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Vitamins and Minerals in the Prevention and Treatment of Cancer

Maryce M. Jacobs

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Preface

The American Institute for Cancer Research (AICR) sponsored the first of a series of Annual Conferences on nutrition and cancer. The theme was "Vitamins and Minerals in the Prevention and Treatment of Cancer." The Conference was held October 11–12, 1990 at the Ritz Carlton Hotel in Pentagon City, Virginia. The proceedings of this conference contains manuscripts from each platform presentation and abstracts from each poster presentation. Based on research in humans, animals and cell culture the data presented in this conference helped to elucidate the preventive roles of vitamins and micronutrients in carcinogenesis.

The focus of the proceedings in this volume is on the protective interactions of vitamins and micronutrients in carcinogenesis. Epidemiological associations of low dietary intake of several vitamins, lipotropes, and selenium with human cancers at different sites have been made. Adequate or greater intakes of Vitamin A, retinoids and carotenoids, have been associated with decreased human cancers of the bladder, breast, cervix, colorectum, esophagus, gastrointestinal tract, larynx, lung, oral cavity, pancreas, prostate, skin, and stomach; vitamin C with human cancers of the breast, cervix, colorectum, esophagus, larynx, lung, oral cavity, prostate, and stomach; vitamin E with human cancers of the bladder, breast, colorectum, lung, and stomach; lipotropes (folic acid, choline, methionine, and vitamin B12) with human cancers of the bone marrow, cervix, esophagus, gastrointestinal tract, liver, respiratory tract, and liver; and selenium with human cancers of the breast, colorectum, leukemia, lung, lymphoma, mouth, pharynx, and skin. Experimental animal studies and *in vitro* models have been used to validate these associations and to establish specific mechanisms of protection against carcinogenesis.

Cancer is a multistage process of initiation, promotion, and progression that can be influenced by permissive and protective factors. An estimated 35% of all cancer deaths have been related to diet and an estimated 80% to 90% of all human cancers appear to be due to environmental causes, including diet. Some exogenous factors (*e.g.*, diet) and endogenous factors (*e.g.*, hormones) may be permissive promoting agents by acting on initiated cells to elicit neoplasms. In contrast, other dietary factors may protect against genetically predisposed and intentionally induced cancers. Important among these are the vitamins and micronutrients that act as anticarcinogens, altering cancer incidence, differentiation, and growth.

Dietary intervention studies in individuals with inherited cancer-prone disorders have suggested involvement of interactions between environmental (*e.g.*, dietary) and genetic factors in the multistage process of carcinogenesis. Studies in inbred strains of animals differing in selected genes that confer cancer susceptibility, and studies of cell culture systems and transformation *in vitro* have helped to elucidate the mechanisms of dietary and genetic interactions that affect the course and frequency of neoplasia. Epidemiological, animal, and cell culture data suggest the possibility that certain vitamins and micronutrients may prove to be useful in cancer prevention and in cancer treatment as adjuncts to conventional therapy. For example, studies are

discussed in which dietary supplementation with calcium carbonate decreased proliferation of colon epithelium in people with a genetic predisposition to develop colon polyps and cancer; in them, the morphology of the colon approached that of persons with a low risk for colon cancer.

Several chapters in this volume discuss epidemiological investigations, primarily dietary intervention studies, that help to elucidate the interactions among diet, genetics, and human cancers. Dietary intervention studies in persons with genetic susceptibilities that predispose them for certain cancers have suggested possible synergism between diet and genetics in modulating human cancers of the colon, gallbladder, and esophagus.

Based on one epidemiological study in the Chinese population, a deficiency of riboflavin had the strongest correlation with the high-risk population for esophageal cancer. In an intervention study the combined supplement of riboflavin, retinol and zinc did not reduce precancerous lesions but did reduce the prevalence of micronucleated cells—possibly an early indicator of the carcinogenic process.

In experiments using hamster embryo and mouse C_3H 10T½ cells under conditions of chemical- or radiation-enhanced cell transformation, vitamins A, C, and E, ß-carotene, and selenium protected against excess oxidative stress, suppressing free radical damage. Protective systems affected by these antioxidants included enzyme induction (e.g., catalase, peroxidases, dismutase), supply of thiols, and interference with free-radical mechanisms in the initiation and promotion of malignant transformation.

The epidemiological links between selenium intake or blood levels and human cancers at various sites are discussed. A review of the inhibition of spontaneous, transplantable and chemically-induced tumors in experimental animal studies that suggests selenium inhibits initiation, promotion and progression by a broad variety of mechanisms is presented. Interactions between vitamins or between a vitamin and selenium suggest that either the reversal or enhancement of the independent chemopreventive actions of either vitamins or selenium may occur with the concurrent supplements.

A review of the literature is presented that reviews the suppression of tumorigenesis by the organosulfur compounds, diallyl sulfide and S-allyl-cystine, from allium vegetables. Several possible mechanisms of action are discussed. In large part these involve the apparent inhibition of P450-related activation enzymes and the apparent enhancement of detoxification enzymes. Via these mechanisms the metabolic disposition of carcinogens might be altered, resulting in inhibition of carcinogenesis.

One mechanism of modulating gene expression is by site-specific binding of Zn-finger domains to double-stranded DNA. This research area is reviewed in detail. Zn-finger domains of certain transcription factors, hormone receptors, oncogenes, and tumor-suppressor genes may be potential targets for metal ions. The effects of substituting Ni^{2+} in the finger-loop domains for Zn^{2+} on the conformation and stability of the DNA are discussed.

The relationships between methyl deficiencies and carcinogenesis are presented in several chapters. Deficiencies in choline, methionine, or folate increase susceptibility to spontaneous and chemically induced carcinogenesis. Folate deficiency-induced biochemical and morphological changes are reported in

human cancer patients as well as in experiments from animal and cell culture systems. Associated with dietary methyl deficiency are observed alterations in xenobiotic metabolism, nucleic acid methylation, purine and pyrimidine synthesis, membrane phospholipids, cell adhesive properties, signal transduction pathways, chromosome anomalies (e.g., gaps, breaks, and condensations), and (increased) cell division.

The extent to which physiological methyl insufficiency contributes to the carcinogenic process and alters the transfer of 1-carbon fragments in the folate pool is elucidated. Some of the studies focus on the methotrexate-induced decrease in the bioavailability of methyl groups, perturbed folate metabolism, and enhanced carcinogenesis. Mechanisms associating alcohol consumption, decreased folic acid, and increased risk for certain cancers in humans are proposed.

The controversial issue is raised whereby low serum folic acid levels are observed in cancer patients, yet treatment of the folic acid deficiency might possibly promote tumor growth in these patients. How folate deficiency-induced changes in chromosome stability, cell size, cell cycle distribution, and membrane adherence properties might influence metastatic potential is explored.

Several chapters in this volume present data to elucidate mechanisms by which a number of vitamins might inhibit the carcinogenic process. In one chapter the effects of vitamin D_3 on extrachromosomal oncogene sequences are discussed and a potentially new therapeutic approach is presented. Some episomes, or submicroscopic circular DNA molecules, carry amplified oncogenes as well as amplified drug resistance genes. Studies are described to optimize episome detection and to eliminate episomes from tumor cells. Episome detection is accomplished with alkaline lysis of tumor cells followed by low or high voltage agarose gel electrophoresis, or field-inversion gel electrophoresis. The technique used depends on the topographical state of the episomal DNA. Elimination of the episomes might eventually provide the potential for decreasing tumor progression in patients (by eliminating the amplified oncogenes) or decreasing resistance of a patient's tumor to chemotherapy (by eliminating the drug resistant genes). In preliminary work presented vitamin D_3 is reported to inhibit incorporation of extrachromasomally located amplified c-myc into a chromosomal site, thereby providing a strategy that might make this episome more susceptible to elimination.

Studies with vitamin A metabolites disclose mechanisms by which metabolites of ß-carotene might up regulate gap junctional communication between cells.

Evidence is presented that pyridoxal phosphate, the biologically active form of vitamin B6, can interfere with the ability of the active form of the glucocorticoid receptor to bind DNA. The mechanism of activation/transformation of the cytoplasmic glucocorticoid receptor is proposed. Evidence is presented that specific lysine residues on zinc fingers of the DNA binding domain of the receptor could be targets of pyridoxylation. Experiments in human melanoma cells and mouse B16 melanoma cells suggest that pyridoxal killing of these cells resulted in inhibition of glucocorticoid receptor translocation to the nucleus.

Studies on the antiproliferation activities of vitamin E show that the succinate ester is the most effective form and that tumor cell growth inhibition is probably unrelated to antioxidant functions. In a mechanism similar to active vitamin A

and vitamin D metabolites, the antiproliferative activity of vitamin E appears to involve binding of the vitamin to cytosolic receptors followed by translocation to the nucleus where DNA binding domains on the receptor mediate gene regulatory events. Retrovirus-induced tumorigenesis involves transformation of normal cells into tumor cells that exhibit uncontrolled proliferation and that express immune dysfunction. Evidence is presented that suggests vitamin E might ameliorate the immune dysfunction by interacting with macrophages and/or T lymphocytes. This can result in either the down-regulation of PGE_2, a potent immune response inhibitor, or the up-regulation, enhanced production, of IL-2.

The final chapter reviews the influence of potassium on the cancer process. Studies in humans, in experimental animals, and in cell culture systems generally associate increased potassium with decreased tumor cell growth and inhibition of carcinogenesis. Dietary inhibition of colon and other cancers with potassium and elucidating possible mechanisms by which this inhibition is induced are exciting new areas of diet and cancer research. The physiological relationships among potassium and other electrolytes are discussed.

In summary, in this monograph data from human, animal, and cell culture studies are presented that attempt to elucidate the potential roles of vitamins and micronutrients in the prevention and treatment of cancer. These data are reported from both platform and poster presentations at AICR's first Annual Conference.

The Editor

Maryce M. Jacobs, Ph.D., is presently Vice President for Research at the American Institute for Cancer Research in Washington, D.C. She received her Ph.D. in Biological Chemistry in 1970 from the University of California at Los Angeles. Before her present position she was employed five years at The MITRE Corporation in McLean,VA as a Biochemical Toxicologist, six years at the Eppley Institute for Cancer Research in Omaha, NE, as Associate Professor and Industrial Contract Coordinator, and six years at M.D. Anderson Hospital and Tumor Institute in Houston, TX. While in Houston, she also served two years as Cochairman of the Biochemistry Area of the University of Texas Graduate School of Biomedical Sciences.

Her primary research interest is inhibition of chemical carcinogenesis with dietary factors, particularly selenium. She published some of the earliest studies on selenium inhibition of colon carcinogens, as well as of liver and lung carcinogens. Dr. Jacobs has also reported her research findings on antimutagenic, anticlastogenic, and antiangiogenic properties of selenium. In addition, she has described acute, subchronic, and chronic toxicity parameters of selenium in rodents.

Dr. Jacobs is a member of the American Association for Cancer Research, the American Academy of Clinical Toxicology, the American Association for the Advancement of Science, the American Chemical Society, American Men and Women in Science, and the Society of Toxicology, among other organizations. In addition, she has served as Vice President of the National Capital Area Chapter of the Society of Toxicology.

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