NUTRITION & CANCER

Edited by Myron Winick

Volume 6 in the Wiley Series on Current Concepts in Nutrition, edited by Myron Winick

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A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto

Library of Congress Cataloging in Publication Data:

Nutrition and cancer.

(Current concepts in nutrition; v. 6)
"A Wiley-Interscience publication."
1. Cancer—Nutritional aspects. I. Winick, Myron.
II. Series. [DNLM: 1. Diet—Adverse effects.
2. Neoplasms—Etiology. 3. Neoplasms—Prevention and control. W1 CU788AS v. 6 / QZ202 N976]
RC262.N87 616.9'94 77-22650

ISBN 0-471-03394-4
Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

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Introduction

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Nutrition is involved in at least three aspects of the cancer problem. As Dr. Paul Marks, Director of Columbia Medical School's Cancer Research Center, points out in his introductory chapter nutrition is important in the etiology of cancer. Cancer itself and certain forms of cancer therapy may profoundly affect the nutritional status of a patient and research is beginning to suggest that certain kinds of nutritional manipulations may play an important part in the treatment of certain types of cancer.

This volume is an attempt to organize our knowledge in these three areas and to examine critically what is known, what remains to be learned, and what are the most promising directions for future research. In addition, wherever feasible, practical recommendations for patient management are made.

The book is divided into three parts: Nutrition and the Cause of Cancer; Nutrient Deficiencies; Prevention and Therapy. After the overview by Dr. Marks, the first part continues with a discussion of nutrition and experimental carcinogenesis by David B. Clayson. Total dietary restriction or specifically limiting carbohydrate intake has been shown to reduce the incidence of certain tumors in mice and rats. By contrast, limiting the protein content of the diet generally had very little effect on overall incidence of most tumors. Both the quantity and the quality of dietary fat can influence tumor incidence. Deficiency in lipotropes results in an increased incidence of both spontaneous and induced liver tumors in rats and chickens. Although results are not conclusive it has been suggested that vitamin A and vitamin C may protect against certain types of tumors. Finally, the timing of a dietary stress has been shown to be extremely important. An increasing body of evidence suggests that nutritional manipulations early in life—even in the preweaning period—may alter the incidence of spontaneously occurring tumors and affect ultimate longevity in rats.

Dr. K. K. Carroll discusses the induction of mammary tumors in animals by fat in the diet. He points out that unsaturated fat is a more potent stimulus to tumor genesis than saturated fat. In addition, he postulates that fat acts as a promoting agent, enhancing the potency of certain carcinogens, rather than as a carcinogen itself. These data in rats are reinforced by studies in humans, which demonstrate a strong positive correlation between dietary fat intake and age-adjusted mortality from breast cancer in different countries of the world. Similar but somewhat weaker correlations have been observed between fat intake and certain other types of cancer, including prostatic cancer and ovarian cancer.

The association of high dietary fat and low fiber intake with carcinoma of the colon is discussed in the chapters by Drs. Wynder and Kritchevsky. They discuss the fact that tumors of the large bowel can be related to several dietary components. Thus, there is a positive correlation between bowel cancer mortality and dietary fat consumption. It has also been stated that there is an inverse correlation between incidence of bowel cancer and dietary fiber. Populations ingesting a Western-style high fat diet ingest little fiber and the question of which component is truly responsible for the observed correlations has not been answered.

Proponents of the high fiber hypothesis suggest that the more rapid transit time which results from such diets reduces the duration of contact between exogenous carginogens and the tissue. Support has been lent to the high fat hypothesis by findings of differences in the spectra of neutral and acidic fecal steroids between animals with induced colon cancer and controls. The transformations in fecal steroids are, in large part, a product of the action of intestinal microorganisms. The question then becomes, which influences the spectrum of intestinal flora, fat or fiber? This critical point is far from resolution and data that tend to support both arguments are presented.

Part 2 is concerned with nutrient deficiencies caused by various types of cancer. The problem of cancer cachexia is discussed by Athanasios Theologides. He points out that cachexia occurs in one-third to two-thirds of cancer patients. It is characterized by anorexia, increased basal metabolic rate and energy expenditure despite the reduced caloric intake, marked asthenia, loss of body fat, protein, and other components, anemia, and water and electrolyte disturbances. Although the anorexia leads to reduced food intake, the weight loss can be stopped only temporarily by increasing that intake even with measures such as hyperalimentation. Thus it is the cancer growth itself that contributes to the cachectic syndrome, either by successfully competing for available nutrients or by deranging the host metabolism in some way.

A common finding in patients with cancer bis hypoalbuminemia. Dr. Thomas Waldman has demonstrated that this condition is often caused by a decrease in the synthesis of albumin. In addition, however, certain types of cancer result in an excessive loss of proteins into the gastrointestinal tract. This loss may occur in patients with carcinoma of the stomach or with carinoid tumors of the gastrointestinal tract. Finally, patients with lymphosarcoma or Hodgkin's disease may lose lymphocyte-rich lymph into the gut.

Another recent observation is that patients with various types of cancer may exhibit a variety of vitamin deficiencies. Dr. John Dickerson has observed low plasma levels of vitamin A in patients with advanced disease of the alimentary tract and with squamous and oat cell carcinoma of the lung. Certain patients with lung and breast cancer, especially those being treated with 5-fluorouracil, showed a low thiamin status and high values of thiamin pyrophosphate (TPP). The data suggest an abnormality in thiamin metabolism rather than a dietary deficiency.

In patients with breast cancer and skeletal metastasis low levels of leukocyte ascorbic acid and high levels of urinary hydroxyproline (OHP) were observed. Supplementation with ascorbic acid reduced the OHP excretion within four hours.

These data suggest that in patients with cancer at certain sites the requirements for specific vitamins may be changed and therefore that attention to these changed requirements might be useful in the management of the patient.

Part 3 deals with prevention and therapy of cancer using nutritional means. One of the newest and potentially most exciting approaches to cancer prevention has been the use of vitamin A analogs in experimental animals to prevent the induction of epithelial tumors of the bronchi, trachea, stomach, uterus, and skin. Dr. Michael Sporn points out that these studies, while currently in the experimental stage, are potentially important in a variety of human populations—most notably where precancerous lesions can be identified and where a high risk for cancer is present.

Dr. William DeWys discusses the problem of anorexia and more specifically abnormalities of taste in the cancer patient. In a series of studies, he has demonstrated that patients with limited disease generally had normal taste sensation. By contrast, patients with widespread disease generally showed marked abnormalities in taste. In addition, when treatment has been successful in reducing the size of the tumor, taste perception has returned to normal. These observations may be of value in the management of anorectic cancer patients. Patients with an elevated threshold for sweet taste may be able to increase their food intake

if they increase the seasoning on their food. In patients with a low bitter threshold, there often is a range of preference related to protein source, with beef and pork being less desirable, poultry and fish intermediate, and cheese and eggs often remaining pleasurable.

Dr. Sarah Donaldson describes the consequences of radiation therapy and the use of certain cytotoxic drugs that lead to anorexia, weight loss, and malnutrition. This malnutrition is not only damaging to the patient but may prevent an aggressive therapeutic approach to the patient's primary condition. Dr. Maurice Shils describes the use of special diets for supporting patients, for rehabilitating patients who have been treated successfully, and for preparing patients for various forms of therapy. One method that is being used more frequently is total parenteral nutrition (TPN) using a central venous catheter.

Dr. Shils also discusses how TPN therapy is administered, which patients can most benefit from the use of TPN, and some of the specific indications and contraindications for this form of treatment.

The area of nutrition and cancer is just beginning to receive the attention it should. I would expect much to be learned in the near future. This volume has very few definitive answers. That is not its purpose. Instead, it summarizes what little is known and charts some new directions for the future.

PART 1

Nutrition and the Cause of Cancer

1

Nutrition and the Cancer Problem

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The role of diet is gaining prominence in the investigation of why some people get cancer and others do not. For many years evidence has accumulated that a number of diseases in addition to cancer, such as heart disease, diabetes, arthritis, and dental caries, are related to diet (1). Although there are many clues that associate these diseases with dietary excesses or deficiencies, there is no definitive scientific evidence that any of these chronic diseases is caused by dietary factors alone. Recently an increasing number of studies have related dietary and nutrient excesses, deficiencies, or imbalances to the development of cancers in the esophagus, stomach, colon, pancreas, liver, and breast (2).

Diet and nutrition are of interest not only as determinants of carcinogenesis, that is, of susceptibility or resistance to cancer development. Investigation is also needed to define more precisely the role of diet and nutrition as an adjunct to other therapeutic modalities, such as surgery, radiotherapy, chemotherapy, and immunotherapy, and to discover the role of specific nutritional manipulation in the prevention and therapy of certain cancers.

NUTRITION AND THE CAUSATION OF CANCERS

The suspicion that nutrition may be involved in the cause of cancer has derived primarily from epidemiological studies and a number of animal laboratory studies. It is estimated that over one-half of all female cancer deaths and 30% of all male cancer deaths may be related to nutritional factors (3). This estimate does not include accidental or intentional food

additives that may be carcinogenic. This accumulating evidence suggests that many of the common types of cancer may be caused in part by nutritional factors. Because we can act to alter nutrition, these cancers are potentially avoidable.

The group most conspicuously at risk for cancer is, of course, the elderly. Various models have been proposed to account for clustering of cancer in old age. One reasonable theory of carcinogenesis states that in each cell there are several genes that function independently to prevent cancerous transformation, and that cancer will not occur until each of these genes has been inactivated by mutation. Since a mutation can be introduced in the genome at any time during the life of a cell or of its ancestors, the chances of inactivating all the cancer-preventing genes increase directly with age. This theory predicts that the log of cancer

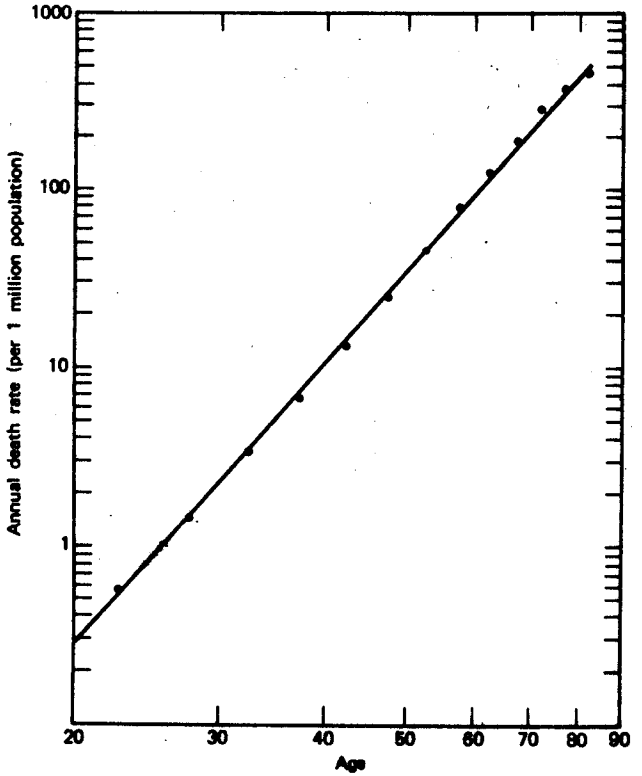

Figure 1. Relationship between age (years) and mortality from all forms of cancer (annual death rate expressed per 1 million population). Reprinted from Carins (4) with permission.

incidence should be linearly related to the log of our age. In fact this relation of incidence to age is observed for a number of cancers (4) (Fig. 1).

This relationship between age and incidence of cancer has several important implications for our consideration of nutrition as a causal factor in cancer. First, it suggests that a given cancer may have several factors contributing to its cause. Second, a cancer may be the end result of several events occurring over a period of a person's life; in other words, we may have to look to the nutritional environment of the early life of an individual to understand the role of dietary factors in the causation of cancer. Various studies of migrant populations suggest that the incidence of certain common cancers may be partly determined by our nutritional habits in youth. Third, the other side of the argument is that potentially it could take many years before an increased incidence of a particular cancer calls attention to the danger of dietary factors.

Many population studies now provide rather convincing evidence that environment, and possibly nutrition, play decisive roles in the causation of cancer. For example, cancer of the stomach is much more common in Japan than in the United States, but cancer of the large intestine, breast, and prostate are much less common (5). Further, there is a change in incidence of various cancers with migration from Japan to the United States (5–7) (Fig. 2). This suggests that cancers are caused by environmental factors that differ in the two countries. The death rates among Japanese immigrants and immigrants' sons tend consistently toward California norms, but the change requires more than one generation. Therefore some of the causative agents must be factors such as diet, which tend to persist as part of a cultural heritage, rather than factors such as air pollution, which tend to be the same for everyone in a given area.

Similar observations have been made among Jewish populations who migrated to Israel from Europe or the United States (8). The immigrants from Europe or the United States have an incidence of cancer that is typical of their country of origin, but their children, born in Israel, have a much lower incidence of almost all kinds of cancers. In this respect they become more like the indigenous Israeli population and like Jewish immigrants from Asia and Africa.

The incidence of cancer of the large intestine among women in 23 countries is closely related to per capita meat consumption in these countries (9–11) (Fig. 3). An alternative nutritional explanation of these data, put forth by various investigators, is that in areas of high incidence of colon cancers, the diet consumed tends to be high in refined foods and low in unabsorbed cellulose or fiber. Differences in bacterial flora as-

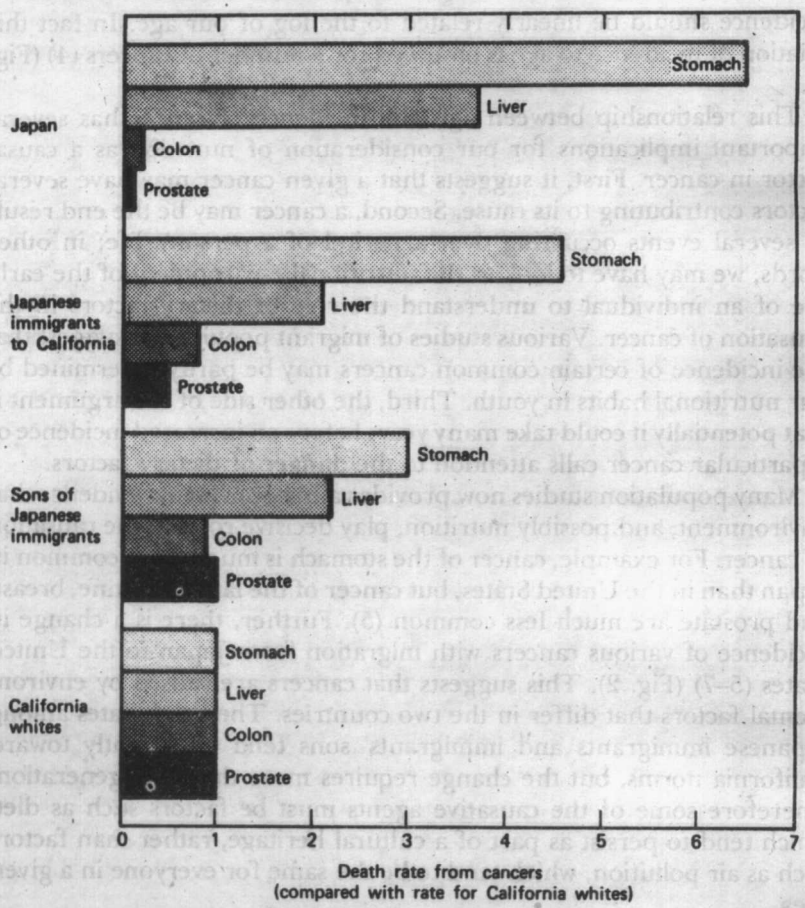

Figure 2. Death rate from various types of cancers among Japanese and Japanese immigrants to California, compared with California whites. Reprinted from Cairns (4) with permission.

sociated with the two types of diet have been documented. There are other studies in progress employing in vitro assays for mutagenesis, attempting to identify specific substances in feces and in urine which are mutagenic and possibly carcinogenic.

In this book several investigators in this field will discuss in detail other studies which persuade us that there is a relationship between neoplasia and dietary practices.

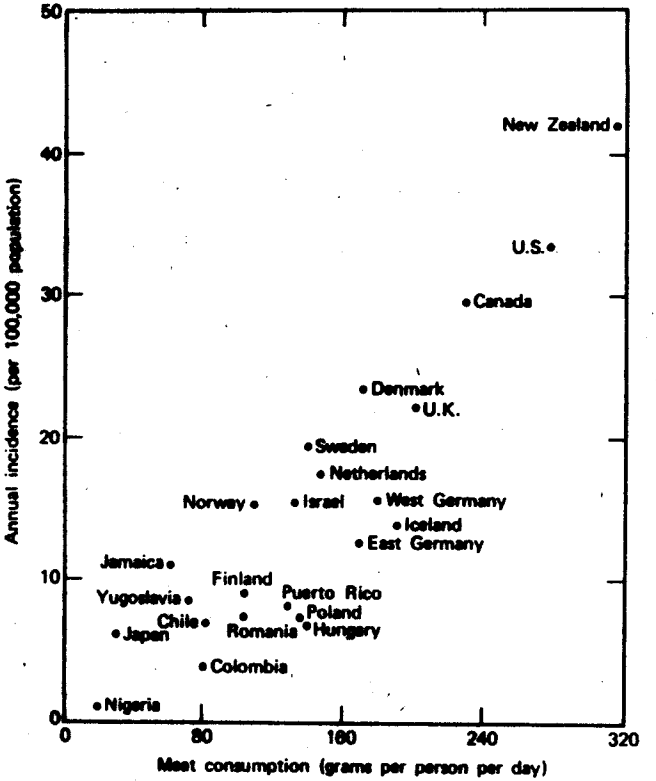

Figure 3. Relationship between incidence of cancer of the large intestine among women in 23 countries and meat consumption expressed as grams per person per day. Reprinted from Cairns (4) with permission.

NUTRITIONAL STATUS AND TREATMENT OF THE PATIENT WITH CANCER

The effects of cancer on the nutritional status of the patient are another important subject to be discussed. The striking and still poorly understood effect of cancer is the marked anorexia associated with a number of neoplasms. Several studies document effects on nitrogen balance, carbohydrate tolerance, and insulin sensitivity which indicate that in patients with cancer there may be abnormalities in metabolism which cannot be explained on the basis of the tumor mass or of the dietary

intake (12,13). Further, therapeutic removal of the tumor or inducing remission with chemotherapy can be associated with return to normal metabolism (for review and references, see (14).

Malnutrition is also associated with direct or indirect effects of a cancer, such as impaired food intake secondary to obstruction of the gastrointestinal tract, or malabsorption associated with obstruction or destruction of the pancreas, or infiltration of the small bowel by neoplasms such as lymphomas or carcinoma, or with lymphatic obstruction. Electrolyte and fluid balance disturbances are associated with tumors in the gastrointestinal tract or with hormone-secreting tumors.

Another major area of interest to us is the use of nutrition as an adjuvant to other forms of treatment of cancer. Treatments for cancer, in themselves, can cause nutritional problems. For example, radiation treatment to the oropharyngeal area can destroy the sense of taste and impair food intake. Radiation to the abdomen or pelvis can damage the bowel and cause acute or chronic diarrhea or malabsorption. Surgical resection of portions of the gastrointestinal tract can cause deficiencies in absorption which can be general or specific with respect to various nutrients. Chemotherapy can be associated with malfunction of the gastrointestinal tract and with fluid and electrolyte disturbances. Malnutrition is harmful to cancer patients because the cachectic patient has a narrower safe therapeutic margin for most chemotherapy and radiotherapy. The cancericidal doses of these agents may be much closer to the lethal dose for normal tissues in the malnourished patient than in the well-nourished patient. For example, Drs. Edward Copeland and Stanley J. Dudrick (15) and others have provided evidence that the application of intravenous hyperalimentation to the treatment of cancer patients is safe, tumor growth is not stimulated, and chemotherapy and radiotherapy are better tolerated. This is an area where more detailed evaluation of the nutritional values and protocols for nutrient administration should be of great benefit in therapy and rehabilitation of cancer patients.

NUTRITIONAL MANIPULATION AS THERAPY FOR CANCER

An exciting area of investigation has been opened with the observation that nutritional manipulation per se may be an approach to treatment of certain cancers. For example, an approach to chemoprevention of forms of epithelial cancer during the period of preneoplasia has been reported with the finding that vitamin A and its synthetic analogs, the retinoids, are potent agents for control of cell differentiation in several epithelial