17 Diet and Carcinogenesis

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17.1 INTRODUCTION

It has been estimated that up to 70% of all cancers are attributed to diet.1 It is often believed that food and nutrition affect cancer risk only because diets may contain specific carcinogenic substances. Although various carcinogens have been identified in foods and beverages, these appear to contribute only slightly to the overall impact of diet on cancer risk. The most important effect of diet may be mediated by substances present in food that inhibit the cancer process. Nearly 200 studies in the epidemiologic literature have been reviewed and relate, with great consistency, the lack of adequate consumption of fruits and vegetables to the incidence of cancer.2-4 The quarter of the population with the lowest dietary intake of fruits and vegetables compared to the quarter with the highest intake has roughly twice the cancer rate for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix and ovary).5 Many components of fruits and vegetables may be responsible for the protective effect: bioactive compounds, micronutrients, fiber, and low caloric intake.
Bioactive compounds and micronutrients can affect carcinogen metabolism. Virtually all dietary or environmental carcinogens to which humans are exposed require enzymatic transformation, known as metabolic activation, to exert their carcinogenic effects. The most common enzymatic process is the addition of oxygen catalyzed by cytochrome P450 enzymes. This type of transformation is referred to as Phase I metabolism and generally makes the molecule more polar and consequently more readily excreted. Some of the intermediates formed in this process may be electrophiles, which can react with nucleophilic sites in critical macromolecules such as DNA, RNA, and protein. Reaction with these macromolecules results in covalent binding products called adducts. DNA adducts that persist unrepaired can cause miscoding and thus produce mutations in critical genes such as oncogenes and tumor suppressor genes. Competing with metabolic activation is detoxification. Some of the Phase I metabolites are detoxified because the addition of oxygen renders them less reactive toward macromolecules than the parent carcinogen. Numerous constituents of plant foods, including flavonoids, isothiocyanates, and allyl sulfides, have been found to be potent modulators of the cytochrome P450 monooxygenases in vitro and in animal models. Dietary components can impede carcinogenesis by blocking metabolic activation, increasing detoxification, or by providing alternative targets for the electrophilic metabolites. A second group of enzymes known as Phase II enzymes adds polar moieties to the oxygenated carcinogen, generally producing highly polar molecules that are readily excreted. Examples include acetyltransferases, glutathione-S-transferases, UDP-glucoronyl transferases, and sulfotransferases. Various components of fruits and vegetables have been shown to affect Phase II enzyme activities.

17.2 DIETARY CARCINOGENS

Carcinogens present in food or as a result of cooking practices include aflatoxins, N-nitroso compounds, polycyclic aromatic hydrocarbons, and heterocyclic amines. Aflatoxin is a generic term for a group of fungal metabolites produced by Aspergillus flavus and A. parasiticus. The most widely studied of the aflatoxin compounds is aflatoxin B1, which can be found in moldy peanuts. Consumption of aflatoxin B1 has been associated with an increased risk of liver cancer in humans. Furthermore, the discovery of an aflatoxin-bound guanine adduct in human DNA and the high correlation between urinary excretion of this adduct and aflatoxin B1 intake further support the relationship between aflatoxin intake and cancer susceptibility.

Nitrites and nitrates are often used as preservatives in meats and other "cured" products. Nitrites and nitrates are not carcinogenic in experimental animals. However, nitrate can be reduced to nitrite, which can interact with dietary substances such as amines or amides to produce N-nitroso compounds. N-nitroso compounds are potent carcinogens in animals. In a study in 24 countries, high urinary nitrate concentrations were associated with increased stomach cancer mortality. Nitrate is also present in large quantities in vegetables. However, concomitant intake of various antioxidants in fresh vegetables prevents oxidation of nitrate to nitrite and counteracts any cancer risk.
Two cooking-derived classes of carcinogens have been shown to induce cancer in animal models. The first class is the polycyclic aromatic hydrocarbons associated with barbecued meats. These compounds are formed from the pyrolysis of fats that occurs when fat drips from the meat onto the coals, forming smoke that is redeposited on the meat surface. A fairly consistent association between grilled fish and meat and stomach cancer suggests that dietary exposure to polycyclic aromatic hydrocarbons may be involved in human gastric carcinogenesis.\textsuperscript{9}

Another class of compounds found in cooked meats are the heterocyclic amines. Amino acid and creatine precursors in meat react chemically to produce these carcinogens during high-temperature cooking by a variety of methods such as broiling, frying, barbecuing, and baking. The major carcinogenic heterocyclic amine found in the Western diet is 2-amino-1-methyl-6-phenylimidazo[4,5-\textit{b}]pyridine (PhIP); it has been shown to induce cancer in the mammary gland, colon, and prostate gland of rat — three organ sites that show a relatively high incidence of cancer in the Western world.\textsuperscript{14-17} Although the concentration of heterocyclic amines in the diet of individuals consuming cooked meat are in the part per billion range, significantly lower than the concentration shown to induce cancer in laboratory animals, heterocyclic amines are regarded as possible human carcinogens.\textsuperscript{16,17}

17.3 ALLIUM COMPOUNDS

The allium vegetable family includes onions, garlic, scallions, chives, and leeks. These vegetables have high concentrations of compounds such as diallyl sulfide and allyl methyl trisulfide.\textsuperscript{18} These compounds have been shown to inhibit cell proliferation and growth, enhance the immune system, alter carcinogen activation, stimulate detoxification enzymes, and reduce carcinogen-DNA binding.\textsuperscript{19-22} The direct effect of diet on DNA adduct formation has been tested by using supplemental garlic. Hageman et al.\textsuperscript{23} examined the effects of supplemental garlic consumption on ex vivo production of benzo[a]pyrene-DNA adducts in lymphocytes. In a nonrandomized pilot study of 9 men, isolated lymphocytes from the blood of participants eating garlic (3 g raw garlic per day for 8 days) developed fewer adducts when incubated with benzo[a]pyrene.\textsuperscript{23} Various studies have shown that garlic can slow the development of bladder, skin, stomach, and colon cancers. A prospective study of 42,000 Iowa women aged 55 to 69 revealed that garlic consumption was inversely associated with cancer risk. Risk of cancer in the distal colon was 50% lower in women with the highest consumption of garlic than in women who did not consume garlic.\textsuperscript{24}

Several lines of evidence support the ability of allium compounds present in garlic to inhibit the synthesis of $N$-nitroso compounds.\textsuperscript{25,26} Habitual consumption of garlic has been reported to correlate with a reduction in gastric nitrite content and reduction in gastric cancer mortality.\textsuperscript{27,28} Additional support for an effect of garlic on nitrosamine formation comes from a human study in which 5 g of fresh garlic consumption markedly suppressed urinary excretion of $N$-nitrosoproline in individuals given supplemental nitrate and proline.\textsuperscript{25} Two ecological studies showed that, in areas where garlic or onion production is very high, mortality rates for stomach cancer is very low.\textsuperscript{9}
17.4 ISOThIOCYANATES AND INDOLES

Isothiocyanates and indoles are released upon chewing of certain cruciferous vegetables, in which they occur as thioglucoside conjugates called glucosinolates. Vegetables of the *Brassica* genus, including cabbage, kale, broccoli, cauliflower, Brussels sprouts, and root crops such as turnips and rutabagas contribute most to the intake of glucosinolates. Many experimental studies have shown that indoles and isothiocyanates given to animals after a carcinogen insult reduced tumor incidence and multiplicity at a number of sites including the liver, mammary gland, and colon.\textsuperscript{29-31} For example, phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphane are effective inhibitors of cancer induction in rodents treated with carcinogens.\textsuperscript{32} A possible inhibitory activity of isothiocyanates and indoles against tumorigenesis apparently stems from their ability to influence Phase I and Phase II biotransformation enzyme activities.\textsuperscript{33-35} Sulforaphane, which is present in broccoli, is a potent inducer of the Phase II detoxification enzymes quinone reductase and glutathione transferase, and an inhibitor of the carcinogen-activating cytochrome P450E1.\textsuperscript{36,37} The effectiveness of sulforaphane in blocking the formation of mammary tumors in rats administered a chemical carcinogen has been demonstrated.\textsuperscript{38}

Indole-3-carbinol can lead to marked increases in the activities of cytochrome P450-dependent monooxygenases as well as induction of glutathione transferase.\textsuperscript{39,40} Recent studies have shown that estrogens are metabolized by specific isozymes of cytochrome P450. Indole-3-carbinol has been shown to have beneficial effects because of alterations in estrogen metabolism. Because the formation of different estrogen metabolites is linked to breast and uterine cancer, the use of indole-3-carbinol in women has produced a beneficial effect through a modification of estrogen metabolism. It appears that indole-3-carbinol may be a very useful preventive agent against hormone-related cancers.\textsuperscript{41}

17.5 PHYTOESTROGENS

Phytoestrogens are naturally occurring plant compounds with estrogenic or anti-estrogenic activity. They are heterocyclic phenols with structural similarities to estrogenic steroids and are constituents of many foods including cabbage, spinach, soy beans, and other soy products, sprouts, grains, and hops.\textsuperscript{42} There are three main groups of phytoestrogens, the isoflavones, coumestans, and lignans.\textsuperscript{42} Isoflavones occur mainly in soybean and whole grain products, various seeds, and seed-containing berries. Some specific isoflavones include genistein, daidzein, and the precursors formononetin and biochanin A.\textsuperscript{9} Phytoestrogens have been shown to bind to isolated estrogen receptors and cause proliferation and gene transactivation responses in vitro.\textsuperscript{42} Some phytoestrogens are structurally similar to tamoxifen, a drug that is being used to successfully treat some types of breast cancer and is currently being tested for cancer prevention in high-risk women.\textsuperscript{18} Genistein, which possesses weak estrogenic activity, has been shown to act in animal models as an anti-estrogen.\textsuperscript{43} *In vitro*, genistein suppresses the growth of a wide range of cancer cells.\textsuperscript{9} In humans, preliminary data indicate plasma concentrations of genistein can reach the low
micromole per liter range, values similar to those required to inhibit in vitro cancer cell growth.\textsuperscript{43}

Other biological activities of phytoestrogens have been described, in addition to their hormonal properties, which may be important in explaining their biological effects. For example, genistein and daidzein have antioxidant properties and are potent scavengers of hydrogen peroxide.\textsuperscript{44} In vitro, genistein inhibits the action of several enzymes involved with tumor growth and development, including enzymes that phosphorylate tyrosine residues on key proteins involved in signal transduction events in normal and tumor cells; it also inhibits DNA topoisomerases and other critical enzymes involved in signal transduction.\textsuperscript{45,46} Genistein and biochanin A have also been shown to induce apoptosis of tumor cells.\textsuperscript{47}

\textbf{17.6 FLAVONOIDS}

Over 4000 flavonoids have been identified in plants. These universal plant pigments are responsible for the colors of flowers, fruits, and sometimes leaves.\textsuperscript{48} Flavonoids are a group of polyphenolic antioxidant compounds with cancer-blocking properties. Flavonoids are present in a wide variety of fruits, vegetables, nuts, whole seeds, spices, tea, and wine. Flavonoids have a common skeleton of diphenyl pyrons, two benzene rings linked through a heterocyclic pyran or pyrone ring. The basic ring structure allows a multitude of substitution patterns giving rise to flavonoids, flavones, catechins, anthocyanadines, and isoflavonoids. Flavonoids have differing antioxidant properties depending upon the degree of hydroxylation of the benzene rings; this property may provide one anticarcinogenic mechanism.\textsuperscript{9,49}

Quercetin is the major flavonoid in vegetables, fruits, and wine. Other common flavonoids include kaempferol, catechin, epicatechin gallate, chrysins, and cyanidin. Flavonoids may defend cells against carcinogens via their ability to increase the pump-mediated efflux of carcinogens from cells or via induction of detoxification enzymes.\textsuperscript{49,51} Quercetin may also interact with specific carcinogens in the gastrointestinal tract, thereby reducing their bioavailability, and may reduce cell proliferation.\textsuperscript{52}

\textbf{17.7 LIMONEN}

Monoterpenes are natural plant products found in the essential oils of many commonly consumed fruits and vegetables. They have been widely used for nearly 50 years as flavor and fragrance additives in food and beverages. A number of recent studies have shown that monoterpenes possess antitumorigenic activities and suggest that these compounds represent a new class of agents for cancer chemoprevention.\textsuperscript{53,54} Limonene, the simplest monocyclic monoterpane, and perillyl alcohol, a hydroxylated limonene analog, have demonstrated chemopreventive and chemotherapeutic activity against mammary, skin, lung, pancreas, and colon tumors in rodent models.\textsuperscript{54-57} They are capable of increasing tumor latency, decreasing tumor multiplicity, and causing regression of mammary carcinomas.\textsuperscript{58,59} Because monoterpenes do not cause systemic toxicity at the doses required to induce regression of mammary tumors, they are currently being tested in Phase I clinical trials on advanced cancer patients in the U.S. and the U.K.\textsuperscript{60,61}
17.8 HERBS

A variety of herbs and herbal extracts contain different phytochemicals that have been shown to be protective against cancer, including the flavonoids, lignans, sulfides, polyphenolics, carotenoids, coumains, saponins, cucumins, and phthalides. The botanical term herb refers to seed-producing plants with nonwoody stems that die down at the end of the growing season. As mentioned above, flavonoids are antioxidants and may induce carcinogen detoxification enzymes. Many commonly used herbs contain substantial amounts of flavonoid antioxidants. These include chamomile, dandelion, ginkgo, green tea, hawthorn, licorice, passionflower, milk thistle, rosemary, sage, thyme, and yarrow. In addition to the flavonoids, a variety of phenolic compounds, are present in many herbs. These phenolic compounds (such as caffeic, ellagic, and ferulic acids, sesamol, and vanillin) are also potent antioxidants and inhibit carcinogenic activity.

Flaxseed contains a rich supply of lignans. These plant lignans are converted to mammalian lignans by bacterial fermentation in the colon and they can act as estrogens. Mammalian lignans appear to be anticarcinogenic; lignan metabolites bear a structural similarity to estrogens and can bind to estrogen receptors and inhibit the growth of estrogen-stimulated breast cancer. Urinary excretion of lignans is reduced in women with breast cancer, whereas the consumption of flaxseed powder increases urinary concentration of lignans severalfold.

Eugenol is the principal constituent (70 to 90%) of the essential oil of clove and is also present in many essential oils of plants, especially basil, cinnamon, and nutmeg. Eugenol has been shown to offer protection against liver cancer in rats and to inhibit lipid peroxidation.

Turmeric is derived from the rhizome of a plant in the ginger family and is the major ingredient in curry powders. Curcumin is the principal compound and the major yellow pigment in turmeric and curry. Curcumin is a phenolic compound that is a strong antioxidant, free-radical scavenger, and a potent inhibitor of nitrosation. Turmeric/curcumin has been shown to suppress the development of stomach, breast, lung, and skin tumors. Studies of humans at risk of palatal cancer because of reverse smoking showed that turmeric (1 g/day for 9 months) had a significant impact on the regression of precancerous lesions.

Turmeric also contains a bioactive peptide, turmerin, which makes up 0.1% of its dry weight. Turmerin has been shown, in vitro, to be a strong antioxidant, a DNA-protectant against oxidative injury, and an antimutagen. It has also been shown to decrease arachadonic release, which may be an important event in membrane-mediated chromosomal damage.

17.9 CAROTENOIDS

Carotenoids constitute a class of over 600 natural compounds occurring predominantly in fruits and vegetables. Some carotenoids such as β-carotene are provitamin A compounds that can be converted into vitamin A in vivo. β-carotene is the most abundant carotenoid and is found notably in orange colored vegetables and fruits and in dark green leafy vegetables, including carrots, pumpkin, winter squash, sweet
potatoes, cantaloupe, apricots, mangoes, kale, spinach, and collard greens.\textsuperscript{18} Carotenoids are present in all foods that contain chlorophyll, and they appear to be the plants’ main defense against singlet oxygen generated as a byproduct of the interaction of light and chlorophyll.\textsuperscript{70} Many carotenoids are potent antioxidants enabling them to neutralize free radicals generated as byproducts of oxidative metabolism in the body or derived from exogenous sources such as cigarette smoking. Free radicals can attack and damage RNA and DNA in cells, as well as inactivate proteins and enzymes by reactions with amino acids. For example, Collins et al. observed an inverse correlation between the frequency of oxidized bases in lymphocyte DNA, an indicator of oxidative stress, and concentrations of carotenoids in blood.\textsuperscript{71} Carotenoids have been shown to be anticarcinogens in rats and mice and may be anticarcinogens in humans.\textsuperscript{72,73}

Although initially β-carotene was thought to exert antioxidant effects potentially suitable for chemoprevention, subsequent basic studies have shown that β-carotene can exert pro-oxidant effects under high oxygen pressures and oxidative stress, such as those occurring in the lung of smokers.\textsuperscript{74,75} This latter finding may help explain the significantly increased risk of lung cancer that was associated with β-carotene in current smokers involved in recent epidemiologic studies.\textsuperscript{76,77} For example, in a large trial carried out in Finland, a significant increase of 18\% in lung cancer incidence was seen among those participants (all smokers) who received β-carotene over a period of 5 to 8 years, compared with those not receiving the carotenoids.\textsuperscript{76} Soon after the publication of this report, another trial (the Beta-Carotene and Retinol Efficacy Trial [CARET], investigating a high-risk population of smokers and/or asbestos workers) was prematurely halted when a trend towards increased incidence of cancer with β-carotene supplementation became evident.\textsuperscript{77}

Tomatoes, watermelon, pink grapefruit, and guava are particularly rich in a red pigment, lycopene, another antioxidant carotenoid.\textsuperscript{78} Recent work demonstrates that lycopene is a more active inhibitor of human cancer cell proliferation than β-carotene.\textsuperscript{73} In vitro, lycopene has been shown to be the most efficient quencher of singlet oxygen among the carotenoids. Investigators have also shown lycopene to inhibit the proliferation of breast, lung, and endometrial human cancer cells in culture.\textsuperscript{73} Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene.\textsuperscript{79}

Another potential mechanism whereby carotenoids may protect against cancer susceptibility involves the formation of retinol and its subsequent role in the regulation of epithelial cell differentiation.\textsuperscript{18} Because lack of proper differentiation is a feature of cancer cells, adequate vitamin A (from either carotenoids or retinol) may allow normal cell differentiation and thus avoid the development of cancer.\textsuperscript{9,18}

There are other biological functions of carotenoids that may be involved in cancer prevention. Many of the carotenoids (β-carotene, canthaxanthin, lutein, lycopene, and α-carotene) have been found to upregulate gap junctional intracellular communication via changes in gene expression.\textsuperscript{80,81} Enhanced cell-to-cell communication would restrict clonal expansion of initiated cells, decreasing the likelihood of cancer occurrence. Furthermore, β-carotene and α-carotene may inhibit cell proliferation and β-carotene may enhance immune function.\textsuperscript{82-84}
17.10 VITAMIN C

Vitamin C is the most abundant water-soluble antioxidant in the body and is unique in that it can be regenerated when oxidized.\(^9\) Specific food sources include citrus fruits, mangoes, papaya, banana, strawberries, melon, broccoli, cabbage, and other green leafy vegetables, peppers, tomatoes, pumpkin, and yams.\(^9\) Epidemiologic studies have indicated relatively consistent inverse associations of vitamin C with stomach cancer, oral cancer, and cancer of the esophagus.\(^8,5\) A cohort study of plasma antioxidant concentrations in Swiss men found that vitamin C concentrations were about 10% lower at baseline (\(p < .01\)) in men that subsequently died from any type of cancer than in those who did not.\(^8,6\)

Via its antioxidant function, vitamin C is able to detoxify carcinogens and may protect cell membranes and DNA from oxidative damage.\(^9\) In humans, supplementation with 100 mg/day has been shown to minimize oxidative damage in lymphocyte DNA.\(^8,7-8,9\)

Vitamin C has also been shown to scavenge and reduce nitrite, thus reducing substrate availability for the formation of N-nitroso compounds. Ascorbic acid supplementation and addition of ascorbic acid-rich foods to a controlled experimental diet have been shown to inhibit endogenous formation of N-nitroso compounds in humans.\(^9,0\) In a controlled dietary study conducted in China, supplements of 75 mg ascorbic acid for 2 days, reduced urinary excretion of N-nitrosoproline by 44%.\(^9,0\)

17.11 VITAMIN E

Vitamin E, the most important antioxidant found within lipid membranes in the body, comes primarily from dietary vegetable oils (including safflower, corn, cottonseed, and soy bean oils) and nuts. Vitamin E occurs in food as compounds called tocopherols and tocotrienols. \(\alpha\)-Tocopherol, the main form of Vitamin E in the U.S. diet, protects polyunsaturated fatty acids in cell membranes from oxidation by scavenging oxygen radicals and terminating free-radical chain reactions. Oxidation results in the production of malondialdehyde, which is possibly mutagenic, and free radicals, which can induce damage in DNA.\(^9\) Vitamin E also functions to keep carotenoids in a reduced state, thereby enhancing their antioxidant capacity, and decreases the formation of nitrosamines in the stomach.\(^9,2,9,3\) Finally, vitamin E also may prevent cancer progression by increasing production of humoral antibodies and enhancing cell-mediated immunity. Humans taking vitamin E supplements (200 U.I./day) for 10 years reduced their risk of colonic cancer by approximately half and evidence suggests a marked protective effect of a supplement (50 U/day) on prostate cancer.\(^9,4,9,6\) Vitamin E also enhances the immune system in humans.\(^9,7\)

17.12 FOLATE

Folate (folic acid) is so-called because it is abundant in foliage (green leafy vegetables). The importance of folate in cancer protection was first demonstrated in animal studies when folate deficiency was linked to enhanced chemically induced carcinogenesis and subsequently in humans in relation to cervical dysplasia and
colon cancer.\textsuperscript{98-100} More recently, the importance of folate for the maintenance of genetic stability and for control of gene expression has further highlighted the potential importance of folate in cancer protection.\textsuperscript{98} Folate, which is central to methyl-group metabolism, may influence both methylation of DNA and the available nucleotide pool for DNA replication and repair. Inadequate intake of folic acid may lead to reduced methylation of cytosine in cytosine-guanine sequences of DNA which, if hypomethylated, may lead to enhanced expression of specific oncogenes.\textsuperscript{99,100}

Folate deficiency, a common deficiency in people who eat few fruits and vegetables, causes chromosome breaks in human genes because of deficient methylation of uracil to thymine, and subsequent incorporation of uracil into human DNA.\textsuperscript{101} Uracil in DNA is excised by a repair glycosylase with the formation of a transient single-strand break in the DNA; two opposing single-strand breaks cause a double-strand chromosome break, which is difficult to repair. Both high DNA uracil concentrations and chromosome breaks in humans are reversed by folate administration.\textsuperscript{101} Folate supplementation above the Recommended Dietary Allowance value minimized chromosome breakage in human genes.\textsuperscript{102} The potential role in human carcinogenesis of uracil misincorporation is supported by two recent studies that show a two- to fourfold lower risk of colon cancer in individuals who are homozygous for the mutant alleles of methylenetetrahydrololate reductase.\textsuperscript{103,104}

17.13 SELENIUM

Other potentially anticarcinogenic substances are not limited to one type of vegetable or fruit but are more widespread. Selenium is found in produce in amounts proportional to the selenium content of the soil in which it is grown. Plants are capable of converting inorganic selenium in soil to organic selenium compounds following the sulfur assimilatory scheme.\textsuperscript{105} For example, seleniferous wheat is known to contain selenomethionine as a major source of selenium.\textsuperscript{106} In some species of Astragalus that accumulate high concentrations of selenium, methylated derivatives such as S-methylselenocysteine, have been isolated.\textsuperscript{105} Selenium is an essential trace element for human health and has received considerable attention for its possible role as an effective, naturally occurring, anticarcinogenic agent. Epidemiologic studies reveal that selenium intake correlates inversely with the mortality from various types of cancer and suggest an increased risk of colon cancer in humans in geographic areas where selenium is low in the soil.\textsuperscript{107-109} In a recent study by Clark et al.,\textsuperscript{109} selenium supplementation reduced the incidence of, and mortality from, carcinomas at several sites in the body including the colon. Diets high in selenium have been shown to suppress carcinogenesis in many different animal tumor models.\textsuperscript{110-115}

However, the chemopreventive effect of selenium depends on its chemical form. For example, we recently observed that 3,2'-dimethyl-4-aminobiphenyl (DMABP)-induced aberrant crypt formation (a preneoplastic lesion for colon cancer) decreased significantly in rats supplemented with 0.1 or 2.0 mg selenium per kilogram of diet as selenite or selenomethionine, but not as selenomethionine, compared to animals fed a selenium-deficient diet (Figure 17.1).\textsuperscript{114}
The biochemical basis for the protective effect of selenium in cancer is unknown. The selenium-containing antioxidant enzymes, glutathione peroxidase and thioredoxin reductase, may be involved.\(^{116}\) Because of the role of glutathione peroxidase in reactive oxygen metabolism, it has been hypothesized by many that changes in glutathione peroxidase activity would provide the mechanism for the chemopreventive activity of selenium. However, it has been found that glutathione peroxidase activity was already at maximum concentrations in tissues of animals fed normal selenium and did not change appreciably as dietary selenium was increased to the ten-fold higher concentrations needed to observe chemopreventive effects in animal models.\(^{117}\) In contrast, various studies have shown that selenite increases the activity of another antioxidant enzyme, thioredoxin reductase, in human cancer cells and in rats fed supranutritional concentrations of selenite.\(^{117}\) In addition to its role in antioxidation, selenium has been shown to suppress cell proliferation and stimulate apoptosis.\(^{118,119}\)

Various forms of selenium have also been shown to alter the metabolism of carcinogens and to inhibit the formation of carcinogen-DNA adducts.\(^{120,121}\) We recently observed that supplementation with either a 0.1 or 2.0 mg selenium per kilogram diet as either selenite or selenate, but not as selenomethionine, resulted in significantly fewer (53 to 70%, \(p < .05\)) DMABP-DNA adducts in the colon, but not in the liver, than in rats fed a selenium-deficient diet.\(^{121}\) This reduction in DMABP-DNA adduct formation in the colon correlates with a reduction in DMABP-induced
aberrant crypt foci. The protective effect of selenite and selenate against DMABP-DNA adduct formation apparently is not a result of alterations in plasma or liver selenium concentrations or altered glutathione peroxidase or glutathione transferase activities, but may be related to differences in the metabolism of the different forms of selenium.\textsuperscript{121}

Although most chemoprevention studies in animals have used inorganic selenite as the source of selenium, it should be noted that, in humans, the ingestion of selenium is mainly in the form of selenomethionine through the consumption of cereals, grains, fruits, and vegetables.

Plants are known to convert inorganic selenium in soil to organoselenium analogues of naturally occurring sulfur compounds.\textsuperscript{105} Vegetables with a rich source of sulfur might, therefore, be expected to concentrate selenium if cultivated in a medium fertilized with selenium.\textsuperscript{105} This idea was tested with garlic, which is abundant in a variety of sulfur compounds.\textsuperscript{105} A major reason for choosing garlic as the experimental crop is because the allyl sulfides present in garlic are known to have anticarcinogenic activity, as discussed in Section 17.3 above. A number of studies have shown that selenium-enriched garlic is an effective anticarcinogen.\textsuperscript{122-124} Furthermore, it has been reported that the chemopreventive activity of selenium-enriched garlic is likely to be accounted for by the effect of selenium rather than the effect of garlic per se.\textsuperscript{125} Cai et al. have identified Se-methylselenocysteine as the predominant selenoamino acid in the selenium-enriched garlic.\textsuperscript{126} A recent study has shown that the forms of selenium in garlic and broccoli are virtually identical and that broccoli can accumulate as much selenium as garlic.\textsuperscript{125} We have recently observed that selenium-enriched broccoli is protective against chemically induced aberrant crypt formation (a preneoplastic lesion for colon cancer) in experimental animals;\textsuperscript{127} this suggests that selenium-enriched broccoli is an effective anticarcinogen (Figure 17.2).

17.14 CONCLUSION

Epidemiologic studies consistently show an inverse relationship between fruit and vegetable intake and cancer susceptibility. Vegetables, fruits, and herbs are rich in many different substances that may decrease cancer risk. These include allium compounds, isothiocyanates, indoles, phytoestrogens, flavonoids, limonene, carotenoids, vitamin C, vitamin E, folate, and selenium. Different mechanisms whereby micronutrients and bioactive compounds exert their chemopreventive effects include: blocked metabolic activation of carcinogens, increased activity of enzymes that detoxify carcinogens, antioxidant effects, decreased cell proliferation, increased cell differentiation, increased apoptosis of cancer cells, blocked formation of N-nitrosamines, altered estrogen metabolism, and increased DNA methylation.

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FIGURE 17.2 Total number of aberrant crypt foci in the colon and rectum of rats treated with dimethylhydrazine and fed either a selenium-deficient torula yeast-based diet, a diet supplemented with 2.0 mg/kg Se diet as selenite, a diet supplemented with 2.0 mg/kg Se diet as selenite and low-selenium broccoli, or a diet supplemented with 2.0 mg/kg Se diet as selenium-enriched broccoli. Values are mean ± SEM, n = 18.


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