# Dietary Control of Cancer (44171)

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*Abstract.* **Many laboratory studies and human epidemiological data suggest that most cancer deaths are attributable to lifestyle, including nutritional factors and tobacco and alcohol consumption. Tobacco consumption is causally related to cancer of the lung, mouth, larynx, esophagus, bladder, kidney, and pancreas. Nutrients and non-nutrient dietary components probably account for cancer of the colon, breast, prostate, and stomach. This report is based on literature and our own data pertaining to the role of dietary fat, calories, and fiber in the development of colon and breast cancer. We also discuss the evidence from epidemiological, mechanistic, and preclinical efficacy studies indicating a protective effect of micronutrients, non-nutrients, and certain antioxidants in food against oral and lung cancers. Given the continuing cancer burden and the relatively slow impact of proven cancer treatment strategies in reducing cancer mortality, it is essential to evaluate promising nutrients and non-nutrients in foods as chemopreventive agents in persons at increased risk for cancer. Development of reliable intermediate biomarkers is valuable for clinical chemoprevention intervention trials. The purpose of this report is to provide the reader with plausible approaches to cancer control.** [P.S.E.B.M. 1997, Vol 216]

In the United States, nearly two-thirds of cancer deaths can be linked to tobacco use and diet (1). The detrimental effects of high amounts of certain fats and of specific nutritional deficiencies on cancer development are well known. The benefits of lowering the intake of dietary fat and eating more fiber, as well as the roles of other macro- and micronutrients in the prevention of several cancers, have also been well studied and continue to be fine-tuned. The interrelation of dietary fat and fiber, the effects of vitamins, trace minerals, and nutrient antioxidants on the multistep carcinogenesis process are important areas of research that continue to be pursued actively in several laboratories along with efforts to identify and then eliminate, reduce, or modify agents in prepared foods that may contribute to cancer etiology. Assays in well-defined animal models have documented the crucial role of dietary modifications in altering the course of carcinogenesis. Knowledge gained from epidemiological studies, though sometimes ambiguous, suggests that diets rich in fruits and vegetables can prevent cancer (2). To elucidate fully how dietary constituents can be effectively harnessed for cancer control, a stepwise approach must be taken. Toward this end, diet modification and chemoprevention constitute valuable and plausible approaches. Thus, we are searching for optimal diets and for naturally occurring agents in routinely consumed foods that may inhibit cancer development. Structural modification of established, naturally occurring chemopreventive agents has led to synthetic agents with even greater efficacy and lower toxicity. Moreover, the combination of several chemopreventive agents (i.e., application of a well-designed "cocktail") may provide an even better strategy for cancer control. Most importantly, on the basis of our current knowledge, we believe that a diet that is low in certain types of fat and has sufficient fiber content, supplemented with the most appropriate chemopreventive agent(s), will have an optimal impact on cancer control.

The broadly aimed chemoprevention research program in our laboratories uses *in vitro* and *in vivo* preclinical model assays. Predictable incidences of tumors are induced by agents such as those present in tobacco products or foods, or—in some instances—with synthetic carcinogens, to provide a yardstick for measuring chemopreventive efficacy of naturally occurring or newly developed synthetic compounds. Several selected agents developed in our laboratories have been characterized as modifiers of cancer through screening in model assays for cancer of the lung, breast, and colon. These compounds are now being utilized in clinical trials sponsored by the Chemoprevention Branch of the U.S. National Cancer Institute. The American Health

Our studies at the American Health Foundation are supported by the following grants: CA 17613, CA 12376, CA 46589, CA 46535, CA 37663, CN 55098-46, CN 157, DE 09514, and CA 68317.

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0037-9727/97/2162-0211$10.50/0

Foundation's long-standing research on nutrition-related cancer began with investigations of the role of dietary fat, progressed to studies on the role of fiber, led to the bioanalytical and oncological examination of likely etiologic agents and active chemopreventive principles in fruits, vegetables, and tea, and culminates in the development of dietary guidelines and chemopreventive supplements for cancer prevention and control.

## Dietary Fat, Calories, Fiber, and Colon Cancer

Colorectal cancer is one of the leading causes of cancer deaths in men and women in Western countries, including the United States and Canada, exhibiting more than a 10-fold excess by comparison with mortality rates in populations in certain parts of Asia, Africa, and South America. Since the pioneering studies of Wynder in 1969 and Burkitt in 1971, which provided evidence for a negative association between colon cancer risk and consumption of fiber-rich foods and a positive association between high dietary fat intake and colon cancer development (3, 4), the database that supports the possibility of cancer control through dietary modification is much broader now, involving human metabolic, epidemiologic, and laboratory animal model studies (5–8).

**Dietary Fat and Calories.** A large body of evidence relating high dietary fat and high caloric intake to the risk of colon cancer is based on epidemiological and laboratory animal studies (5). Diets with especially high fat content, but low in certain fibers, are generally associated with an increased risk of developing colon cancer (6, 7). In addition, dietary fat may be a greater risk factor in the absence of protective factors, such as substantial intake of fibrous foods (8). The importance of the types of dietary fat has become more and more clear. Several epidemiological studies suggest that mortality from colon cancer is somewhat lower in areas where olive oil is the predominant type of fat consumed, and also in areas where the consumption of fish or other marine animals is highly common (9–11). The high levels of monounsaturated fatty acid, namely oleic acid in olive oil and highly polyunsaturated n-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in marine oils, appear to have rather unique effects. Studies in laboratory animals may provide evidence that the colon tumor-promoting effect of dietary fat depends not only on the total fat but specifically on the types of dietary fat given to them (5). There is considerable interest in the relationship between total caloric intake and colon cancer risk. Several case-control studies have shown that high caloric intake is a risk factor (6). In this context it is of interest whether the effect of dietary fat on colon cancer risk is due to the specific action of fat or to an associated caloric effect of fat. Evidence in laboratory animals indicates that the effect of high caloric intake on colon cancer risk is independent of total dietary fat (9).

Several investigations have examined the effect on chemically induced colon carcinogenesis of diets, of which 40% or 10% of calories came from beef fat, lard, corn oil, olive oil, safflower oil, or fish oil. These studies demonstrated that high intake of beef fat, lard, corn oil, and safflower oil had greater tumor-enhancing effect than diets low in these fats (5). In contrast, diets with high olive oil or fish oil content had no colon tumor-promoting effect. The varied effects of different types of fat on colon carcinogenesis suggest that the fatty acid composition of dietary fat may be one of the determining factors in colon tumor promotion. In addition, model studies in laboratory animals have provided evidence that caloric restriction inhibits chemically induced colon tumor incidence by about 20%–40% over the incidence rates observed in animals fed *ad libitum* (11).

With regard to possible mode(s) of action of colon tumor promotion by dietary fats, metabolic epidemiology studies have revealed that populations at high risk for colon cancer excrete high levels of secondary bile acids, deoxycholic acid, and lithocholic acid (8). From model studies with laboratory animals we learned that such secondary bile acids induce cell proliferation and act as promoters of cancer of the colon (5). It is important to note that a high concentration of luminal secondary bile salts and fatty acids also increases the activity of colonic epithelial ornithine decarboxylase, a rate-limiting enzyme in polyamine biosynthesis, and cell proliferation (11, 12). It is also conceivable that increases in colon tumor promotion due to high fat intake may be based on the alteration of membrane phospholipid turnover and prostaglandin synthesis (12).

**Dietary Fiber.** Intracountry comparisons and most case-control studies of colon cancer mortality in relation to dietary fiber intake strongly support the hypothesis that especially fiber from cereal sources protects against colon cancer. An examination of a total of 13 case-control studies on diet and colon cancer—involving the records for 5,287 colon cancer cases and 10,470 control subjects—provided substantive evidence that the intake of fiber-rich foods is inversely related to colon cancer risk (13). This analysis implies that the risk of colon cancer in the U.S. population could be reduced by about 31% if an increase in fiber intake to 25 g/day could be attained.

Mechanisms by which certain dietary fibers may act to reduce the risk of colon cancer are thought to involve the dilution, absorption, and removal of carcinogens, cocarcinogens, and/or tumor promoters that are present in the gut (11). Also, dietary fiber affects the gut microflora by modifying both its metabolic capabilities and its composition, which in turn alters the breakdown products of nonstarch polysaccharides, fat, and protein in the gut (11). These breakdown products can act either as tumor promoters and/or inhibitors in the colon. Model assays in laboratory animals have helped to establish which types and amounts of dietary fiber can be effective inhibitors of colon tumor development. The results thus far generated suggest that (i) the inhibitory effect depends on the type of fiber, and (ii) wheat bran appears to inhibit colon tumor development more consistently than the other types of fiber (11).

**Diet Intervention in Humans.** In view of the significance of secondary bile acids in the pathogenesis of colon cancer, the effects of modulating types and amounts of fiber in relation to type and amount of dietary fat on these fecal constituents was studied in healthy subjects. In one such study, the diet was supplemented with wheat bran plus rye fiber, and the effects on fecal bile acids were examined. Healthy men and women who were before this study consuming high-fat/moderately low fiber diets, were then given daily about 10 g of supplemental fiber (whole wheat and rye) in the form of bread with the three main meals to ascertain a fiber intake of 27 g/day. The fecal bile acids, especially the secondary bile acid concentrations, were significantly reduced during the period of fiber supplementation compared with the baseline period.

How dietary fat and fiber affect fecal bile acids has also been studied in healthy subjects consuming high-fat/low-fiber Western diets with experimental protocols that were similar to those described for fiber studies, except that subjects usually eating a high-fat (40% calories from fat) and low-fiber (14 g/day) diet were given a low-fat (20% calories from fat) and high-fiber (25 g/day) diet for 6 weeks. Stool samples collected during the high-fat/low-fiber and low-fat/high-fiber periods were then analyzed for bile acids. A significant decrease in the concentration and excretion of total secondary bile acids was observed during the period of low fat/high fiber administration (8, 11).

## Dietary Fat and Breast Cancer

Laboratory animal studies and international correlations of fat intake by humans and their breast cancer mortality provide strong evidence for a tumor promoting effect of dietary fat in postmenopausal breast cancer (14, 15). In contrast, the results of large-scale cohort studies have consistently failed to demonstrate a low risk of breast cancer in women who eat a low-fat diet (16). This conflicting evidence has created a controversy in public policy with regard to research priorities and dietary recommendations for breast cancer prevention. Two major reasons for this impasse are (i) the weight of over half a century of animal model research into the influence of the type and amount of fat and underlying biological mechanisms has largely been ignored, and (ii) the lack of association found in cohort studies likely occurs from the difficulty in measuring fat intake accurately, particularly within populations with similar eating patterns (14, 17).

**Animal Model Studies.** More than 50 years ago, Tannenbaum and others demonstrated that a high-fat diet stimulated mammary tumor development in mice (18). These studies further showed the tumor response to fat was nonlinear in nature (19). Three decades later, Carroll and Khor (20), and, still later, also Abraham and Hillyard (21), using chemically induced tumors in rats, showed that the enhancing effect of fat was exerted during the promotion phase of carcinogenesis. Supporting the idea that fat exerted its effects after the initial carcinogenic event were studies with transplantable mammary tumors showing that tumor growth was stimulated in host animals fed a high-fat diet.

These animal model studies have been further extended to include mammary tumor metastases as well. Katz and Boylan using a rat model, and Rose *et al.,* using human breast cancer cells inoculated in nude mice, demonstrated that high fat intake increased the size and number of pulmonary metastases in mice (22, 23).

Understanding the quantitative aspects of the fat effect in animal models is important because the variation in fat intake within a given population such as in the United States is not nearly as great as that seen between different countries. For example, at this time fat intake constitutes about 25% of calories in Japan, while it is 35% of calories in the United States (24). However, 25 years ago, fat intake in Japan was under 20% and that in the United States close to 40% of calories (25). Hence, women in their postmenopausal years in Japan and the United States consumed markedly different amounts of fat in their earlier years. Recent within-country cohort studies reported fat intake over a range between 44% and 28% of calories; a small percentage of U.S. women fall below 30% of calories from fat (16). Studies by Cohen *et al.* (26) and Tang *et al.* (27) in the rat and by Zevenberger *et al.* (28) and Tannenbaum and Silverstone (18) in the mouse model support the hypothesis that the effect of fat quantity is nonlinear and involves a threshold of fat above which promotion occurs and below which it does not occur. Precisely where the threshold level for fat intake lies remains to be determined, but it appears to be below 25% of calories. If this is so, then the null effect reported for cohort studies in Western countries may be due to the small number of women in these countries consuming <25% calories as fat (16).

Also of interest is that the type of fat is an important determinant of the tumor promoting effect of dietary fat. For example, fats with high levels of monounsaturated fatty acids (olive oil), long-chain n-3 polyunsaturated fatty acids (fish oil), and short- and medium-chain saturated fatty acids (coconut oil) lack tumor-promoting effects in animal models compared with conventional fats containing high levels of n-6 essential fatty acids (corn oil, sunflower oil) and long-chain saturated fatty acids (beef, butter) (28–31). The reasons for these differences remain to be determined, but most evidence points to the involvement of the eicosanoid pathway leading from the major n-6 polyunsaturated linoleic acid to prostaglandin and other eicosanoids (32). It is of interest with respect to human populations that the low rates of breast cancer in Mediterranean countries and Japan are associated with high intake of olive oil and fish oil, respectively (33, 34).

**Mechanisms.** Various biologically plausible mechanisms have been proposed to explain the tumor-promoting effects of dietary fat. They support a causal relationship rather than a mere association between fat intake and breast cancer risk (15, 35). Among these are direct effects such as (i) modulation of the enzymes (desaturases) involved in the

conversion of linoleic acid to arachidonate and to various eicosanoids, short-lived hormone-like substances involved in cell proliferation, motility, and inflammatory responses; (ii) reaction of polyunsaturated fatty acids with molecular oxygen to produce free radicals which damage DNA and promote tumor growth (36); and (iii) induction of altered gene expression by specific fatty acids (37). Indirect effects include (i) effects on the endocrine system including estrogen metabolism; (ii) alterations in the immune system; and (iii) changes in membrane structure and function.

Although none of these mechanisms have been proven definitively, when viewed together with epidemiological and animal model evidence they strongly suggest that dietary fat is a major determinant of breast cancer risk.

**Future Directions.** Clearly, there are unresolved issues regarding the epidemiological evidence. Although a meta-analysis of case-control studies found an effect of dietary fat in breast cancer (38), recent null findings of Hunter *et al.* (16) in a combined analysis of several prospective cohort studies have again cast doubt on the validity of this association. Much of the problem lies in the inadequate methods for assessing food intake (39, 40). Food disappearance data, used in global comparisons, are likely overstating fat intake; nonetheless, the strong and consistent international correlations have proven valid. There is considerable inconsistency in case-control and cohort studies, which is not surprising given (i) the relatively narrow range of fat intake within countries such as the United States, and the insensitivity of dietary instruments to assess fat intake; (ii) underreporting of caloric intake; and (iii) the small number of women who really eat low-fat diets in countries like the United States.

## Dietary Factors and Oral Cancer

Cancer of the oral cavity represents a significant health problem with over 30,500 new cases being forecast for 1997 in the United States alone (41). Extensive epidemiological studies have established that a combination of chronic ethanol consumption and cigarette smoking is a major risk factor for squamous-cell cancer of the oral cavity (42–44). Indeed, the relative risk for oral-cavity cancer among heavy drinkers and smokers was already in 1979 more than 20 times above that for nonsmokers and nondrinkers (43). However, in recent years an increased incidence of oral-cavity cancers, apparently unrelated to tobacco use and alcohol consumption, has been observed. It is mostly due to higher incidences of cancer of the tongue in young males (45–48). Finally, in a recent study of gender differences in oral cancer susceptibility, female smokers were found to be at significantly greater risk than male smokers (49).

**Role of Nutritional Deficiencies.** Several lines of evidence suggest that nutrition may play an important role in oral carcinogenesis (50–52). Early evidence for this was obtained from investigations of the high incidence of oral cavity and esophageal cancers among Swedish women (53, 54). Although the exposure of these women to tobacco smoke or other obvious carcinogens was limited, they did exhibit a high incidence of Plummer-Vinson syndrome, a condition associated with iron and riboflavin deficiencies. After the implementation of a national program of iron and vitamin supplementation of flour in Sweden, the incidences of both Plummer-Vinson syndrome and cancers of the upper alimentary tract were significantly reduced (55).

Since this initial finding, numerous epidemiological and clinical studies have described potential vitamin and mineral deficiencies, particularly in iron, riboflavin, vitamin A, β-carotene, and vitamin C, in populations at high risk for cancer of the upper aerodigestive tract (52, 56, 57). In a metabolic epidemiology study of nutritional status and oral cancer, we observed lower serum levels of vitamin A and iron in cases than in controls, particularly among never-smokers (58). Similar nutritional deficiencies have also been implicated as etiological factors in the development of oral leukoplakia (59). However, little is known regarding the factors responsible for determining the risk of malignant progression in these lesions (59, 60). Laboratory animal studies have also supported a role for antioxidant vitamins in the protection against oral cancer. Retinoids, vitamin C, and vitamin E have shown a significant chemopreventive effect in the hamster cheek pouch model (61–64).

The results of epidemiological and early intervention studies have prompted the initiation of several large-scale clinical trials aimed at preventing secondary primary cancers or premalignant lesions of the oral cavity through the use of β-carotene, vitamin A, and related compounds (60, 65, 66). Results to date have demonstrated an effectiveness of retinoids, particularly 13-*cis* retinoic acid, in reversing or preventing oral leukoplakia (66) as well as in reducing the occurrence of second primary malignancies when used as an adjuvant therapy in patients with oral cancer (67). However, due to the relatively high toxicity of these agents, their clinical use for oral cancer prevention is limited. Thus, a number of studies have been initiated using less toxic antioxidants such as β-carotene (65, 66).

**Biomarkers.** The development of appropriate intermediate markers of various stages in carcinogenesis has been emphasized in the design of clinical studies. Potential markers include the formation of micronucleated cells in the buccal mucosa, mutagen-induced chromosomal sensitivity in lymphocytes, and oral tissue autofluorescence (68–70). In studies aimed at identifying genetic changes in premalignant lesions of the oral cavity, we found that mutations in the *p53* tumor suppressor gene occur in biopsy samples from a small segment of individuals with oral leukoplakia and that the presence of this mutation in these lesions of the oral cavity is likely indicative of an enhanced potential for malignancy (71, 72). These results suggest that *p53* mutations may serve as a useful biomarker of cancer risk in individuals with oral leukoplakia; such a biomarker would be of great value for the design and implementation of clinical trials.

**Mechanisms.** The mechanisms by which nutrient

deficiencies may enhance carcinogenicity are not known but may involve their role in the redox status and detoxification capacity of the oral mucosa (52). Small quantities of toxic free radicals, such as superoxide and hydroxyl radical, are produced in the mitochondria as by-products of oxidative metabolism (73). Several detoxification systems protect against such damage, including superoxide dismutase, free radical scavengers (e.g., glutathione), vitamin C, and β-carotene (74, 75). If left unchecked, radicals can lead to lipid peroxidation and to the production of DNA-damaging agents such as malondialdehyde (76, 77). Also, several tobacco carcinogens are known to be activated by oxygen free radicals (78). Both iron and riboflavin play essential roles in oxidative metabolism. For example, the entire electron transport chain is composed of a variety of iron- and flavin-containing proteins. Thus, a deficiency in either nutrient could disrupt the normal flow of electrons and lead to an increase in free radical production.

Oxidative damage may also play a role in the mechanism by which ethanol enhances oral cancer (46). The effect of ethanol consumption on nutritional status has been extensively studied and deficiencies of a number of antioxidant/vitamins and trace metals known to be important in oral-cavity cancer have been observed in alcoholics. The deficiencies include those of the vitamins A, E, and C, as well as iron and zinc (79). In addition, there is ample evidence through studies in laboratory animals and in humans that alcohol consumption leads to aggravated oxidative damage in various tissues, including the oral cavity (80).

**The Role of Glutathione.** While much attention has been paid recently to the role of vitamin/antioxidants and related compounds in the regulation of oral cancer risk and as chemopreventive agents, little attention has been given to glutathione (GSH), the major endogenous antioxidant. Aside from its role as a critical reducing agent, GSH also has numerous essential functions in detoxification and cellular homeostasis (81). A specific involvement of GSH in protection against carcinogenesis has been suggested (82). This notion is supported by the major role of this compound in the detoxification of carcinogens by conjugation, protection against free radical and oxidative damage, and maintenance of immune function (81). Several other chemopreventive agents currently being tested effectively enhance GSH levels or the GSH detoxification system. This indicates a specific role of GSH in their mechanism of action. Finally, since tissue GSH levels are depleted during the aging process, this loss likely results in an increased susceptibility toward the actions of carcinogens in the elderly (82).

We are therefore now investigating whether the GSH content of the oral epithelium is a key factor for the regulation of carcinogenesis and whether low GSH levels are associated with increased cancer risk. As described above, this is consistent with known risk factors for oral cancer including low dietary intake of nutrient-related antioxidants, and aging. In addition, GSH deficiency may also be involved in the mechanism by which alcohol consumption increases cancer risk since GSH play a key role in protecting against the toxic effects of alcohol (83) and GSH levels are depleted by both acute and chronic alcohol consumption (84).

Laboratory studies have supported a role for GSH in protection against oral cancer. In a recent study by Trickler *et al.* (85), a decreased tumor incidence was observed in the hamster cheek pouch after 8, 10, 12, and 14 weeks in animals treated with DMBA and GSH compared with those receiving DMBA alone. GSH was also effective in combination with other antioxidant/nutrients (86). On the basis of the experimental designs used, it could not be ascertained whether the chemoprotective effects of GSH were due to inhibition of events during initiation or postinitiation, or both. Finally, decreased GSH levels have been suggested to play a role in enhancing carcinogenicity by alcohol consumption in the hamster/DMBA model (87).

**Future Studies.** There are few epidemiological data on GSH and cancer risk. In a small study of diet and oral cancer, an association between increased intake of GSH from fruits and vegetables and a decreased risk for cancer was observed (OR = 0.5) (88). To our knowledge, metabolic epidemiology studies regarding GSH status and cancer risk have not been conducted. However, recent data from our laboratory indicate the feasibility of assaying GSH levels in blood in large-scale human studies (89, 90). Such studies are necessary to determine the extent to which GSH depletion relates to increased risk for cancer.

## Chemoprevention of Tobacco-Related Lung Cancer by Green Tea and Its Components: Model Studies with a Tobacco-Specific *N*-Nitrosamine

An estimated 25%–40% of all cancers in the United States can be attributed to tobacco use (91). About 50 million people in America still smoke cigarettes in spite of efforts to reduce the prevalence of smoking. However, many smokers apparently cannot or will not quit, and are expected to continue the habit. Cancer of the lung has been the leading cause of cancer deaths among men in the United States, and has in recent years surpassed breast cancer as the leading cause of cancer mortality among women (41). This continuing epidemic is expected to spread through many developing countries, such as China and India, due to the sharp increase in the prevalence of cigarette smoking in recent years. Because it is so difficult to effectively modify lifestyles in large populations, there is an imminent and practical need to search for chemopreventive agents that can counteract the carcinogenic effects of smoking.

**Natural Chemopreventive Agents.** A major interest of researchers at the American Health Foundation is to identify active ingredients in human diets, particularly those in cruciferous vegetables and tea, that have anticarcinogenic activity against lung cancer. It is well documented that vegetable consumption has a protective effect against tobacco-

related human lung cancer (92). However, the exact nature of all ingredients in vegetables that may be responsible for such an effect is still not quite clear. Epidemiological studies have shown that there is an inverse relationship between vitamin A and β-carotene intake, and lung cancer, suggesting a protective effect of these agents. Whether these micronutrients actually protect humans against cancer is an important and challenging question in the field of nutritional carcinogenesis. As stated in a report by the National Academy of Sciences Committee on Diet, Nutrition, and Cancer, "because the indices of vitamin A intake in these studies were derived from foods that also contain other natural inhibitors of carcinogenesis, it is also possible that dietary constituents other than preformed vitamin A or β-carotene are relevant risk-reducing factors" (93). The well-publicized intervention study with β-carotene signifies the complexity of these studies and points to the need for a more thorough evaluation of other dietary constituents (94).

**Model Studies for Tobacco-Related Lung Cancer.** Numerous constituents in cigarettes induce or promote tumors in laboratory animals. The most intriguing tobacco carcinogens are the abundant, nicotine-derived *N*-nitrosamines (95). The most potent of these, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), has high specificity for the induction of lung tumors in several animal species (96). This organo-specificity of NNK toward the lung is independent of the route of administration. Because of its potency and organotropism, NNK is believed to be one of the key compounds in tobacco that have major responsibility for the development of lung cancer in smokers.

**Epidemiologic Leads.** Lung cancer mortality among men in Japan is much lower than among their counterparts in the United States, although the average consumption of cigarettes by the Japanese is considerably higher than that by American men (97). Many factors, such as race, smoking patterns, and diet could account for the observed difference in risk among the men in these two countries. It has been suggested that the lower dietary fat intake in Japan compared with that in the United States might contribute to this difference in lung cancer, along with the prevalence of green tea consumption in Japan (97, 98).

**Prophylactic Agents in Tea.** Prophylactic functions have been ascribed primarily to the polyphenols, which constitute 10%–20% of green tea (98). These compounds are powerful antioxidants, capable of scavenging $H_2O_2$ and superoxide anion, thus preventing $H_2O_2$- and oxygen free radical–induced cytotoxicity. The polyphenol fractions of green tea have been shown to protect against mutagenic and carcinogenic effects (99). (−)-Epigallocatechin gallate (EGCG), a major polyphenol of tea, inhibited skin tumors in mice in assays with DMBA as the initiator and with teleocidine as promoter (100). The antipromoting activity of EGCG was demonstrated in mice against development of tumors induced in the duodenum by *N*-ethyl-*N*-nitro-*N*-nitrosoguanidine (101). These results prompted us to test the hypothesis that green tea and its major component EGCG, and perhaps also caffeine, protect against lung carcinogenesis induced by NNK, the potent lung carcinogen in cigarette smoke.

**Green Tea and Its Components as Inhibitors of Lung Tumor Development in a Model Assay with NNK.** In the bioassay for NNK-induced lung tumorigenesis, six-week-old female A/J mice were divided into seven groups as shown in Table I. They were maintained on AIN-76 diet and 2% green tea infusion, or 560 ppm of EGCG or 1120 ppm of caffeine were given as chemopreventive agents in drinking water. The concentrations of EGCG and caffeine in solutions were identical to those found in the 2% tea infusion. After consuming the test substances in drinking water for 2 weeks, mice were given NNK (11.65 mg/kg body wt in corn oil) by gavage three times weekly for 10 weeks while continuing to receive the test agents. One week after the last NNK treatment, mice were switched back to tap water. Six weeks after the last NNK treatment the mice were sacrificed. Table I shows the effects of tea, EGCG, and caffeine on the formation of lung adenomas in mice treated with NNK. While the tumor incidences are the same in all groups, mice that drank tea, or water containing EGCG, developed only 12.2 and 16.1 tumors per mouse, respectively, compared with 22.5 tumors per mouse in the group of NNK-treated mice that drank water only. These tumor multiplicities correspond to a 45% and a 30% reduction of lung tumors in these groups, respectively. Interestingly, the caffeine group also showed marginal inhibition. Mice given only green tea, or water with EGCG or caffeine, had no greater tumor multiplicity and incidence than is normally seen in untreated mice.

Our studies on the mechanism of tumor inhibition further demonstrated that the inhibiting properties of green tea and EGCG parallel the agent's abilities to suppress the formation of 8-hydroxyguanine, an oxidative lesion usually developing in the lung DNA of rats treated with NNK (99, 102).

**The Role of Caffeine in Tumor Inhibition by Green Tea.** In the tea preparation used in this bioassay, caffeine constituted about 5.6% by weight. As a major component of tea, caffeine has been shown to inhibit chemical carcinogenesis; however, the exact mechanism by which it

**Table I.** Effect of Tea, EGCG, and Caffeine on NNK-Induced Lung Adenomas in A/J Mice

| Groups | Number of animals | Tumor/mouse (±SD) | % of mice with tumors |
|---|---|---|---|
| NNK | 30 | 22.5 ± 4.7 | 100 |
| Tea + NNK | 25 | 12.2 ± 4.3[a] | 100 |
| EGCG + NNK | 25 | 16.1 ± 5.3[a] | 100 |
| Caffeine + NNK | 15 | 19.2 ± 4.8[b] | 100 |
| Tea | 15 | 0.1 ± 0.2 | 7 |
| EGCG | 15 | 0.3 ± 0.6 | 20 |
| Caffeine | 15 | 0.3 ± 0.6 | 20 |

[a] Compared with NNK group, $P < 0.001$ using Student's *t* test.
[b] Compared with NNK group, $P < 0.05$ using Student's *t* test.

does so is not clear. Lagopoulous *et al.* had reported that the reduced body weight gain caused by caffeine treatment correlates with decreased hepatocarcinogenesis by diethylnitrosamine (103). In our studies, even though the pattern of diet consumption was unchanged by caffeine treatment, the body weight gains in the caffeine-treated groups were considerably lower than those in the EGCG and NNK control groups. Therefore, the slight but significant reduction in lung tumor multiplicity by caffeine treatment could be related to its negative effect on body weight. Vander Ploeg *et al.* have suggested that the inhibition of metabolic activation of 7,12-dimethylbenz[*a*]anthracene by caffeine is the main reason for the suppression of tumor induction by this carcinogen in the mammary glands of rats (104). Regardless of mechanism, the potential protective effect of caffeine should not be ignored, because of the widespread consumption of caffeine-containing beverages throughout the world.

## The Role of Selenium in the Prevention of Lung, Mammary, and Colon Cancer

Many epidemiological studies have shown an inverse relation between selenium concentrations in serum and the incidence of human cancer (105). In the Linxian cancer prevention trials, the treatment groups receiving selenium, β-carotene, and α-tocopherol had significantly lower incidence and lower mortality from stomach cancer than the placebo groups (106). Moreover, the outcome of a recent clinical intervention trial in the United States supports that selenium protects against cancer of the prostate, colon, and lung (107). Reviews of the experimental studies revealed that, in most experiments with laboratory rodents, selenium was added to the diet or to the drinking water in its inorganic form (sodium selenite, sodium selenate, or selenium dioxide) (108, 109). Clearly, selenium protected the animals against chemically or virally induced cancers. Unfortunately, inorganic selenium compounds are toxic at just about the levels needed for effective cancer prevention. Therefore, the need for testing other forms of selenium was apparent. In fact, the naturally occurring seleno–amino acids (selenomethionine and selenocysteine) have been found in certain foods, but they amount to only about 50% of all selenium present. Because humans consume selenium in its organic forms, the logical experiments to carry out were those involving exposure of rats and mice to some of these naturally occurring seleno–amino acids. On the basis of assays with such compounds, no advantages over the inorganic forms were found. However, recently Cai *et al.* characterized organoselenium compounds, other than seleno–amino acids, in garlic, onions, and chives (110, 111). The efficacy of these new compounds remains to be determined.

One of our major research goals is the development of effective cancer preventive organoselenium compounds for which there is greater tolerance than for some of the historical selenium compounds, such as sodium selenite. Ideally, such agents would be capable of inhibiting tumor development that is initiated in different organs by various environmental carcinogens. A series of organoselenium compounds has therefore been synthesized and evaluated for chemopreventive efficacy *in vivo*. Parallel to these studies, short-term *in vitro* and *in vivo* assays were carried out to provide insight into the mechanism of action and to allow for rapid evaluation of the efficacy of chemopreventive compounds that will qualify for long-term preclinical investigations. We demonstrated that one of the most effective of these organoselenium compounds, 1,4-phenylenebis-(methylene)selenocyanate (*p*-XSC), is capable of inhibiting tumors in the mammary gland, colon, and lung of animals in these efficacy studies.

Dietary *p*-XSC inhibited mammary tumor development induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) during both the initiation and postinitiation phases of carcinogenesis in female CD rats (112, 113). *p*-XSC also blocked DMBA-DNA adduct formation in the mammary glands and inhibited thymidine kinase in mammary tumor cell lines derived from both humans and rats (114). In mammary carcinoma cell lines, *p*-XSC inhibited cell growth and induced a dose-dependent increase in cell death by apoptosis (115). In these assays, *p*-XSC appears to be superior to selenite and naturally occurring seleno–amino acids.

Dietary *p*-XSC inhibited colon tumor induction by azoxymethane in F344 rats during both phases of carcinogenesis (116). Although dietary *p*-XSC administered during the initiation and postinitiation periods inhibits colon carcinogenesis in rats maintained on low-fat or high-fat diets, the chemopreventive efficacy was more pronounced when the compound was given along with a low-fat diet (unpublished data). This study taught us that the low-fat dietary regimen will be an important adjunct to clinical chemoprevention trials. The inhibitory effect of *p*-XSC on colonic aberrant crypt formation showed a similar trend. Selenium-dependent glutathione peroxidase (GSPx) activity in the colonic mucosa was increased, and prostaglandin $E_2$ was reduced in animals fed the *p*-XSC diet compared with animals receiving the control diet. GSPx was also evaluated in other extrahepatic tissues upon feeding diets supplemented with *p*-XSC.

Dietary *p*-XSC inhibited the formation of DNA adducts in the lungs of rats and mice, as well as lung tumor development in A/J mouse model assays with the tobacco-specific carcinogen NNK, while selenite had no effect (117, 118). These observations are important because smokers are exposed to NNK and could conceivably be protected against tumorigenesis by supplementing their diet with effective organoselenium compounds.

## The Causes and Prevention of Cancer of the Stomach

The optimal cancer control is through primary prevention. Prevention can be effective and is economical, in contrast to diagnosis and therapy as modalities of cancer control that are usually costly long-term efforts with only moderate success.

There are two basic types of gastric cancer, the diffuse kind and cancer of the glandular stomach. The diffuse type is relatively uncommon, it occurs in many part of the world, and its etiological factors are practically unknown. On the other hand, with the more prevalent type of glandular stomach cancer, a great deal of knowledge has accrued on causative elements, on modifying factors, and on the underlying mechanisms, setting the stage for definitive recommendations for prevention. Intriguing is the possible contribution of *Helicobacter pylorum* as an etiologic factor, probably operating by a promoting mechanism through mucosal cell damage and biochemical changes in the cellular environment (119).

At the beginning of the 20th century, glandular stomach cancer was recorded as having a high incidence almost everywhere in the world, including the United States. However, happily, the incidences of this major disease began to decline about 1930 in the United States, and it currently affects a relatively small number of people. ACS data show for 1996 estimates of gastric cancer mortality in 14,000 people, i.e., 8,300 men and 5,700 women, with a disproportionately high mortality in 2,213 African-Americans, 523 Asians, and 885 Hispanics (120). While glandular stomach cancer has begun to decline in other areas of the world, it still displays a high incidence in Asia, particularly the northern regions of China and Japan, in parts of Central and South America and in Northern and Eastern Europe (121). The interesting decrease of the incidence of gastric cancer in the United States has been described by Howson *et al.* (122) under the title "The Decline in Gastric Cancer: Epidemiology of an Unplanned Triumph." This important document reviews the history of gastric cancer and presents hypotheses on the reasons for the decreased risk of this disease in the United States.

Considerations of geographic pathology have suggested that nutritional elements play a decisive role in causing cancer in the glandular stomach (123, 124). For example, it still has a high incidence in the northern area of Honshu Island of Japan and specifically in Akita prefecture. Individuals in the high-risk area frequently eat specific kinds of fish preserved with salt and saltpeter (sodium nitrate). In contrast, in much of the Western world, the practices of food preservation, involving heavy use of salt and saltpeter, have changed dramatically with the ready availability of commercial and electric home refrigeration, permitting low-temperature storage of perishable foods, instead of using the older means of food preservation. Also relevant to a description of etiological factors is that protective fresh fruits and vegetables are available on a year-round basis in most of the Western world. Indeed, they are beginning to be available thus in Japan, but regrettably not yet in other high-risk areas. In the past, fresh fruits and vegetables were available in the northern regions only at harvest time, late summer and fall. In southern regions, this availability was mostly year-round. However, with effective rail and air transport it is now possible to purchase fresh fruits and vegetables economically on a year-round basis in most of the Western world and in Japan. These are the main risk-lowering elements that Howson *et al.* regard as contributors to the decline of gastric cancer in the United States (122).

**Experimental Studies.** To explore specific etiological factors, we acquired from a local Japanese food store in the northeastern United States, Sanma Hiraki, Aji, and Iwashi fish, and processed the meat from these fishes in a manner mimicking food preservation customs prevalent in northern Japan, or as they were used at the beginning of this century, and even earlier in the United States and Europe (125). Typically, this involved covering the fish with a brine containing 2% salt (sodium chloride) and 0.5% saltpeter (actually sodium nitrite was used to expedite the reaction. In the old-fashioned pickling process, sodium nitrate was also used; it was reduced slowly as food was stored at room temperature, and with the help of fermentation processes then yielded nitrite. This lowered the pH to 3–4.5). Initially, it was found that the three fishes so treated displayed high levels of direct-acting mutagenicity in the Ames test with *Salmonella typhimurium* TA1535. This mutagenicity is consistent with that of a direct-acting carcinogen typically affecting the first storage organ reached, namely the stomach. Mutagenic activity was produced from a fish homogenate supernatant solution treated with salt and sodium nitrite at pH 3; however, the similarly treated solids yielded little activity. This simplified the isolation of the mutagen by high-performance liquid chromatography (HPLC) techniques (126). Indeed, three mutagens were actually present. Repeated HPLC runs and other analytical approaches permitted the isolation in a pure state of one of these mutagens. This fraction was subjected to chemical analytical methods, including low- and high-resolution mass spectrometry, NMR, UV, and infrared techniques. Analysis of the combined data led to the conclusion that this mutagen had the structure 2-chloro-4-methylthiobutanoic acid (CMBA). This is a new compound, never before described in the chemical and biochemical literature.

The chemical structure of CMBA suggested that it might be derived from the amino acid L-methionine. This was readily confirmed by subjecting L-methionine to a solution containing 2% salt and 0.5% sodium nitrite at pH 3. The chemical isolated by HPLC was identical to the chemical found in salted and pickled Sanma Hiraki fish. The important finding was made that the chlorine atom attached to the 2 position actually stemmed from the use of sodium chloride. Indeed, without sodium chloride, methionine yields the expected 2-hydroxy analog. A dose-response curve showed that the production of the hydroxy compound declined, and that of CMBA increased with increasing salt concentrations.

Furihata and colleagues (127) demonstrated that intubation of CMBA into male F344 or ACI strain rats led to the induction in the gastric mucosa of cells displaying an increased rate of S-phase synthesis, and to a definite but lesser production of cells showing unscheduled DNA synthesis

(UDS). Studies done in parallel with the classic animal gastric carcinogen MNNG gave similar results, except that MNNG induced UDS to a greater extent. We are currently conducting a bioassay in F344 rats to verify that CMBA indeed has the capability of inducing gastric cancer. This would be a model for the situation prevailing before food preservation methods were altered, and heavy salt, used together with sodium nitrate, was the classic means of storing perishable foods.

These results provide a new view on processes leading to gastric cancer. Indeed, it was previously assumed that gastric carcinogens might form in the stomach under the influence of a high environmental nitrate concentration, together with salt, such as might be prevailing in parts of Latin America, including Chile and countries on the west side of the Andes. In contrast, our results show that the gastric carcinogen is present in salted, pickled foods such as fish or certain meats. Food preservation using both salt and the smoking of foods, as used to be the practice in Iceland, accounts for the presence of these kinds of carcinogens in smoked and salted foods, because the fire generating smoke contains nitrosating chemicals.

The mandate for approaches to prevention clearly involves abandoning the formerly used procedures for food preservation with salt and saltpeter. In Japan, under the influence of Professor Dr. Sugimura, the Nakasone plan was introduced in 1986, involving education of the Japanese people to progressively decrease their salt intake (128). This plan was just extended for another 10-year period. Also, in Belgium, Joossens and Kesteloot (129) made such a recommendation almost 30 years ago. Gastric cancer in Belgium has declined more sharply than in parts of Europe where such a plan was not implemented. Extensive salt use, 15 g or more per day, in the absence of protective potassium ions from fruits and vegetables, and calcium ions from some vegetables and dairy products, is a major cause of high blood pressure in sensitive individuals and thus a cause of cerebrovascular accidents. With lower salt use, stroke has declined sharply in the United States and Belgium, and is beginning to decline in other areas of the world where less salt is being used. Yet, in the United States there are about 30 million individuals presenting with high blood pressure. Thus, greater efforts are needed to educate people, restaurateurs, the canned-food industries, and other suppliers of food, to decrease the salt content of marketed foods. Also important are efforts to increase education of the public to consume five to nine fruits and vegetables per day, as recommended by the National Cancer Institute, the American Cancer Society, and other agencies, including the American Health Foundation and its Food and Nutrition Council. Such public health actions would go a long way toward lowering the risk of major chronic diseases, such as stroke and cancer of the stomach or esophagus (prevailing in parts of China). Dietary changes need to be implemented from childhood onward. Indeed, data show that migrants from high-risk regions such as Japan, Northern, or Eastern Europe to the United States still have such a risk if they lived in their native countries for the first 20 years of their lives (130). Salted food is an acquired taste; thus, every effort needs to be made to modify our gustatory habits early in life.

These studies provide evidence for underlying mechanisms and etiologic factors for major diseases and how they can be controlled through alteration of dietary habits, food processing techniques, and nutritional supplements. Prevention is the definitive, economic solution for lifelong good health.

## Conclusions

**Dietary Fat, Calories, Fiber, and Colon Cancer.** The role of overall caloric intake and of macronutrients in the etiology of colon cancer has become increasingly apparent. The combined epidemiologic and laboratory evidence is sufficiently convincing to conclude that there is an enhancing effect as a function of high intake of total fat, calories, and certain types of fat, and that there is a protective effect of certain types of dietary fibers in colon cancer. Recommendations for cancer control include low-fat diets (<25% calories from fat, preferably olive oil) and wheat bran as fiber additive (25 g/day).

**Dietary Fat and Breast Cancer.** Dietary fat appears to be a poor indicator of risk within Western countries but does appear to be associated with the age-specific incidence and mortality of breast cancer among countries. The most rigorous evaluation of the role of fat in breast cancer promotion would require a large-scale prospective dietary intervention trial. This is not likely to occur, due to the enormous cost and logistic difficulties of such a study. Trials on a smaller scale in high-risk women are currently underway. For example, the Womens Intervention Nutrition Study (WINS) (131) involves randomizing women with breast cancer into either a low-fat (15%–20% of calories) diet group or a conventional diet group after their surgery, and the study assesses rates of recurrence. In another study, Boyd *et al.* (132) reported a reduction in the area of mammographic density, a risk factor for breast cancer, in women enrolled in a low-fat (21% of calories from fat) dietary regimen after a 2-year follow-up. Advances in this field will require reliable biomarkers of breast-cancer stages, improved methods of dietary assessment in populations, development of methods to assure compliance, and long-term follow-up of intervention trials already in progress.

**Dietary Control of Oral Cancer.** Tobacco and alcohol drinking are established major risk factors for oral cancer, except perhaps for a recent surge of cancer of the tongue among young men. Women who smoke cigarettes are at significantly higher risk than men who smoke. There is evidence that deficiencies in vitamins, especially in antioxidant vitamins, and trace minerals are also involved in the etiology of oral cancer. Laboratory studies with animals have corroborated that supplementing feed with retinoids and vitamins C and E exerts chemopreventive effects on

chemically induced oral carcinogenesis. Clinical trials in humans with such supplements are aimed at preventing second primary cancers. Potential biomarkers of stages of oral carcinogenesis include formation of micronucleated cells in the buccal mucosa, mutagen-induced sensitivity in lymphocytes, tissue autofluorescence, and perhaps *p53* mutations, but definitely various indices of oxidative damage. Glutathione, the major endogenous antioxidant has been shown to have a protective role in experimental carcinogenesis. This is in line with evidence of an increased oral cancer risk when glutathione is depleted as a consequence of alcohol consumption or immunosuppression, or as a function of aging. Whether glutathione supplementation in humans provides protective compensation for such depletion needs to be confirmed. It is also important to establish whether chemopreventive effects of glutathione are exerted during initiation, or postinitiation, or during both phases of carcinogenesis.

**Control of Tobacco-Related Lung Cancer.** Green tea infusion was able to inhibit lung tumor development in mice that had been treated with the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Whereas the daily consumption of tea by humans is, on a per kg body weight basis, considerably less than that by the mice in the described assay, the NNK dose to which smokers are exposed is also far below that used in the lung tumor assay with A/J mice. The inhibitory effect of green tea appears to be due largely to the antioxidant activity of its major polyphenol EGCG. That green tea appears to have a protective effect against NNK-induced lung tumorigenesis in mice supports the hypothesis that green tea consumption in Japan may be responsible, in part, for a lower lung cancer mortality rate among Japanese cigarette smokers. Bioassays in several animal species and more detailed mechanistic studies in conjunction with well-designed intervention trials are needed to verify the protective role of green tea in humans. Our findings thus far have firmly established that EGCG is a major active compound in green tea. Unlike caffeine, EGCG exerts little adverse effect on body weight. It is therefore a far more suitable candidate for a prophylatic agent that could be given to smokers as a dietary supplement.

**Organoselenium Compounds as Chemopreventive Agents against Cancer of the Mammary Glands, Colon, and Lung.** In contrast to the observations with naturally occurring organoselenium compounds, such as selenomethionine and selenocysteine, our findings and those reported in the literature indicate that *p*-XSC and similar organoselenium compounds are capable of inhibiting tumors in mammary glands, in the colon, and in the lung of animals in model assay systems. The results of short- and long-term bioassays (133–135) are encouraging and will assist in the design of chemopreventive organoselenium agents that are even more efficient yet less toxic than *p*-XSC for application in preclinical assays and in subsequent clinical intervention in humans. In combination with low-fat diet the chemopreventive efficacy of *p*-XSC can be significantly improved. We are also continuing to determine the chemical structures of the as yet unidentified forms of organoselenium compounds in common foods, to probe whether new structures with optimal chemopreventive potential might be found. Organoselenium compounds lend themselves also to further development of chemopreventive "cocktails," i.e., co-administration with other micronutrients and antioxidants.

**Dietary Control of Gastric Cancer.** Epidemic proportions of glandular stomach cancer in the United States have declined to much lower rates of incidence and mortality over four decades in what has been termed "an unplanned triumph" (122). This phenomenon is attributed to changes in food preservation methods and to the year-round availability of fresh fruits and vegetables. In Japan and in other countries where populations face a high risk of gastric cancer, pickling of fish and meat, based on the use of salt and saltpeter, and smoking of foods, as well as the low supply of fresh fruits and vegetables, account for the prevailing high rates of this type of cancer. Studies in Japan and at the American Health Foundation have established mutagenic activities in extracts of fish preserved with traditional methods of salting and smoking. Recent studies at the American Health Foundation have led to the isolation and characterization of a previously unknown chemical compound, the mutagen 2-chloro-3-methylthiobutanoic acid, from salted fish (126). The formation of this L-methionine–derived mutagen is directly related to increasing salt concentrations. Mandates for the control of gastric cancer include educational measures leading to changes in food preparation and generally lowering salt use in addition to adherence to the recommendations for five to nine daily servings of fresh fruits and vegetables.

The authors thank Mrs. Ilse Hoffmann for her collaboration in editing this manuscript and Mrs. Patricia Sellazzo for her word-processing skills.

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