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NATURALLY OCCURRING ANTICARCINOGENIC SUBSTANCES IN FOODSTUFFS

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INTRODUCTION

It is becoming increasingly clear that dietary traditions and habits play an important role in the causation and development of a number of major human cancers (24, 81, 151); this conclusion is well supported by evidence obtained from experimental animal models (95, 152). For instance, diets high in fat and low in fiber are associated with increased risk of cancer of the colon, breast, prostate, endometrium, pancreas, and possibly other organs (95, 140, 152).

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Besides these major dietary components that act as modulators of the carcinogenic process, the development of highly sensitive analytical methods and the increasing use of short-term tests for mutagenicity reveal numerous chemicals, present in much smaller amounts in the diet, that can act as initiators of carcinogenesis. Examples of these include *N*-nitroso compounds, polycyclic hydrocarbons, heterocyclic amines, aflatoxins, and mycotoxins generally. However, foodstuffs are also a source of naturally occurring anticarcinogenic agents that hinder the formation of carcinogens from precursors or that act protectively to lessen or eliminate the effects of carcinogens (Table 1). Identification of these naturally occurring anticarcinogens and elucidation of their mechanisms of action may ultimately provide a practical means of inhibiting cancer.

Most chemical carcinogens can be converted by cellular enzymes to highly reactive electrophilic forms (ultimate carcinogens) that can react with and modify the function of macromolecular nucleophiles, most importantly DNA (71), thus initiating the carcinogenic process. Such carcinogens are categorized as "genotoxic" or DNA reactive. In contrast, there are compounds, including agents classified as promoters, that upon administration to animals also result in the development of cancer, yet do not exhibit DNA reactivity; these are

Table 1 Naturally occurring anticarcinogenic compounds in foods

Inhibitor	Typical dietary source	Reference
Aromatic isothiocyanates (benzyl isothiocyanate, phenethyl isothiocyanate)	Brussel sprouts, cabbage, cauliflower	130
Ascorbic acid	Citrus fruits, leafy vegetables	26
β-Carotene	Carrots, yams	26
Coumarins, lactones (α-angelica lactone, limettin, coumaranone, etc)	Citrus fruits, vegetables	137
Fibers[a]	Cereal (bran) products, fruits, vegetables	26
Flavonoids (quercetin, myricetin, kaempferol, chrysin, etc)	Most fruits, vegetables, grains	7, 33
Indoles (indole-3-acetonitrile, indole-3-carbinol, 3, 3'-diindolymethane)	Brussel sprouts, cabbage, cauliflower	63
Phenolic acids (caffeic acid, ferulic acid, chlorogenic acid, ellagic acid, etc)	Coffee, tea, soybeans, oats, apples, potatoes	112
Protease inhibitors	Soybeans, seeds, nuts, legumes	101
Selenium compounds	Grains (from Se-rich soil), Brazil nuts, clams, mushrooms	15, 26
α-Tocopherol	Oils, nuts, asparagus	26

[a]It is important to distinguish distinct types of fibers based on mechanisms. Cereal bran fiber increases stool bulk and lowers concentration of intestinal carcinogens and promoters. Lignin and pectin fibers have multiple effects, including those on the metabolism of carcinogens and on the enterohepatic cycling of metabolites.

categorized as "epigenetic" (148). This category also includes chemicals playing an important role in promoting the development of major types of human cancer (81, 95).

The cytochrome P-450-dependent, mixed-function oxidases, localized in the endoplasmic reticulum of the cell, play a central role in activating genotoxic carcinogens. For instance, in the case of *N*-nitrosamines (108) and of aliphatic azoxy compounds such as azoxymethane (27), mixed-function oxidases catalyze the hydroxylation of α-carbon atoms to form species with short half-lives. The α-hydroxylated metabolites of *N*-nitrosamines rapidly decompose nonenzymatically to aldehydes and highly reactive electrophilic alkyldiazonium ions. The latter alkylate cellular nucleophiles, including DNA. The α-hydroxylated metabolite of azoxymethane, methylazoxymethanol, similarly yields an alkylating species and formaldehyde, but this reaction is enzyme catalyzed. Aromatic and heterocyclic amine carcinogens are initially activated by mixed-function oxidases to *N*-hydroxy metabolites (71, 153). These can form DNA-reactive electrophilic nitrenium and carbonium ions nonenzymatically, or after enzymatic esterification of the *N*-hydroxy group (71). Mixed-function oxidase-mediated hydroxylations of carbon atoms of the parent aromatic and heterocyclic amines yield phenolic metabolites that represent detoxication products and are excreted in the form of sulfates and glucuronides. Polycyclic aromatic hydrocarbon carcinogens such as benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) are metabolized by cytochrome P-450-dependent, mixed-function oxidases (18) to reactive epoxides at various positions of the hydrocarbon skeleton. The epoxides can spontaneously isomerize to phenols, or can be hydrated via epoxide hydrase to dihydrodiols. Conjugation products of epoxides with glutathione, or of phenols and dihydrodiols with the biologically active forms of sulfuric and glucuronic acids represent detoxication reactions. There is strong evidence that the metabolic activation of BP and DMBA is initiated by specific epoxidations at carbons 7 and 8 of BP and carbons 3 and 4 of DMBA. Specific enantiomers of the resulting bay region diol epoxides represent the ultimate carcinogens.

Protective cellular agents counteracting the effects of genotoxic carcinogens include (*a*) enzymes that divert the metabolic conversions from pathways of activation to those leading to detoxified products, and (*b*) enzymes that catalyze the reactions of active electrophilic species with noncritical cellular nucleophiles such as glutathione. As described below, many naturally occurring anticarcinogens act by inhibiting enzymes involved in activation, by increasing levels of the enzymes and cofactors involved in carcinogen detoxication, or by scavenging the ultimate carcinogens. These inhibitors are denoted as functioning at the stage of initiation.

Should the electrophilic form of the carcinogen elude these primary cellular defenses and react with DNA, altered DNA segments can be removed and restored by special repair enzyme systems, and the cell may recover. Thus far,

naturally occurring anticarcinogens acting at this locus have not been identified.

Cells that have undergone initiation by chemical carcinogens may remain dormant with respect to the altered genotype, or may undergo progressive changes to form a neoplasm. The regulatory factors involved in these processes are not yet completely understood. However, by the use of animal models, certain foodstuffs and naturally occurring compounds have been identified that can either facilitate ("promoters") or hinder this progression. We designate the latter class as anticarcinogens acting at the postinitiation stage. In some cases, anticarcinogenic activity in naturally occurring compounds has been observed to occur at more than one stage of the carcinogenic process; in other cases, the loci of action have not yet been identified. For overview, the steps in this complex process are summarized in greatly simplified form in Figure 1.

Space constrictions prevent a complete coverage of this important subject; we therefore limit this review to aspects related to our personal research interests. For additional sources on naturally occurring anticarcinogens, the reader is referred to excellent reviews by Wattenberg (136, 137, 137a) and to a bibliography of 197 citations on a similar topic compiled by Wexler (146).

INHIBITION OF CARCINOGEN FORMATION

N-Nitroso Compounds

The majority of *N*-nitrosamines and *N*-nitrosamides examined have been found to be carcinogenic, producing tumors in diverse tissues of experimental animals (25). *N*-nitroso compounds are formed with great facility by the interaction of a

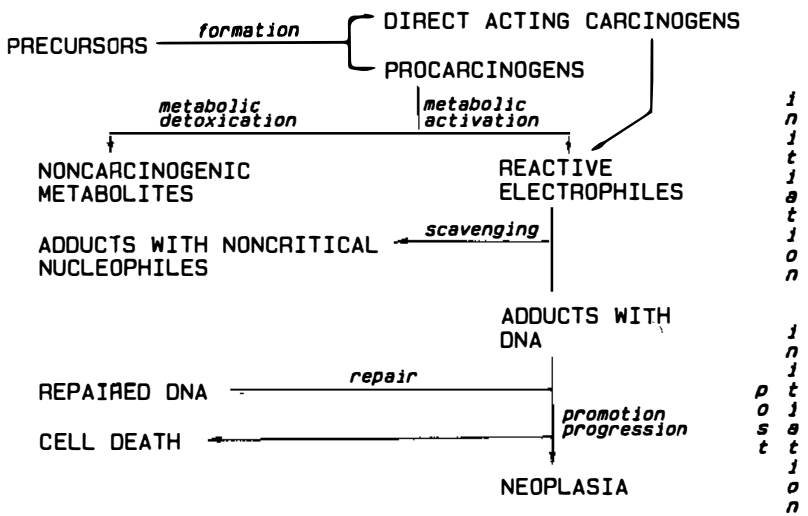

Figure 1 Summary of events in the carcinogenic process.

nitrosating species such as nitrogen trioxide, N_2O_3, or dinitrogen tetroxide, N_2O_4, with primary, secondary, or tertiary amines, or with secondary amides (73). These reactions can occur in aqueous and organic media as well as in the gas phase. In acidic aqueous solutions, the nitrosating species can be generated from nitrite according to the equation:

$$2NO_2^- + 2H^+ \rightarrow 2HONO \rightarrow H_2O + N_2O_3.$$

The formation of potentially carcinogenic *N*-nitroso compounds under such a wide variety of conditions from commonly occurring precursors accounts for their ubiquitous presence in the environment. Endogenous formations of *N*-nitroso compounds in the human as well as in the animal stomach have also been demonstrated (85, 86). Nitrite for such in vivo reactions can originate from exogenous sources, from the reduction of nitrate by the microflora of the oral cavity (124), or from microbial activity in the intestine (104, 123). Significant increases in salivary nitrite following ingestion of nitrate-rich vegetables or vegetable juices are well documented (45, 117). Fortunately, the vegetables also contain ascorbate, a scavenger of nitrite. Epidemiological studies show that enhanced incidence of stomach cancer is correlated with high nitrate content of the soil and/or drinking water in certain parts of the world (28, 36), or the intake of salted, pickled, or smoked foods that contain nitrate, nitrosamines, or diazo compounds (152, 154). Adding nitrite to foodstuffs enhances color and inhibits the growth of *Clostridium botulinum,* but it also causes *N*-nitroso compounds to form in meats and meat products such as sausage and frankfurters and to form during the frying of bacon (73, 82). Fermentation processes, including pickling and brewing, generate nitrite from nitrogenous precursors, as does the microbial activity occurring during nonrefrigerated storage of certain foods (142, 143). Such nitrite can serve in the formation of *N*-nitroso compounds either in the foods or beverages, or within the human body after its ingestion.

Very high rates of nitrosation can occur in lipid media in which both the active nitrosating species, such as N_2O_3, and the reactive form of amines (i.e. the free bases) are generally more soluble than in water, and the formation of emulsions further accelerates such reactions (87). Nitrosations in the lipid phase have special significance in the production of nitrosopyrrolidine during the frying of nitrite-treated bacon, of various other *N*-nitroso compounds in cosmetics, and possibly in the gastrointestinal (GI) tract. Thiocyanate present in tobacco smoke can catalyze such nitrosations.

Ascorbic acid was the first naturally occurring substance found to effectively block the formation of *N*-nitroso compounds (20, 72–75). Ascorbic acid and, more so, the ascorbate anion (72) reduce N_2O_3 to nitric oxide, NO, thus decreasing the concentration of N_2O_3 available for nitrosation of amines and amides. The inhibition of nitrosation by ascorbic acid/ascorbate (pK_a=4.3) is

most effective for slowly nitrosated amines such as dimethylamine and for those nitrosated at moderate velocities, such as morpholine and piperazine; in rapidly nitrosated amines such as *N*-methylaniline, inhibition is incomplete. Excellent reviews of this subject were presented by Mirvish (72, 73). The current practice in the US is to add about 550 ppm sodium ascorbate or sodium erythorbate (sodium isoascorbate) in conjunction with 120 ppm nitrite to foods such as frankfurters. This substantially inhibits the formation of *N*-nitrosamines without interfering with the preservative and cosmetic properties of nitrite.

Various experiments show that ascorbate can effectively inhibit carcinogenicity by decreasing the formation of *N*-nitroso compounds in vivo. Thus, treating pregnant rats or hamsters with ascorbate together with nitrite and ethylurea (precursors of ethylnitrosourea) completely inhibited the induction of tumors in the offspring (46, 102). In a different experimental system, high levels of sodium ascorbate in the diet markedly reduced the incidence of lung adenomas in Swiss or Strain A mice treated with morpholine, piperazine, *N*-methylaniline, methylurea, or ethylurea along with nitrite (75). Inhibition of *N*-nitroso compound formation by ascorbic acid, as reflected in lower urinary levels of nitrosoproline, was also demonstrated in humans (40, 85).

Many naturally occurring phenolic compounds also inhibit the formation of *N*-nitrosamines. However, some phenols or polyphenols can actually accelerate the process. In general, phenolic compounds that are easily oxidized to quinones by the nitrosating species, which itself is reduced to NO, can function as inhibitors. On the other hand, phenols can also be nitrosated to *C*-nitroso phenols, which, on further reaction with nitrite, may yield species such as nitroso quinoneoximes with enhanced nitrosating properties; this can result in increased formation of *N*-nitrosamines (11, 22). Thiols as well as phenols can be nitrosated, and the resulting nitrosothiols can also function as powerful nitrosating species (21), although inhibition of *N*-nitrosation, as with cysteine, has also been observed (72).

Table 2 lists some naturally occurring phenols and polyphenols that have been found to affect the formation of *N*-nitroso compounds. Possible reasons for the apparently conflicting properties of compounds such as chlorogenic acid, which has been reported as both an inhibitor and a catalyst of *N*-nitrosation, are discussed by Davies et al (21).

The inhibition of *N*-nitrosation reactions by α-tocopherol was reviewed by Newmark & Mergens (82). This lipid-soluble, water-insoluble vitamin is an effective inhibitor of *N*-nitrosation reactions in dispersions, and thus could be effective in inhibiting the formation of *N*-nitroso compounds in the GI tract. In reacting with a nitrosating agent such as N_2O_3 (which is itself lipid soluble), α-tocopherol is oxidized to α-tocoquinone, and the nitrosating agent is reduced to NO.

α-Tocopherol, in dispersions, is more effective than ascorbic acid at pH 3, but as the pH is increased to 5, the reaction of α-tocopherol with the nitrosating

Table 2 Effects of naturally occurring phenolic compounds on *N*-nitrosation reactions[a]

Inhibition	No effect	Enhancement
Beer constituents (93)	Caffeic acid (132)	Catechin (91, 132)
Caffeic acid (58, 82)	Chlorogenic acid (132)	Chlorogenic acid (61)
Catechol (132)	Ferulic acid (132)	Guiacol (91)
Chlorogenic acid (91)	Fisetin (132)	Kaempferol (132)
Ferulic acid (58)	Naringin (132)	Naringenin (132)
Gallic acid (72, 75, 92, 119)		Phenol (91, 132)
Pyrogallol (132)		Phloroglucinol (132)
Tannic acid (72, 119)		Quercetin (132)
α-Tocopherol (70, 82)		Resorcinol (91, 132)

[a]Pertinent references in parentheses.

agent decreases whereas that of ascorbic acid (which increasingly dissociates to ascorbate anion) increases. Thus, at neutral or slightly acidic conditions, ascorbic acid is the better scavenger. Most commercial preparations of α-tocopherol (as vitamin E) are in the form of acetate and hemisuccinate esters; such esters are inactive as scavengers of nitrosating species, moreover they are only slowly and incompletely hydrolyzed to the active phenol in the GI tract. Because of its lipid solubility, α-tocopherol has been used to reduce *N*-nitrosamine formation during the frying of bacon. At 500 ppm, α-tocopherol consistently reduced the levels of *N*-nitrosopyrrolidine to below 5 ppb in the fried product (70).

Cooked Food Mutagens-Carcinogens

Subsequent to the discovery of mutagenic activity towards *Salmonella typhimurium* during the broiling or frying of fish and meats (17, 79, 141), intensive efforts were made to identify the compounds responsible. Direct isolation as well as analyses of the pyrolysis products of individual amino acids led to the discovery of new classes of compounds, the majority of which fell into the category of heterocyclic amines (121). More than a dozen such compounds are now known, including 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoline (MeIQ), 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ), 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), 2-amino-3,7,8-trimethylimidazo[4,5-*f*]quinoxaline (Me_2IQx), 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), 2-amino-6-methylpyrido[1,2-*a*:3',2'-*d*]imidazole (Glu-P-1), and 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1). These compounds comprise some of the most powerful mutagens for *S. typhimurium* strain TA98 (with liver S-9 activation) yet discovered. The above series is arranged in order of descending mutagenicity, with MeIQ yielding some 6.6×10^5 revertants per μg and Trp-P-1 yielding 3.9×10^4 revertants per μg (121). Those compounds tested are also potent inducers of unscheduled DNA synthesis in the Williams hepatocyte DNA repair assay

(156). The carcinogenicity of IQ, Trp-P1, Trp-P2, Glu-P-1, Glu-P-2 (2-aminodipyrido [1,2-*a*:3'2'-*d*]imidazole) in mice and rats has been established (68, 122, 141); the presence of compounds of this type in the human diet may be related to the development of human cancers such as those of the colon, breast, and prostate (144).

Because such mutagenic and carcinogenic compounds, formed to various degrees according to the mode of cooking, are extensively consumed by humans, means of preventing their formation are of obvious importance. While various oils and fats, irrespective of their degree of saturation, have an augmenting effect on mutagen formation (118), the addition of butylated hydroxyanisole, ethylene diamine tetraacetic acid (EDTA), or the natural products soy protein or chlorogenic acid (2, 133) to beef hamburger significantly decreases mutagenic activity formed during cooking.

INHIBITION AT THE STAGE OF INITIATION

Inhibitors of Carcinogen Activation

The subject of metabolic activation of *N*-nitrosamines to ultimate carcinogenic forms was expertly covered in a recent review (108). The critical step in the process is the hydroxylation of the α-carbon atom; this reaction is catalyzed by cytochrome P-450–dependent, mixed-function oxidases. Modulation of the enzyme activities responsible for α-hydroxylation of *N*-nitrosamines through induction, activation, or inhibition can be expected to result in changes in the patterns of carcinogenicity and/or organotropism.

Acute (1 mmol/kg body weight by gavage, 2 hr prior to sacrifice) and chronic (0.003–0.03 mmol/g of diet, 2 weeks of feeding) treatment of rats with methoxyphenol, cinnamic acids, coumarins, indoles, and isothiocyanates both affect the ability of liver microsomes to α-hydroxylate *N*-nitrosopyrrolidine and of rat esophagus cultures to α-hydroxylate *N'*-nitrosonornicotine; these effects were examined by Chung et al (12). Acute pretreatment with benzyl isothiocyanate, allyl isothiocyanate, phenethyl isothiocyanate, phenyl isocyanate, and benzyl thiocyanate but not sodium thiocyanate inhibited the α-hydroxylation of both nitrosamines, but after chronic treatment only phenyl isothiocyanate and sodium thiocyanate were effective in this respect. Chronic treatment with *p*-hydroxycinnamic acid, 4-hydroxy-3-methoxycinnamic acid, coumarin, umbelliferone, limetine, indole, indole-3-carbinol, indole-3-acetonitrile, and L-tryptophan resulted in greater activity for α-hydroxylation in both systems.

The heterocyclic amine, cooked food mutagens-carcinogens are metabolically activated by *N*-hydroxylation, catalyzed by cytochrome P448 type monooxygenases (153). This step is necessary for the covalent reaction with DNA, but noncovalent physiochemical interactions also play an important part

in the very high mutagenicity of those compounds in the *Salmonella* assay (89). Various substances occurring in foodstuffs significantly inhibit the mutagenicity of these compounds, although the mechanisms involved are not as yet clear. Such substances include hemin (1), oleic acid (37), chlorophyll (59), and juices of vegetables such as cabbage, radish, turnip, and ginger (54).

Compounds Enhancing Detoxication Systems

The cellular levels of glutathione (GSH), a powerful nucleophile as well as an antioxidant, together with the enzymes GSH transferases and GSH peroxidases, are critical in maintaining a defense against a wide variety of noxious and carcinogenic agents. As a nucleophile, GSH reacts with electrophiles, including the proximate or ultimate forms of chemical carcinogens, to yield GSH conjugates that are excreted, usually after further metabolism. Most such reactions are catalyzed by the GSH transferase enzymes (51). Increased rates of reaction of active carcinogen metabolites with GSH will decrease the probability that they will react with DNA and other critical nucleophiles. An interesting exception is the case of the synthetic industrial chemicals of the 1,2-dihaloethane type where an enzyme-catalyzed reaction with GSH represents the first of several activation steps (129, 147).

Because genotoxic organochemical carcinogens of diverse types share the common denominator of either being electrophilic per se or being metabolically activated to electrophilic species (71), it is evident that anticarcinogenic agents acting through enhancement of the GSH–GSH transferase system could offer the possibility of being especially effective in the human setting, where the causative chemical agents for cancers have not, in most cases, been conclusively identified and may well be multifactorial. Indeed, the ability to induce GSH transferases in animal tissues has been used as an important criterion in the screening of naturally occurring potential anticarcinogens (114, 116).

Diet and dietary constituents have been found to markedly influence the levels of GSH transferases. Sparnins et al (115) reported that mice fed an unrefined diet (Purina Lab Chow) had higher liver and intestinal GSH transferase activities than did mice fed a semipurified diet (casein-starch-corn oil-salt mix-vitamin supplement). The inclusion of chopped dried green coffee beans, Brussels sprouts, instant tea, or powdered tea leaves in the semipurified diet significantly increased GSH transferases in both organs. Interestingly, a diet containing 20% cabbage increased the enzyme in the small intestine but not the liver. Coumarin, α-angelicalactone, indole-3-carbinol and indole-3-acetonitrile, which are constituents of Brussels sprouts and cabbage, but not umbelliferone or γ-valerolactone also significantly increased GSH transferase in liver and small intestine. Inclusion of dried green coffee beans in the diet of Sprague-Dawley rats prior to the administration of DMBA significantly reduced the incidence of mammary tumors (137). The active components of

green coffee beans responsible for the induction of GSH-transferase were isolated and identified as palmitate esters of the dieterpenes kahweol and cafestol (60). However, the effects of the pure compounds on carcinogenicity have not yet been reported.

Spamins & Wattenberg (116) correlated levels of GSH transferases, acid-soluble sulfhydryl compounds (R-SH), and the susceptibility of the mouse forestomach to benzo(*a*)pyrene (BP) carcinogenesis. α-Angelicalactone at 0.03 mmol/kg in semipurified diet increased forestomach GSH transferase levels about 80–95% and inhibited forestomach tumors due to BP intubation by 50–80%. Benzylisothiocyanate increased GSH transferase about 150% and caused an 80% inhibition of tumors. Again, umbelliferone and γ-valerolactone were ineffective in increasing GSH transferase, and also provided no protection against BP-induced forestomach tumors. α-Angelicalactone, coumarin, and benzylisothiocyanate also significantly increased the forestomach R-SH levels, but umbelliferone and γ-valerolactone did not. The authors suggest that the reduced carcinogenic response of the mouse forestomach to BP is associated with an enhancement of GSH transferase of about 75%.

The roles of cytochrome P-450s and epoxide hydrase in the metabolic activation of various polycyclic aromatic hydrocarbons, including BP and DMBA, were recently summarized in a comprehensive review (18). Specific enantiomers of the bay region diol epoxides of BP (BP-7,8–9,10-epoxides) and of DMBA (DMBA-3,4-diol-1,2-epoxides) represent the ultimate carcinogens. Such species represent only minor metabolites; the major metabolic pathways result in detoxification. A convenient assay for determining the capacity of tissue preparations to metabolize polycyclic hydrocarbons is based on the fluorometric determination of BP phenols produced (BP hydroxylase). Although the assay does not indicate the extent of formation of the proximate or ultimate carcinogens, compounds found to increase BP-hydroxylase generally protect also against carcinogenesis by polycyclic aromatic hydrocarbons (137).

Little or no BP-hydroxylase activity was present in the intestine and lung of starved rats or mice or of animals fed purified diets, but substantial levels of activity were found when animals were maintained on conventional commercial diets; this indicates the presence of BP-hydroxylase inducers. The alfalfa component of such diets was found to have strong inducing ability (63). A number of cruciferous plants, including Brussels sprouts, cabbage, cauliflower, and broccoli, were also found to have BP-hydroxylase-inducing ability, and the principal compounds responsible were identified as indole-3-carbinol, 3,3'-diindolylmethane and indole-3-acetonitrile, listed in order of decreasing activity (139). When administered p.o. to female Sprague Dawley rats 20 hr prior to DMBA, indole-3-carbinol and 3,3'-diindolylmethane inhibited mammary tumors, but indole-3-acetonitrile was not effective. All three indoles were effective in inhibiting BP-induced forestomach cancer in ICR/Ha mice when administered in the diet.

The naturally occurring aromatic isothiocyanates, benzyl isothiocyanate and phenethyl isothiocyanate, inhibited mammary carcinogenesis in female Sprague-Dawley rats when given orally (23–50 mg) two or four hours prior to DMBA, but had no effect when administered four hours after DMBA. Continuous administration of benzyl isothiocyanate or phenethyl isothiocyanate (5 mg/g diet) in a diet containing DMBA also inhibited forestomach and pulmonary carcinogenesis in ICR/Ha mice. Under similar conditions, administration of benzyl isothiocyanate in a diet containing BP also inhibited forestomach tumors in mice (135). The narrow time frame during which these compounds exert their anticarcinogenic effect suggests that they function during the state of initiation, but the mechanism has not been further characterized.

Flavone and naturally occurring methoxylated flavonoids such as tangeretin and nobiletin are also moderately powerful inducers of BP-hydroxylase in rodent tissues. In contrast, polyhydroxylated flavonoids, as exemplified by rutin (3,3',4',5,7-pentahydroxyflavone-3-rutinoside), by far the most abundant forms of flavonoids occurring in nature, are weak or noninducers (138). Because of the unavailability of many of these compounds in quantities sufficient for feeding studies, synthetic analogues such as β-naphthoflavone and quercetin pentamethyl ether have been used as models for natural flavonoids in studies on anticarcinogenesis. β-Naphthoflavone is a potent inducer, producing as much as a 53-fold elevation of BP-hydroxylase in mouse small intestine, with smaller increases observed in the lung and liver. Quercetin pentamethyl ether produced a 10–11-fold increase in the small intestine, a 3–3.8-fold increase in the lung, and no increase in the liver. Rutin produced a 3-fold increase of BP-hydroxylase in the small intestine, with no effect on lung or liver. The ability to induce BP-hydroxylase paralleled the potency of these compounds to inhibit BP-induced pulmonary adenoma formation in A/HeJ mice: a diet of 3 mg/g naphthoflavone almost completely blocked carcinogenicity; a diet of 5 mg/g quercetin pentamethyl ether blocked carcinogenicity about 50%; and rutin, at 5 mg/g diet, had no effect.

It is of interest to compare the in vivo results above with studies performed in vitro. Buening et al (8) observed that the addition of the polyhydroxylated flavonoids, apigenin, chrysin, fisetin, galangin, hesperitin, kaempferol, morin, myricetin, or naringenin, to a human liver microsomal system significantly inhibited its ability to hydroxylate BP. Addition of flavone, 5,6-benzoflavone (β-naphthoflavone), 7,8-benzoflavone (α-naphthoflavone), which contain no phenolic hydroxyl groups, or of nobiletin or tangeretin, in which all of the phenolic groups are methylated, resulted in increased BP hydroxylase activity. Flavanone, although not hydroxylated, caused inhibition. Flavone, nobiletin, tangeretin, and 7,8-benzoflavone also increased the microsomal metabolism of aflatoxin B_1 to 2,3-dihydro-2,3-dihydroxyaflatoxin B_1 and enhanced its metabolism to products mutagenic to *S. typhimurium* TA98. Quercetin, morin, and kaempferol are potent inhibitors of cytochrome c

(P-450) reductase, which indicates that the polyhydroxylated flavonoids may act by inhibiting the reduction of cytochrome P-450. Besides their inhibitory effects on BP metabolism, polyhydroxylated flavonoids also directly inhibited the mutagenicity of (±)7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo(*a*)pyrene (BP-7,8-diol-9,10-diol-9,10-epoxide-2), an ultimate mutagenic and carcinogenic metabolite of BP (42). Myricetin was especially effective in this regard, but flavonoids without hydroxyl groups or with methylated hydroxyl groups were ineffective. The antimutagenic activity of the hydroxylated flavonoids was apparently due to their direct interaction with the diol epoxide since myricetin, robinetin, and quercetin accelerated the disappearance of the mutagen from dioxane-water solutions at rates that correlated with their ability to inhibit mutagenicity.

Similar results were obtained with the plant phenols, ellagic acid, chlorogenic acid, caffeic acid, and ferulic acid (149). These compounds were shown to inhibit the mutagenicity of BP-7,8-diol-9,10-epoxide-2 in both *S. typhimurium* TA100 and in Chinese hamster V79 cells. As in the polyhydroxylated flavonoids, the plant phenols were shown to accelerate the disappearance of the mutagen from solution, with the rates of reaction being 100:1.1:0.6:0.3 for ellagic, chlorogenic, caffeic, and ferulic acids, respectively. The degree of reactivity with the diol epoxide paralleled the ability of the phenols to inhibit mutagenicity. Ellagic acid was by far the most powerful inhibitor, and in this respect was about 2–4-fold more effective than the polyhydroxylated flavonoid, myricetin (42). Two adducts of ellagic acid with BP-7,8-diol-9-10-epoxide-2 were identified as the *cis* and *trans* isomers, involving the hydroxyl on position 4 of ellagic acid and the C_{10} position of the BP moiety (105). Ellagic acid and, to lesser extent, ferulic acid and chlorogenic acid were active in inhibiting BP-induced pulmonary adenoma formation in A/J mice (62) when administered by i.p. injection; ellagic acid was effective also when fed in the diet. Ellagic acid, but not ferulic acid or chlorogenic acid, was effective in inhibiting DMBA-induced skin carcinogenesis in NMRI Swiss mice. Ellagic acid is a potent inhibitor of the epidermal metabolism of BP, of its DNA binding in liver and skin of BALB/c mice, and also of BP-induced skin carcinogenesis (78, 78a). These results are in general agreement with the data obtained from the above mutagenicity and chemical studies.

INHIBITION AT THE STAGE OF PROMOTION

Quercetin, applied topically to the skin of CD-1 mice at a level of 30 μmol per mouse, significantly inhibited the promoting effect of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) on skin tumor formation initiated by DMBA (56). Accompanying this effect was a dose-dependent inhibition of TPA-induced ornithine decarboxylase activity, but inhibition of TPA-induced

DNA synthesis was not observed. Similar effects on the inhibition of TPA actions were also obtained with morin, kaempferol, and fisetin (80). Quercetin strongly inhibits mouse skin lipoxygenase, an observation in agreement with previous studies on the inhibition, by various flavonoids, of lipoxygenase and prostaglandin synthetase (4), and its antipromotional activity could well be due to an effect at this locus.

Plant sterols, including β-sitosterol, stigmasterol, and campesterol, account for about 1% of the adult human diet; however, only about 5% of an orally administered dose of β-sitosterol was found to be absorbed in man. In studies with rats (14), administration of β-sitosterol in the diet at 200 ppm to F344 rats significantly reduced both the incidence and multiplicity of colon tumors due to the intrarectal administration of methylnitrosourea (MNU), a direct acting carcinogen that does not require metabolic activation. In these studies, β-sitosterol was also found to counteract the promoting activity of dietary cholic acid.

Recently, it was observed that administration of calcium salts reduced the toxicity of bile acids and of intestinal fatty acids (83). Additional research will be needed to determine whether or not calcium salts play a role in inhibiting the promoting effects of bile acids in carcinogenesis of the large bowel.

INHIBITION AT BOTH THE INITIATION AND POSTINITIATION STAGES

Protease Inhibitors

Results from various experimental approaches suggest that natural or synthetic products with antiprotease activity can protect against radiation-induced cell transformation in vitro as well as against spontaneous and radiation-induced or chemically-induced carcinogenesis in animals (57, 155, and references therein). Seed foods, soybeans, and soybean preparations are particularly rich in polypeptide protease inhibitors. The Bowman-Birk protease inhibitors, which bind to and inhibit both trypsin and chymotrypsin, and the Kunitz trypsin inhibitor remain unchanged by the food processing involved in canning chick peas and kidney beans, and in preparing soybean curd (tofu); these compounds also survive inactivation by stomach digestion in rodents (155). In vitro studies indicate that protease inhibitors may function as suppressors of both initiation and promotion (57); in animals, a major mechanism in protecting against carcinogenesis may involve a partial block of protein absorption, in turn leading to alterations in general or selective metabolic reactions (127).

Selenium and Vitamin E

In this review, "selenium" is used as a generic term. Experimentally, usually selenite or selenate are used; epidemiologically, in the human environment,

selenium is often present in organically bound forms such as selenomethionine.

Evidence relating selenium intake to an influence on the incidence of human cancer is largely suggestive. Epidemiologic studies indicate an increased incidence of colorectal and breast cancer in geographic regions where selenium is deficient (31, 52, 107, 110). However, in Finland, where the soil is deficient in selenium, the relatively low incidence of colon cancer could be explained in part by the fact that the Finns consume diets high in cereal fiber (53, 98), and their high level of fiber consumption may be a factor compensating for the effects of selenium deficiency on colon cancer. The blood of cancer patients generally contains less selenium than the blood of healthy individuals (103), but whether or not low blood selenium in cancer patients contributes to the disease or is an early effect of accompanying anorexia or cachexia cannot be determined.

Vitamin E is an important intracellular antioxidant and theoretically could inhibit carcinogenesis through decreased lipid peroxidation and/or increased detoxication of carcinogenic compounds. Another possibility is that vitamin E may affect the metabolism of selenium. Supplemental α-tocopherol and ascorbic acid reduced levels of fecal mutagenicity in individuals on a Western diet (23). However, no epidemiologic studies correlating vitamin E consumption and international cancer incidence rates have been reported. Because vitamin E is present in a variety of commonly consumed foods, it is difficult to identify population groups with substantially different levels of intake.

Beginning with the work of Clayton & Baumann (13), experimental evidence for the cancer inhibitory activity of selenium has been found in animal models in skin (109), liver (32), colon (48, 49), and mammary gland (43, 44, 69, 126). Jacobs et al (48) reported that 4 ppm of selenium in drinking water inhibited the induction of colon tumors in rats by 1,2-dimethylhydrazine (DMH), a carcinogen related chemically and metabolically to azoxymethane (27). Selenium (4 ppm) given in drinking water before DMH administration and during DMH treatment, reduced the colon tumor incidence in Sprague-Dawley rats fed an open-formula basal diet (Wayne Lab-Blox). New findings suggest a correlation between the tumor-inhibiting effect in the colon and the tissue concentration of selenium (1a).

Harr et al (35) reported that dietary supplementation with 0.5 or 2.0 ppm selenium delayed the development of 2-acetylaminofluorene-induced mammary and hepatic tumors in rats. Dietary selenium inhibited the postinitiation stage of methylnitrosourea-induced mammary carcinogenesis in female rats (126). Exposure of virgin C_3H mice to 2 ppm of selenium in their drinking water from weaning resulted in an 80% reduction of spontaneous mammary tumors compared to untreated controls (106).

The mechanism by which a dietary excess of selenium exerts its inhibitory effect is not completely understood, but the above animal studies suggest that in

certain organs selenium is effective at both the initiation phase and the postinitiation (promotion) phase.

Selenium was shown to have antimutagenic effects in bacterial and mammalian cells, effects that seem to be concentration dependent. Using the Ames *Salmonella*/mammalian microsome assay system, selenium reduced the mutagenicity of 2-acetylaminofluorene, DMBA, and 3,2'-dimethyl-4-aminobiphenyl (50, 67, 97).

Wattenberg (136) discussed a number of experimental studies analyzing the anticarcinogenic properties of α-tocopherol. Several of these studies suggest an inhibitory effect of vitamin E in mammary carcinogenesis (34, 136). A recent study by Cook & McNamara (19) indicated that 600 ppm of vitamin E in a diet containing 25% fat significantly inhibited DMH-induced colon adenocarcinomas in mice. In bacterial systems, vitamin E reduced DMBA-induced mutagenesis in the *Salmonella*/mammalian microsome assay system (97).

The interrelationships and synergistic effects of vitamin E and selenium have been well recognized in selenium nutrition (39). Selenium and vitamin E are involved in the inhibition of peroxidation of polyunsaturated fatty acids (PUFA). Several observations support a role for selenium and other antioxidants in the influence of PUFA on chemical carcinogenesis. Ip & Sinha (43) noted that 2.5 ppm of selenium, as sodium selenite, inhibited DMBA-induced mammary tumor induction in Sprague-Dawley rats, compared to controls with 0.1 ppm of selenium. This finding was made with diets containing 5 or 25% corn oil (carcinogen level, 5 mg DMBA) or with 24% hydrogenated coconut oil (plus 1% corn oil as source of essential fatty acids; carcinogen level, 10 mg DMBA); this suggests that the inhibitory effect of selenium is not mediated by its antioxidant properties. Further support for this view came from the fact that TBA values or glutathione peroxidase were hardly affected by the dietary selenium. Selenium deficiency increased mammary carcinogenesis in rats fed diets high in PUFA, but not in rats fed diets high in saturated fatty acids, with a dose of 5 mg of DMBA (44). However, with a dose of 10 or 15 mg of DMBA, the selenium deficiency led to more mammary cancers than with an adequate dietary selenium.

Although vitamin E and selenium have been studied primarily from the viewpoint of their antioxidant properties, recent evidence suggests that they may function in other, more subtle ways in vivo (5, 39, 125). Selenium per se is not an antioxidant (39) but may be a precursor of a compound or a complex capable of carrying out antioxidant functions (16). The general mechanisms involved may include the inhibition of lipid peroxidation, acceleration of peroxide decomposition, free radical scavenging, repair of molecular damage, and incorporation into enzymes with important protective functions for the cell (e.g. glutathione peroxidase) (5). The mechanism by which vitamin E inhibits lipid peroxidation may not be based simply on its antioxidant properties (16,

64, 120). Vitamin E can also act as a stabilizer of lipid-lipid and protein-lipid bonds. It is of interest that several derivatives of vitamin E without antioxidant properties, such as α-tocopherol acetate and α-tocoquinone can exert a protective effect against membrane lipid peroxidation. The consequences of lipid peroxidation, which include altered membrane function and production of toxic decomposition products, may be relevant at several levels of carcinogenesis. Peroxidation of PUFA produces malondialdehyde, a compound with enzyme-inhibiting properties and possibly mutagenic activity. In addition, the free radicals generated during lipid peroxidation could be involved in the activation of chemical carcinogens. Hence, antioxidants may serve as anticarcinogens by blocking the production of malondialdehyde, by inhibiting the free-radical-mediated activation of procarcinogens to reactive forms, and/or by increasing the detoxication of carcinogens. Since altered membrane properties are a characteristic of tumor cells, alterations in membrane phospholipids through peroxidation could be important in the later stages of tumor development (41).

Vitamin A and β-Carotene

Vitamin A is a nonspecific term referring to two different families of dietary factors, one comprising the various types of preformed vitamin A (mainly retinyl esters, retinol and retinal) and the other including various types of provitamin A, chiefly β-carotene (88). The various types of preformed vitamin A are converted efficiently by the human body into retinol, and a variable fraction of dietary β-carotene is converted in the human intestine into retinal.

At least two epidemiologic studies have reported that low serum retinol levels are associated with an increased risk of cancer (55, 131). Both of these were retrospective-prospective case-control studies in which vitamin A levels were measured in serum samples that had been collected and stored frozen from individuals in whom cancer subsequently developed, and from suitable matched controls. Other studies conducted in India, Pakistan, East Africa, United Kingdom, and the United States suggest that blood retinol or β-carotene levels are lower in patients with cancers of the oral cavity, nasopharyngeal cavity, lung, and gastrointestinal tract (88). However, the association of low serum retinol levels with an increased cancer risk was not confirmed in another study (88).

Peto et al (88) concluded that the risk of cancer in humans may be inversely correlated both with the level of retinol in blood and with the dietary intake of β-carotene. However, a recent unpublished study in Brazil, where β-carotene-rich palm oil is consumed, failed to find a protective effect. Recent case-control studies suggest that the index of β-carotene consumption is negatively associated with the risk of cancer of the cervix (66), dysplasia, and carcinoma in situ (150). Shekelle et al (111) and Bjelke (6) found that intake of dietary carotene or vitamin A was inversely related to lung cancer incidence. The mechanism of

this effect may not depend on the provitamin A activity of the carotenoids, but could be due to the intrinsic activity of β-carotene. Therefore, prudent nutritional practice should involve selecting foods from each of several major groups, including the vegetables and fruits that contain substantial amounts of β-carotene. Regular intake of yellow-green vegetables has been correlated with a protective effect against a number of different types of cancer (6, 30, 38).

There is some evidence in animal models that vitamin A inhibits tumor induction. Retinyl acetate inhibited experimental oral cancer in hamsters when administered after precancerous oral lesions had developed and carcinomas had begun to form (9). This finding is of some significance in the overall management of human oral leukoplakia of the precancerous variety, especially when lesions are extensive.

The importance of vitamin A compounds in the inhibition of cancer has been supported by studies in breast cancer models (76, 77, 145). Retinyl acetate feeding can suppress the development of DMBA- and methylnitrosourea-induced mammary cancers in rats (77, 145). Retinol acetate inhibited microsomal lipid peroxidation and provided partial protection against a lethal dose of dioxin (TCDD) in female Sprague-Dawley rats (120).

Dietary Fiber

Burkitt (10) observed that populations consuming a diet rich in fiber have a low incidence of colon cancer, whereas those eating refined carbohydrates with little fiber have a higher incidence of the disease. In several populations consuming diets high in total fat, dietary fiber acts as a protective factor for colon cancer risk. Recent studies comparing rural and urban populations in Finland, Denmark, and Sweden, and urban populations in New York, indicated that one of the factors contributing to the low risk of colon cancer in rural Scandinavia, in contrast to New York, appears to be high dietary fiber intake that is mainly in the form of whole-grain cereals, even though all of these populations have a high fat intake (53, 96, 98). Likewise, the lower colon cancer risk in Seventh Day Adventist vegetarians or in omnivorous Latter Day Saints (Mormon) might stem from a higher cereal fiber intake, which increases stool bulk (65, 90, 113).

Fiber comprises a heterogenous group of carbohydrate compounds including cellulose, hemicellulose, pectin, and a noncarbohydrate substance, lignin, that are resistant to digestion in the gastrointestinal tract.

The protective effect of dietary fiber depends on the composition and source of fiber in the diet (94). The protective effect of dietary fiber may be due to adsorption, dilution, and/or the inhibition of the metabolism of cocarcinogens, promoters, and yet-to-be identified carcinogens by fiber components. In the stool, different types of nonnutritive fiber could bind the tumorigenic compounds, alter the enterohepatic circulation of their metabolites, and act by

diluting potential carcinogens and cocarcinogens through a bulking effect. Thus, those humans consuming relatively large amounts of certain fibers would have greater protection against carcinogenic and cocarcinogenic compounds than individuals consuming lesser quantities of these fibers.

Although the concept of dietary fiber as a protective factor in human colon carcinogenesis appears well established, studies examining the possible role of various types of dietary fiber in animal models provide conflicting results (94). Such discrepancies might in part be due to the nature of the carcinogen used, to differences in the susceptibility of rat strains to the carcinogen, to variation in the composition of diets, to qualitative and quantitative differences in administered intact fibers and their components, to differences in food intake by the animals, and/or to differences in experimental design and duration of the experiment. In general, high amounts of fiber, such as 20%, in the diet may have a dual effect: (*a*) protective, because of larger stool bulk that can result in the dilution of carcinogens or promoters (84, 94), and (*b*) enhancing, because of luminal surface irritation that can result in increased cell turnover rates favoring carcinogenesis (128).

In a study by Bauer et al (3) groups of rats were fed a fiber-free diet or a diet containing 20% wheat bran from 3 days prior to the first injection of a colon carcinogen (DMH) until 14 days after the last injection. They were then transferred to standard rat pellet diet for about 10–12 weeks before sacrifice. No difference was found in the incidence of colorectal tumors among the dietary treatments. In another study (47), colon adenomas and adenocarcinomas were increased in rats fed a 20% wheat bran diet during DMH treatment compared to those fed a fiber-free diet. However, inhibition of colon tumors occurred in rats fed the 20% wheat bran diet after the carcinogen treatment.

The effect of a diet containing 15% alfalfa, wheat bran, or citrus fiber on colon carcinogenesis by the i.r. administration of methylnitrosourea, a direct-acting carcinogen that does not require metabolic activation, and by the s.c. administration of azoxymethane, a procarcinogen (27), was studied in F344 rats (100, 134). The animals fed the 15% alfalfa diet and treated with methylnitrosourea had a higher incidence of colon tumors than those fed a control diet containing only 5% cellulose or 15% wheat bran. The incidence of colon tumors induced by azoxymethane in rats fed a diet containing wheat bran or dehydrated citrus fiber was lower than that in rats fed a control diet.

The influence of dietary fiber components on colon cancer has also been studied. Freeman (29) compared the incidence of colon tumors induced by DMH in Sprague-Dawley rats fed either a fiber-free diet or a diet containing 4.5% purified cellulose or pectin. Those animals ingesting cellulose had fewer colonic neoplasms, and the total number of colon tumors in this group was lower than in the groups on the pectin or fiber-free diets. The effect of a diet containing 15% pectin on colon carcinogenesis by methylnitrosourea and

azoxymethane was studied in F344 rats by Watanabe et al (134). Pectin greatly inhibited the incidence of colon tumor induced by azoxymethane, but not the yield of colon tumors induced by methylnitrosourea. Reddy et al (99) showed that the incidence and multiplicity of small intestinal tumors as well as the multiplicity of colon adenocarcinomas induced by the procarcinogen 3,2'-dimethyl-4-aminobiphenyl were lower in F344 rats fed a 7.5% lignin diet than in rats fed the control diet containing 5% cellulose. These results emphasize that the effect of fiber components in colon carcinogenesis depends on the type of carcinogen used as well as the composition of the fiber. Such experiments provide background information to delineate the underlying relevant mechanisms.

CONCLUSION

Inspired to a great degree by the pioneering work of Wattenberg (136, 137), interest in and research activity on chemicals and dietary components that inhibit the carcinogenic process are increasing. A large body of data has accumulated on this subject. Unfortunately, in most instances, the actions of such agents are still only imperfectly understood. International population studies, experimental laboratory studies, and animal models yield information on the causative and promoting elements of the main human cancers linked with nutrition. Some of the traditional diets consumed in parts of the world (such as the Orient, parts of Latin America, Northern and Eastern Europe) that involve smoked, salted, and pickled foods present a high risk for head and neck and stomach cancers. These diseases have a lower incidence in the United States. Studies of migrants from high-risk regions to those of lower risk determined that the lower risk ensues from consuming yellow and green vegetables more frequently. This general finding led to investigating which specific elements within the group of yellow-green vegetables confer protection.

In contrast, when applying the same experimental techniques to consideration of the high risk for cancers of the colon, breast, prostate, ovary, endometrium, and also pancreas incurred by people in the Western world, particularly the United States, the results suggested that the major factor associated with the traditional Western diet is the total fat level, amounting to 40% or more. However, within populations of the Western World, protective elements were noted, namely, the regular intake of cabbage or other yellow-green and cruciferous vegetables. There are substantial data supporting these findings in specific animal models for cancer of the breast and large bowel. Additionally, cereal fibers decrease the risk for large bowel cancer by increasing stool bulk.

In this review, we described compounds, limited to those occurring naturally in various foods, that can protect against carcinogenesis by minimizing carci-

nogen formation, or by inhibiting events at the stages of cancer initiation and postinitiation. In following this particular format, we attempted to emphasize the mechanistic aspects of the subject, in the belief that an understanding of the mechanism of action of compounds influencing carcinogenesis will lead not only to the identification and/or development of more effective chemopreventive agents, but also to a better understanding of the complex relationships between diet and cancer, as well as of carcinogenesis in general.

Much research still remains to be done in this important area. In particular, the question of dose response in animal models needs to be thoroughly investigated so that the impact of dietary anticarcinogens on the human situation can be more exactly defined. Also, better collaborations between cancer researchers, phytochemists, nutritionists, and organic chemists might help to establish more complete structure-activity relationships for naturally occurring anticarcinogens. It is also important not to be overly enthusiastic about the positive effects of chemicals with anticarcinogenic properties but to maintain objectivity with the view of determining other, possibly adverse, effects. Together with information as to mechanisms at the molecular level, such bases of knowledge could permit future investigations deliberately and rationally to seek out protective agents that may truly provide an effective means of prevention of prevalent forms of human cancer.

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