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DIET, NUTRITION, *and* CANCER: A CRITICAL EVALUATION

Volume I
Macronutrients and Cancer

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PREFACE

Although the concept that diet and nutrition might influence cancer is not new, until recently this relationship has received surprisingly little detailed attention. During the 1930s, a number of laboratories, including that of Tannenbaum, were interested in the possible influence exerted by nutritional factors on susceptibility to cancer, but the question soon lost the interest of both the scientific and lay community.

During the past 2 decades, renewed interest in nutritional carcinogenesis has developed. Epidemiologic studies have investigated the incidence pattern between and among population groups, differences in the rates of the disease between the sexes, changes in disease rates over time, demographic and socioeconomic distribution of diseases, effects of migration, and the dietary habits of different population groups, and have led to the conclusion that nutritional factors play a significant role in the etiology of certain types of cancer. However, it must be recognized that the correlation between nutritional factors and certain forms of cancer does not prove causation. Many factors may be necessary for cancer causation, but the modification of only one of the contributing factors, such as diet, may be sufficient to retard the chain of causative events.

Studies in experimental animal models also point to dietary factors as important modulators of certain types of cancer. These studies have generally shown that increased macronutrient intake, especially fat, and certain micronutrient deficiencies lead to increased in tumor incidence in several organ sites, whereas diet restriction and dietary excess of certain micronutrients lead to a lower tumor incidence.

These 2 volumes bring together a wide variety of studies concerning the role nutrition plays in the etiology of various types of cancer, namely, cancer of the esophagus, upper alimentary tract, pancreas, liver, colon, breast, and prostate. The purpose of each chapter is to provide a critical interpretive review of the area, to identify gaps and inconsistencies in present knowledge, and to suggest new areas for future reasearch. Scientifically valid data supporting an association between nutrition and cancer comes from three sources: epidemiology, clinical studies, and experimental studies in laboratory animal models. Throughout the volumes, attention is given to the potential and limitations of each discipline; and the need for closer cooperation between epidemiologists, clinicians, and experimentalists is emphasized. Specific areas of concern include extrapolation of data from animal models to humans, methods of diet evaluation, the formation and occurrence of mutagens in cooked food, and the role of naturally-occurring inhibitors of carcinogenesis.

We have tried to present in 19 chapters (9 chapters in Volume I, 10 chapters in Volume II) a comprehensive view of nutrition's role in cancer. The broad coverage of diet, nutrition, and cancer provided by these chapters is intended to serve both as an introduction to readers unfamiliar with the field, as well as a source of new information for researchers. It is indeed hoped that these 2 volumes will promote a better understanding of the role of nutritional factors in the induction and inhibition of cancer, and that this understanding will lead to a reduction in cancer rates in the current generation and the prevention of cancer in future generations.

Obviously, the compilation of these volumes could not have come about without the cooperation of the various authors. We most sincerely thank each of the authors for their contribution and continued assistance in submitting and editing the manuscript.

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Chapter 1

DIET AND GASTRIC CANCER

Pelayo Correa

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I. INTRODUCTION

There is a general consensus implicating diet as the main factor in human gastric cancer etiology. This concept has developed over the years and is based mostly on circumstantial evidence. There is, however, no scientific proof for it and no general agreement on the specific components of the diet supposedly responsible for gastric cancer.

Extensive reviews of the pertinent literature are available.[1-4] Rather than repeating or updating such reviews, this chapter attempts to screen the relevant literature and select out those items which appear to have resisted the test of time and survived as viable candidates in the chain of events which may eventually lead to gastric cancer. Finally, their specific role in a proposed etiologic model will be considered.

II. WHY DIET?

Ingested materials are first detained and acted upon by digestive enzymes in the stomach. It is, therefore, not surprising that diet is considered a prime candidate for gastric carcinogenesis. Several mechanisms have been mentioned to explain the role of diet in gastric carcinogenesis: (1) presence of carcinogens in food; (2) introduction of carcinogens during food preparation; (3) absence of protective factors; (4) synthesis of carcinogens by interaction of food items; (5) irritants in food resulting in cancer promotion.[2,5]

Some support for the speculation has been provided by the geographic distribution of the disease. Figure 1 is based on available data on gastric cancer incidence. The intercounty contrast is very prominent but geography by itself cannot explain why some subpopulations display risks several times greater than others inhabiting the same land. Chinese have rates several times greater than Malays in Singapore. Similar contrasts are observed between Maoris and whites in New Zealand; Japanese and whites in Hawaii; Indians and whites in New Mexico; blacks and whites in California; and Jews and Arabs in Israel.

In the contrasting situations mentioned above, racial and cultural differences exist between subpopulations inhabiting the same land. The role of race has been studied in migrant populations. Immigrants from high-risk areas to generally low-risk environment of the U.S. display slightly lower risks of gastric cancer in the first generation, but the second generation displays a dramatic drop in their risk.[6] In some racial groups, like the Japanese, the risk reduction cannot be explained by interracial marriages. Similar experiences have been reported for immigrants to Austrialia, Canada, and Brazil.

Descriptive epidemiology studies, therefore, clearly indicate that race and geography are not the main determinants of gastric cancer frequency. Culture is strongly implicated. One of the main cultural differences between subpopulations at high and low risk is the diet. No contrast in gastric cancer risk is on record among populations with similar diet.

III. THE HIGH-RISK DIET

Great diversity exists between the diets of populations at high gastric cancer risk. This probably explains why there was so much discrepancy in the results of the earlier dietary studies in several countries: rice was suspected in Japan, fried foods in Wales, potatoes in Slovenia, grain products in Finland, spices in Java, and smoked fish in Iceland.[2] More recent studies have emphasized salty foods.[7-9] The most remarkable trend, however, has been the realization that some old and some new studies are more prominently showing negative associations than positive associations.[7-8, 10-13] The analytical epidemiologic data, therefore, strongly point to the presence of protective factors in the diet.

Looking for common factors in the diet of high-risk populations and taking note of descriptive, correlational, and analytical studies, the "gastric cancer diet" has been characterized as follows:[14]

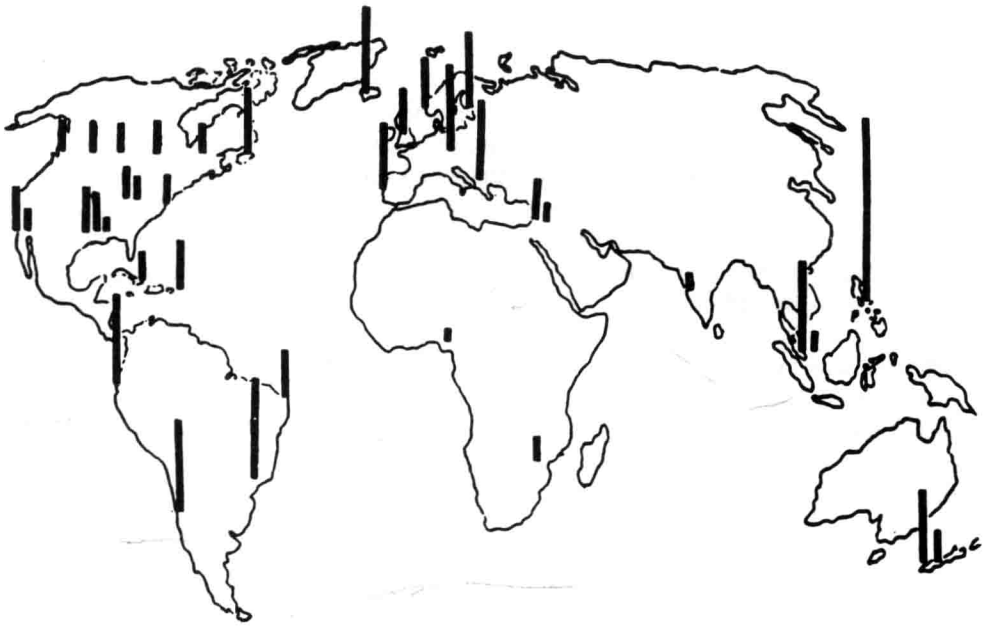

FIGURE 1. Diagram representing age-adjusted incidence rates of stomach cancer in different populations. (From *Cancer Incidence in Five Continents*, Vol. 4, International Agency for Research on Cancer, Lyon, 1976.)

1. Low in animal fat and animal proteins
2. High in complex carbohydrates
3. A substantial proportion of the protein is obtained from vegetable sources, mostly grains
4. Low in salads and fresh, green, leafy vegetables
5. Low in fresh fruits, especially citrus
6. High in salt

An additional, somewhat controversial, item which should be considered is the presence of nitrates in the diet. The evidence implicating the above items is reviewed in the following paragraphs.

A. Animal Fats and Proteins

Most populations at high gastric cancer risk have diets low in animal fats and proteins. The protective effect of milk has been found prominently in Japan.[7] Fat is needed for the proper utilization of lipid-soluble vitamins such as A and E, which may play a protective role. There are, however, many populations whose intake of animal fat and proteins is very low and still display very low risk of gastric cancer. Such is the case of most African aboriginals and most inhabitants of the tropical and subtropical lowlands, including most of Brazil and the Caribbean basin.

The evidence available cannot totally deny a possible role of low-fat diet in some situations but does indicate that other factors are needed to induce gastric cancer in humans.

B. Abundance of Complex Carbohydrates

The situation concerning this item is similar to the low-fat diet: it applies to most high-risk populations but it is equally prevalent in large populations displaying low risk. There appears to be a distinction, however, in the type of vegetables frequently consumed. In most

situations high-risk populations base their diet on grains and roots which are subjected to involved cooking techniques. These populations are not inclined to eat fresh, uncooked vegetables. Not enough data exist to determine cultural differences between high- and low-risk populations with a predominantly vegetable diet. One recent study in Colombian rural villages found that a vegetable-based diet was predominant in all villages, but only the low-risk villagers were addict to fresh items (fruits and salads).[14] The abundance of complex carbohydrates, therefore, is not a strong determinant factor in gastric carcinogenesis. The protective role of this type of diet in colon carcinogenesis is discussed elsewhere, but it should be mentioned here that large populations with high intake of complex carbohydrates have very low rates of both gastric and colon cancer: Brazil, Africa, and the Caribbean.

C. Salads and Fruits

The negative association between these items and gastric cancer is one of the most consistent findings: old and new studies in populations of different race and culture coincide on this point. Stocks reported it in England in 1933;[15] Dunham in 1946, Haenszel in 1958, Higginson in 1959, and Graham in 1972 in the U.S.;[11,16-18] Meinsma in Holland 1964;[13] Hirayama in Japan in 1963;[7,19] Paymaster in India in 1968;[20] Bjelke in Norway in 1970;[21] and Haenszel in Hawaii in 1972.[8] The specific kind of fresh fruit or vegetable associated with low risk varies according to cultural dietary patterns, but it appears obvious that some common factor or factors exist in many fresh fruits and vegetables that may play a protective role in gastric carcinogenesis. The search for the common factor has led investigators to estimate the intake of micronutrients based on their concentration on specific food items, the usual size of a typical serving of each food item, and the frequency with which the item is reportedly eaten by cases and controls. The result of these calculations is usually expressed as an "index".[22] Such indexes may be adequate for hypothesis building but not for hypothesis testing because they are fraught with potential errors in the basic assumptions. Marked differences in the concentration of a micronutrient in a specific food may result from soil composition and fertilization patterns: the concentration of vitamin C in grains is considerably greater when in soils fertilized with ammonium molybdate than in those deficient in that element.[23] Most dietary surveys have to limit the number of dietary items for logistic reasons; it is entirely possible that some items rich in a specific micronutrient are left out of the questionnaire. The dietary questionnaires have to cover periods prior to clinical disease, making quantitation only reliable for rather gross categories. Indexes of micronutrients based on case-control studies have been calculated for ascorbic acid[21] and vitamin A.[24] In Japan, a large cohort study has revealed a negative association between green-yellow vegetable intake and gastric cancer risk; such vegetables account for approximately 50% of vitamin A intake and 25% of vitamin C intake.[25] Similar calculations tend to implicate vitamin E in gastric cancer precursors.[14] All indexes, however, show an association with gastric cancer risk which is somewhat weaker than the direct association with the intake of fresh fruits and vegetables, from which they derive. This may indicate that more than one micronutrient is involved in the process. Indexes of micronutrients may, on the other hand, be indicators of other, nonnutrient, protective factors in food. The list of such factors is large and so far insufficiently explored.[26,27]

D. Salt

It has long been suggested that high salt concentration in the diet increases gastric cancer risk. Sato reached that conclusion in 1959 after correlating gastric cancer death rates in Japanese prefectures with local customs of salting foods, especially vegetables.[28] Similar results have been reported in more recent surveys.[29] The hypothesis was tested and found correct in case-control studies in Japan,[7,30] in France,[31] and in Hawaii.[8] Extensive international correlation studies between death rates from cerebrovascular accidents and gastric

cancer has led Joosens to conclude that both are related to excessive salt intake.[32] Similar conclusions have been reached in Colombia for gastric cancer precursors.[14] One recent Japanese report failed to detect an association between salt intake and prefecture-specific gastric cancer death rates, probably reflecting recent dietary changes in Japan which may affect future (but not present) death rates. Epidemiologically, the case for a role of excessive salt intake in gastric carcinogenesis appears very strong. This conclusion is reinforced by experimental studies showing that salted food causes severe gastritis (a strongly suspected cancer precursor) in man[33] and in experimental animals.[34] The hypothesis has also been tested in experimental carcinogenesis studies. It has been found that salt increases the yield and size of tumors of the glandular stomach of Wistar rats when administered before or during MNNG administration. Salt alone is not a complete carcinogen or an initiator. When given after the carcinogen MNNG it is ineffective and therefore can not be called a promoter.[35,36] It does appear that salt is an etiologic factor of gastric cancer that does not conform to the stereotypes of the initiator-promoter classification. Its role may be in inducing chronic gastritis (which increases cell turnover rates) and facilitating the contact of the carcinogens with their target cells, probably by disruption of the mucus barrier.

E. Nitrates and Nitrites

The extensive literature linking nitrate and nitrite to gastric cancer has been recently reviewed.[37] A positive intercountry correlation was found between gastric cancer death rates and estimates of nitrate consumption in the diet. Correlations between the use of nitrate-rich well water and gastric cancer risk has been found in Colombia.[38] A correlation between nitrates in water supplies and gastric cancer rates was reported from England[39] but later interpreted as reflecting socioeconomic gradients and occupational patterns in the country.[40] A model for gastric carcinogenesis has been proposed, which postulates intragastric bacterial reduction of nitrate to nitrite and subsequent synthesis of carcinogenic nitroso compounds.[5] Nitrate itself is not considered a precursor of carcinogens because it will not react with amines or other nitrogen-containing molecules to form *N*-nitroso compounds. Nitrite, on the other hand, is a strong carcinogen precursor because it avidly nitrosates amines, amides, ureas, and similar compounds.

What matters, therefore, is the exposure to nitrites in the gastric cavity. Most of the nitrite exposure in humans results from reduction of dietary nitrate, but nitrate is present in all human diets in quantities more than adequate to provide high nitrite levels if subjected to bacterial reduction. It is pointless, therefore, to attempt to reduce nitrate levels in the diet.

Dietary nitrate as well as nitrate excreted by the salivary glands is in part reduced to nitrite in the buccal cavity. This has led to the study of salivary nitrate and nitrite as possible indicators of gastric cancer risk with negative results.[41] Salivary nitrate and nitrite levels in some populations may reflect the intake of fresh vegetables (rich in nitrate) and therefore result in a negative association of gastric cancer risk. Salivary nitrite is not an indicator of nitrite levels in the gastric cavity. The latter is most probably determined predominantly by the presence of reductase-containing bacteria in the gastric cavity, associated with chronic atrophic gastritis and bacterial proliferation due to partial loss of gastric acidity.[5] It has recently been shown that a given dose of nitrate administered to patients with chronic atrophic gastritis results in concentrations of nitrite in the gastric juice that are approximately ten times highter than those of normal subjects receiving the same dose of nitrate.[42] Gastric microenvironment (not buccal microenvironment) is therefore the pertinent parameter.

The role of nitrates and nitrites in gastric carcinogenesis cannot be considered proven. In part, it hinges on the etiologic hypothesis postulating intragastric nitrosation of nitrogen-containing compounds. The hypothesis is not proven but has received considerable support. It should be, however, understood that dietary nitrate is not the key etiologic factor. Reduction of dietary nitrate to nitrite in the gastric cavity is the key issue.

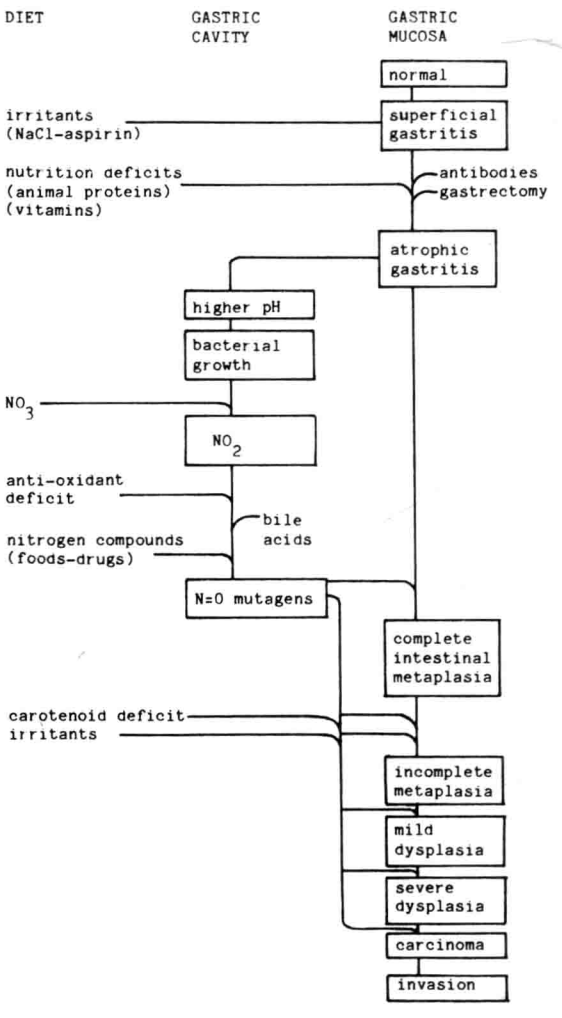

FIGURE 2. Diagramatic representation of the etiologic hypothesis of gastric cancer.

The intragastric nitrosation hypothesis is supported abundantly by laboratory evidence. A direct mutagen has been found in the gastric juice of patients with high nitrite levels.[43] High levels of nitrites and nitrosamines have been reported in the gastric juice of patients with atrophic gastritis.[44] Gastric tumors have been induced in rodents by simultaneous administration of nitrite and amines.[45] Fish commonly used in Japanese diet can be nitrosated to produce carcinogenic substances which induce experimental tumors in rodents.[46]

IV. ETIOLOGIC HYPOTHESIS

Information on gastric carcinogenesis, from several scientific disciplines, has been utilized to postulate an etiologic model which has been recently updated.[5,47] The hypothesis centers around the gastric microenvironment playing a key role in the pathogenesis of gastric cancer. The microenvironment is determined by three basic elements: what is ingested (diet), what is secreted or produced locally in the gastric cavity, and what changes take place in the target organ: the gastric mucosa. The hypothesis is outlined in Figure 2.

In this hypothesis diet plays an overriding role since it can have a decisive influence on the gastric secretions and the gastric mucosa itself. The first element of the diet to be considered is the presence of irritants which can damage the gastric mucosa directly. The most important of those irritants is probably salt, as discussed above. Other irritants of importance are alcohol and aspirin. Irritants are probably responsible for the chronic gastritis, a precursor of gastric cancer.

The next step in the process is that of atrophy, one of the least understood steps in the chain of precursor lesions. Whether diet plays a role in gastric atrophy is unknown. In some high-risk populations protein supply is indadequate, which could interfere with proper regeneration of epithelial cells lost because of the chronic gastritis process. Gastrectomy and pernicious anemia are causes of atrophy not related to diet.

Once atrophic gastritis sets in, drastic changes take place in the microenvironment: the pH is progressively elevated and bacterial proliferation occurs in the lumen and in the secretions immediately covering the epithelial cells. The bacterial growth in the lumen is well documented and includes several species with nitrate reductases.[48] Nitrate present in the food is then reduced by bacteria and nitrite appears in the gastric secretions. To what extent bacteria are also present in the mucosal tissue itself is not well documented. Nitrite is a very active molecule which can react with a large number of nitrogen-containing species to produce *N*-nitroso compounds, many of which are mutagenic and carcinogenic. This is a central theme in the hypothesis and it has received support from several recent findings, summarized below.

In spite of the fact that nitrite disappears from the stomach soon after its formation, relatively high levels of nitrite are found in the gastric juice of persons at high gastric cancer risk,[49] incuding patients with pernicious anemia[50] and post-Bilroth II gastrectomy.[51] A direct correlation has been found between increasing pH and nitrite level of fasting gastric juice. High levels of total nitrosamines and of volatile nitrosamines have been reported in the gastric juice of high-risk populations.[52] Some questions remain unanswered, however, concerning the meaning and relevance of this work since volatile nitrosamines are not expected to be carcinogenic unless metabolized by the liver. Mutagens have been detected in the gastric juice of patients with atrophic gastritis.[43] Several food items frequently eaten by high-risk populations yield potent mutagens after nitrosation. Japanese fish after nitrosation yield a mutagen which has induced gastric carcinomas in experimental animals when administered via gastric tube.[46] In Colombia, fava beans are consumed abundantly by some high-risk populations. When nitrosated, fava beans yield a potent mutagen.[53]

Other candidates for nitrosation are bile acids. *N*-nitroso bile acids are mutagens and can be formed under simulated gastric conditions.[54] These compounds could explain the so-called stump carcinoma of post-Bilroth II gastrectomy patients.[55] Experimentally, gastric cancer can be induced by Bilroth II gastrectomy or gastroentrostomy without the administration of a carcinogen.[56]

Many drugs can be nitrosated and some may yield mutagens after nitrosation. Frequently used blockers of gastric secretion such as cimetidine and ranitidine yield mutagens after nitrosation but there is no proof that the products are carcinogenic.[57] Some pre-anesthesia sedatives have been reported to undergo nitrosation and yield mutagens within the gastric mucosa itself, in areas of intestinal metaplasia.[58] This may indicate that nitrate is absorbed into the mucosa from the gastric lumen or that bacterial colonization of the mucosa itself has taken place. That nitrosation does take place in vivo has been demonstrated by the so-called Bartsch test based on the detection of nitroso-proline in the urine after ingestion of nitrite and proline.[59]

The diet of populations at high risk is generally deficient in fresh fruits and vegetables. The meaning of this well-established cross-cultural finding is not well understood, especially since those food items contain hundreds of pro- and anticarcinogenic compounds whose

effects in human populations is almost completely unknown.[26] The interpretations of the above findings have concentrated on two hypotheses: deficiency of antioxidants and deficiency of carotenoids. Antioxidant deficiency is suspected to play a role because of their well-known capacity to block nitrosation. The best-known compounds of this kind are ascorbic acid which acts in hydrosoluble mixtures and alpha-tocopherol which acts in liposoluble mixtures.[60] Many other compounds efficiently block nitrosation, such as caffeic acid found in coffee and propylgallic used for food preservation.[61] Ascorbic acid may also have an anticancer role even after the invasive state has been reached: it promotes fibroplasia and apparently creates obstacles for the spread of tumors.[62]

Carotenoid deficiency has been implicated in many epidemiologic studies, not only in relation to gastric cancer, but to several other epithelial tumors.[63] Their mechanism of action is not understood. It is suspected to be related to their conversion to retinol, a promoter of differentiation, and as such may interfere with the gradual loss of differentiation postulated in the model, especially the stages after complete metaplasia. Extensive evidence supports the preventive role of retinoids,[64] but little experimental work on carotenoids is available.

The model suggests that although the basic mechanisms may be similar, they may be operating with different ingredients in populations at high risk to gastric cancer. Although diet may be etiologically implicated, it may reach the same point with different components: for instance, it may be that a carcinogen from nitrosated fish plays a role in Japan while a carcinogen from nitrosated fava beans plays a role in Colombia. Prevention, therefore, may be tailored to the needs of each population.

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