the relations between cancer and nutrition. It provides the foundation for a new paradigm in oncology and should be studied by everyone involved in the prevention or treatment of cancer.

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