Reflections on Diet, Nutrition, and Cancer

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The recent report by the National Research Council-National Academy of Sciences Committee on Diet, Nutrition, and Cancer covered a broad range of nutritional factors that appear to relate to human carcinogenesis (30). The Committee carefully evaluated the various parameters whereby diet does or could influence cancer development, made recommendations to the scientific community and the public based upon its findings, and concluded that, of all the nutrients that affect the development of cancer in humans, only for dietary fat was there sufficiently convincing evidence to term its effect on breast and colon cancer development as "causative." The report reflects the majority opinion of experts in nutritional, experimental, and human carcinogenesis. It is a significant document and a valuable resource to everyone concerned with nutrition and cancer. As such, the Committee's recommendations are likely to serve as a catalyst for future progress in an important area of environmental carcinogenesis and thus in cancer causation and prevention.

The report has caused many to reflect on the broad scientific and public health opportunities that have emerged from the study of nutrition and cancer. It is not that the concept of nutrition affecting human cancer is new; in fact, as early as 1937, Frederick Hoffman (19), an actuarial statistician and lawyer, wrote a provocative 750-page book on cancer and diet. In the middle 1940's, Tannenbaum (40) conducted a series of elegant studies demonstrating the effects of diet in terms of total calories and fat on breast tumor growth in animals. In the 1950's and 1960's, increasing epidemiological evidence came forth, linking, first, specific life-style habits such as alcohol consumption to human cancer and, subsequently, a broad range of dietary intakes, including both micro- and macronutrients.

Particularly within the last decade, epidemiological evidence supported by extensive experimental studies has steadily advanced the concept that nutrition does, in fact, affect human carcinogenesis at specific target organs by various mechanisms, some of which are as yet unclear (1, 31, 50).

However, in contrast to such fields as genetics, immunology, and virology, the number of investigators who have been engaged in the study of nutritional carcinogenesis has been relatively small. Unfortunately, there has been a tendency to regard nutrition as being out of the mainstream of academic science in cancer studies even when its biological effects have been soundly documented through: (a) observations in humans in studies of epidemiology and geographic pathology in populations with varied specific dietary customs; (b) deliberately planned human studies of metabolic epidemiology; (c) carefully designed studies attempting to assess the effect of certain dietary components, such as fat, fiber, and β-carotene, in appropriate animal models; and (d) certain mechanistic considerations derived from such studies in man and in animals in the light of contemporary concepts of the mechanisms of carcinogenesis and cancer causation. In turn, there are problems with: (a) nutrition methodology to delineate typical dietary patterns in populations; (b) classification of the mode of action of key dietary components involved in nutritional carcinogenesis; (c) the biological plausibility of the relationship between nutritional elements and certain cancers; and (d) societal implications. These elements will be discussed.

METHODOLOGICAL CONSIDERATIONS

Nutritional intake within a given population is difficult to study because of inherent difficulties with nutritional surveys and interview techniques (13, 15). The problem is magnified by the fact that the intake of various dietary components is interrelated. Thus, population groups who get a preponderance of calories from fat are likely to have a low intake of starches and vice versa. Conclusions generally have to be reached indirectly by comparing nutritional intakes in different geographical population groups, such as Japanese versus Western customary diets, or in migrant populations, or in special groups within a population, such as Mormons, Seventh-Day Adventists, or members of religious orders (6, 17, 18, 38).

A further problem is that nutrition exerts its major impact on carcinogenesis at important target organs in humans, such as the colon, breast, endometrium, or prostate, as a modifier rather than an initiator of tumorigenesis (7, 8, 27, 28). The question of the significance of the dietary and fecal mutagens in the context of these types of cancer awaits clarification and documentation (30, 31, 46). It is true that generally we are trained to think in terms of carcinogens, whether chemical, viral, or physical, as a key to carcinogenesis (17, 46). Thus, it is more difficult to formulate concepts related to agents that act as enhancers of growth and development of initiated cells. Even those scientists who deal with the mechanistic aspects of tumor promotion are concerned largely with such potent but unphysiological factors as croton oil (phorbol esters) rather than with physiologically relevant agents that may be involved in the promotion process such as alcohol, bile acids, or hormones and their effect on endocrine balances (14, 35, 36).

Yet, as concluded by the Committee, nutrition and diet play major roles in human carcinogenesis. While an understanding of the exact mechanism by which nutrition and diet can affect human carcinogenesis may not be essential to establishing causation, it would be of great value in the attempt to define a cause-and-effect relationship and is of obvious importance in designing lasting preventive strategies.
MECHANISTIC CONSIDERATIONS

Each kind of cancer has specific causes and modifying factors. The deliberate study of the causes for each type of cancer, such as cancer of the stomach, colon, or pancreas, has delineated specific risk factors or modifying components. The exacting analysis of the mode of action and the role played by each such factor has provided the current knowledge relative to organotropic carcinogenesis.

The diet can include genotoxic carcinogens such as, for instance, aflatoxin or polycyclic aromatic hydrocarbons or may provide precursors for the formation of nitrosamines or nitrosamides (10, 21, 28, 37, 46). It is likely, however, for most of the kinds of cancer seen in man that the most important effects of nutrition are associated with nutritional deficiencies, and even more so with excesses as seen in the association of a Western diet with cancers of the breast, endometrium, colon, and prostate.

As an example of deficiencies, the high incidence of esophageal cancer in certain parts of Iran and China has been suggested to be related to dietary deficiencies, specifically diets low in fresh fruits and vegetables, and hence with low estimated intakes of vitamin A, vitamin C, and riboflavin (9, 23). It has also been suggested that dietary nutritional deficiencies such as zinc, magnesium, nicotinic acid, and riboflavin in populations at high risk for esophageal cancer may also occur in alcohol abusers and might increase the susceptibility of the esophageal epithelium to neoplastic transformation (43). Vitamin A and its analogues and derivatives may preserve the integrity of epithelial cells by maintaining them in a differentiated state, thereby protecting them to some extent (33, 39). Vitamin C and vitamin E block the formation of nitrosamines and nitrosamides, an action that may be important in the etiology of gastric cancer where a seasonal low consumption of vitamin C appears to be a factor (21, 29, 32, 37, 46). Dietary deficiencies of certain compounds found in vegetables, for example, having the capacity to inhibit neoplastic effects of chemical carcinogens may also play a role (22, 44).

In the instance of dietary excesses, the role of fat has been reviewed recently (12, 30). The stage of carcinogenesis at which dietary fat operates appears to be primarily the promotion phase (7, 8). There are numerous mechanisms whereby the level of dietary fat intake can and does control tumor growth. With regard to colon cancer, dietary fat increases bile acid secretion and hence the amount of colon bile acid metabolites that are possible tumor-promoting agents. Dietary cereal bran and related fibers reduce the concentration of bile acids and also other as yet unknown compounds associated with neoplasia in the large bowel and thus appear to lower colon cancer risk in humans and in animal models (5, 35). Dietary fat also influences the synthesis and release of prolactin (and also other hormones), a potential mammary gland tumor promoter, in both rats and humans (35, 36). Furthermore, dietary fat may affect the hormonal milieu within the breast with respect to steroid hormone levels and balances and can bear on the composition and physical characteristics of membranes, thus influencing the interactions between peptide hormones and their membrane-bound receptors (25, 34, 48). The production of growth-regulating substances such as prostaglandins, which are derivatives of dietary essential fatty acids, may also be influenced by fat intake (20). There is also evidence that dietary fat affects breast cancer survival rates, particularly in postmenopausal women, perhaps by regulating the biosynthesis of estrogens from extraovarian sources via the aromatization of androgens (48). The above illustrate some of the mechanisms whereby total fat levels, both saturated and unsaturated fats, can influence tumor growth and where the action of total fat in carcinogenesis differs from the role of fat in atherosclerosis in which only the saturated fatty acid component appears to have the most deleterious effect.

Except for the cases of esophageal and stomach cancer (10, 21, 24, 37), the main effect of nutrition is seen largely as depending on developmental, enhancing phenomena of an epigenetic nature rather than genotoxic processes (46). We may conclude that experiments with nutritional factors have to involve larger concentrations and the agents need to be present over a longer period of time, in contrast to tests dealing with genotoxic agents (4, 11, 47). Extrapolation of such experiments to the human setting suggests that lower concentrations of modifying, epigenetic agents at the target organ would meaningfully reduce disease risk, especially since their action is reversible up to a certain point (48). Since most currently known nutritional and dietary factors such as the levels of fat or fiber, for example, act at the promotional phase of carcinogenesis, manipulation of promotion with dietary means would seem to be a sound, feasible, and effective method of preventing fatalities due to certain cancers.

BIOLGICAL PLAUSIBILITY

As stated in the Surgeon General’s first report on Smoking and Health (42) published in 1964, “the causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.” The criteria upon which such a judgment is based include the consistency, strength, specificity, and coherence of the association, as well as the empirical relationship of the events involved. Using these criteria, it seems eminently plausible that dietary deficiencies or excesses could play an important role in carcinogenesis by leading to the formation of tumor promoters or by affecting metabolic parameters which, in turn, can affect activation or deactivation of carcinogens. The epidemiological evidence is particularly plausible because of extensive support from animal experiments. Thus, the relative lack of attention given to the field of nutritional carcinogenesis by oncologists is especially perplexing given the fact that the relationship has had considerable biological plausibility, rationale, and internal consistency from the very beginning.

SOCIETAL IMPLICATIONS

The Committee of the National Academy of Sciences recommended a dietary pattern quite similar to that of the previously published national dietary guidelines of the United States Department of Agriculture (41) as well as those suggested by the American Health Foundation (3, 26, 49). Whereas these earlier recommendations were directed towards reducing the risk for cardiovascular disease, the present suggestions are directed towards the prevention of certain types of cancers, providing an even more powerful incentive for the public to heed the recommendations since benefits would accrue in terms of lower risk both for important types of cancer and for coronary heart disease.

The responsible segments of the American agricultural and food industries can make it easier for the public to adhere to the
guidelines by providing leaner meats; lower fat-containing dairy products and baked goods; by producing an attractive variety of fresh and frozen vegetable products, fruits, and juices; by lowering the salt content of products; and by providing whole-grain breads, cereals, and other food products enriched with fibers that increase stool bulk (26). Moreover, through their managerial and promotional skill, industry can help to motivate the acceptance of those more healthful foods for our largely sedentary public.

Since dietary habits are established early in life and since biological parameters may also be set relatively early in our development, it is of particular importance that we apply the dietary guidelines to children, preferably starting with infants right after breast feeding or at the beginning of bottle feeding. Here, the active help of the obstetrician, the pediatrician, the parents, and the school system is essential (2, 51).

As these dietary modifications become accepted, nutritional epidemiologists will continue to examine changing rates of cancers within populations and among migrating populations (17, 38), while concurrently studying the changes that nutrition is making on human metabolic parameters that will take place before changes in disease patterns are evident (35). In so doing, many of the gaps in our knowledge, as discussed in the Committee’s report, could be bridged. Nutrition and cancer research is an exciting area for the emerging scientist. Here the scientist can combine fundamental research with relevant, practical applications.

Among the many beneficial effects the report will have on the food industry, the public, epidemiologists, nutritionists, and the experimental oncologists, one can only hope that the overwhelming lesson to be learned is that many of our diseases today, including certain types of cancer, relate to what the late René Dubos has termed an unfortunate state of today’s world in that malnutrition can combine fundamental research with relevant, practical applications.

REFERENCES

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Letter to the Editor

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