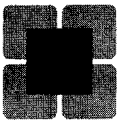

Dietary anticarcinogens and cancer prevention

AS IT has become increasingly clear that management of existing malignant neoplasms is unsatisfactory, the search for strategies to prevent the development of such tumors has intensified. Over the past several years, extensive analytical and epidemiologic studies of geographical and temporal variations in cancer incidence in a variety of cultures and occupations have suggested that environmental factors may contribute significantly to the development of cancer.[1] Thus, the identification and elimination of these factors is an important and practical way to reduce cancer risk.

Furthermore, it is now widely accepted that chemical carcinogenesis in many tissues or organs is a stepwise process involving altered cell populations at initiation, promotion, and progression stages. The initiation stage is an essentially irreversible step in which genetic changes occur, possibly in a gene or genes controlling differentiation, but the promotion stage leads to formation of visible lesions through epigenetic mechanisms.[2] This has led to the concept that inhibitors of these mechanisms could have the capacity to diminish tumor formation evoked by the carcinogenic agents.

■ *See Dwivedi et al (pp 561–564)*

Chemoprevention is a means of cancer control in which disease occurrence is prevented by administration of one or a combination of several chemical agents. One of the exciting findings in this area is the identification of a large number of compounds having great structural diversity, which have shown promise in several animal bioassay systems. These compounds either inhibit the steps essential for cancer initiation or inhibit biological processes essential for tumor production; many inhibit both initiation and promotion. One of the most impressive findings in this field is the presence of these compounds in the human diet. Therefore, it is possible that simple changes in eating habits could significantly lower cancer risk.

Most of the chemical carcinogens, like the polyaromatic hydrocarbons (the ubiquitous environmental pollutants generated by the incomplete combustion of organic substances), are relatively inert but are metabolized to highly reactive electrophilic metabolites, which are oncogenic. The step of conversion from precarcinogens to ultimate carcinogenic metabolite(s) often involves the metabolism of the parent compound by the cytochrome P-450-dependent enzymes. It is the binding of these ultimate carcinogenic metabolites to DNA that is believed to initiate cancer. Thus the various compounds, such as the plant phenols that inhibit cytochrome P-450-dependent enzyme activities, may act as chemopreventive agents.

Similarly, by inhibiting nitrosation reactions, ascorbic acid (vitamin C) has been shown effective in inhibiting the carcinogenic effects of amines and amides (which are nitrosated to exert their carcinogenic effects). Other components in the diet, such as α-tocopherol, caffeic acid, and gallic acid, also inhibit formation of nitrous compounds. The other compounds, known as blocking agents, react with the ultimate carcinogenic metabolites and remove them before they bind to crucial macromolecules to manifest their carcinogenic response.

Reactive metabolites of the inert precarcinogens are usually detoxified by the cellular enzymes. Another category of compounds possesses the ability to induce the activities of such enzymes, which in turn lead to rapid removal of the carcinogenic metabolite, leading to cancer prevention. Among these enzymes, glutathione-S-transferase, UDP-glucuronyl transferase, epoxide hydrolase, and NAD(P)H:quinone reductase are particularly important. NAD(P)H:quinone reductase catalyzes the reduction of toxic quinones to corresponding phenols, and thus helps in maintaining the redox state

of the cell system. Epoxide hydrolase catalyzes the decomposition of highly reactive electrophilic epoxides to corresponding dihydroxy derivatives. Glutathione S-transferase and UDP-glucuronyl transferase provide major conjugating systems capable of forming conjugates with the carcinogens that are water soluble and are rapidly excreted. This eventually reduces the effective concentration of the carcinogen in the body.[3] Thus the induction of the activities of these enzymes may often help in the formation of water-soluble polar conjugates of lipophilic carcinogens, thereby facilitating their faster excretion.

Similarly, a high-fiber diet is known to increase the stool quantity, thus diluting the effective carcinogenic concentrations. Another possibility, that carcinogens may bind to fiber and be excreted through stool, cannot be ruled out. The likelihood that certain substances naturally occurring in a variety of vegetables may inhibit the development of neoplasms in humans has been explored. This is consistent with epidemiological observations indicating an inverse correlation between the consumption of cabbage and the occurrence of colon cancer and also a low cancer incidence among Seventh Day Adventists, who are strict vegetarians. Similarly, there is evidence to suggest that green and yellow vegetables may provide protection against epithelial cancers.[4]

Dwivedi et al,[5] in this issue of the *Cleveland Clinic Journal of Medicine*, describe the efficacy of calcium glucarate dietary supplements against skin-tumor-initiating activity of 7,12-dimethylbenz(a)anthracene, which is a potent chemical carcinogen widely employed to study the mechanisms of skin carcinogenesis. Their data suggest that feeding of calcium glucarate in diet retards the process of tumor promotion. As described by the authors, the inhibition of skin carcinogenesis by calcium glucarate is probably due to an increased clearance of initiating and promoting agents through cellular enzyme reactions, thus leading to a suppressed carcinogenic response. Various other compounds like antioxidants, inhibitors of enzymes involved in the cascade of tumor promotion, and inhibitors of arachidonic acid metabolism may also act as antitumorigenic agents.

Antioxidants are also potent inhibitors of tumor promotion. Evidence suggests that tumor promotion involves oxygen-radical production. Agents that trap these oxidants act as antipromoting agents. In diet, various constituents (hydrophilic agents such as ascorbic acid and plant phenols and lipophilic agents such as α-tocopherol and β-carotene) have been known to act as antioxidants and anticarcinogens and many of these compounds are present in virtually all nonvegetarian as well as vegetarian diets.

The existence of a large number of compounds with great structural diversity indicates that inhibition of carcinogenesis is not a highly selective phenomenon. Different strategies, therefore, can be followed by supplementing the human diet with various inhibitors. Although many of these compounds are present in the human diet, no quantitative association between their uptake and incidence of cancer has been established.

A central problem in this research is the extrapolation of animal data to humans, and within this heterogeneous population, extrapolation among individuals. Multiple experimental test systems in animals and corroborative epidemiological data pertaining to humans (particularly at the molecular level) are needed to find a better solution to the problem. Additional research is also needed to establish quantitative relationships. Once such information is available, the recommendations for minor changes in diet may prove effective and practical for human cancer prevention.

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