# 49

# *Chemoprevention of Cancer in Humans by Dietary Means*

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This section will attempt to describe succinctly the basis for prevention of cancer by dietary means. An understanding of the processes involved in carcinogenesis is vital to any efforts in prevention. Reference 1 provides information on the metabolic activation of chemical carcinogens to the ultimate forms, which interact with the genetic material of the cell. In addition, the separate stages in carcinogenesis are described; namely, initiation or the first step, promotion or enhancement of the process, and progression or increased growth and expansion of the cancerous cells. Examples of how the different stages can be inhibited or altered are provided.

Diet or nutrition is an essential part of life, for it furnishes the food elements needed to sustain life, wards off some disease conditions, and helps insure a reasonable level of well being. The choices we make for our diets can have an appreciable impact on our health and vigor. Balanced and varied diets of natural foodstuffs, high in whole-grain products, fruits, and vegetables, are more likely to enhance our health than diets of highly refined foods. For a proper balance, various macronutrients, vitamins, minerals, and even non-nutritive food constituents are necessary, as discussed herewith.

## Macronutrients

### Carbohydrates

Carbohydrates, either simple sugars or starches, are formed in plants through the process of photosynthesis from carbon dioxide and water, and thus represent the means by which the energy from the sun is converted into food. The simple sugars of dietary carbohydrates are mono- and disaccharides such as glucose, sucrose, and fructose. Oligo and higher polysaccharides, which include both starch and non-starch polysaccharides constitute the major portion of dietary fiber. Starch occurs in cereals, legumes, roots, tubers, plantains, and bananas; it is the energy source for plants, equivalent to liver glycogen in animals.

Starch which is resistant to digestion in the small intestine occurs in whole grains, legumes, and potatoes, for example. This resistant starch is metabolized by the bacteria in the large intestine to compounds which are important for both the growth of endogeneous bacteria and for colonic epithelial cell proliferation. Nonstarch polysaccharides, along with

lignan from plant cell walls comprise dietary fiber, which plays an important role in regulation of stool bulk and weight. Dietary fiber is considered to have a preventative effect against colorectal cancer, since by increasing stool bulk, it dilutes any toxic material.[2]

Dietary carbohydrates should account for about 40 to 85% of total energy. Diets outside these guidelines may be lacking in other needed constituents.[3] Preferably, dietary carbohydrates should include high fiber sources, since besides decreasing the risk of colorectal cancer, there may be a preventative action for pancreatic and breast cancer. Conversely, high starch diets or those high in refined starch may increase risk for stomach cancer. Thus, the type of dietary carbohydrate can either be beneficial or deleterious with respect to cancer risk.

### Fats

Fats, often maligned as relatively undesirable dietary constituents, are nevertheless essential components of food. They are necessary building blocks for biological membranes, have a high nutritive value, are a source of certain essential fatty acids and vitamins, impart a pleasant feel to foods, solubilize or carry many of the flavor components of foods, and serve as an energy storage depot. Chemically, fats are composed chiefly of the triesters of long-chain aliphatic carboxylic acids with glycerol, along with minor amounts of free acids and mono- and diacylglycerols. The composition of fat is affected by the source — animal or vegetable, growth environment, type of food if from an animal, climate, and location.

During the digestive process, fats are hydrolyzed by lipases to the respective acids which serve as an energy source. The major acids from most domestic food animals are stearic, palmitic, and oleic acids, while plant fats yield more of the unsaturated acids such as oleic, linoleic, and linolenic. Fish oils, although containing some palmitic and stearic acids, have varying amounts of other unsaturated fatty acids. As for nomenclature, the double bond position is determined by counting from the methyl end of the aliphatic chain, using the notation Ω (omega). Fatty acids from fish contain large amounts of Ω-3 fatty acids; those from plants contain more of the Ω-6 type. The "shorthand" description of the fatty acid depicts the number of carbon atoms in the chain and the number, positions, and configurations (cis/trans) of the double bonds (see Table 49.1).

The acids derived from fats or oils, besides being energy sources, have a role in enhancing or promoting, and suppressing or inhibiting, the processes involved with carcinogenesis. Generally, oleic acid and the Ω-3 unsaturated acids from fish oils appear to suppress neoplastic effects, both in experimental and epidemiologic studies. Although epidemiologic studies cannot be controlled to the extent of animal studies, they indicate that populations consuming diets richer in olive oil have a lower breast cancer incidence.[4,5] In some cases, higher fish consumption was associated with possibly decreased risk for cancer of the larynx, pharynx, liver, colon, endometrium, and kidney.[6,7] There are many confounding factors in such studies, but the indications are that olive and fish oils are beneficial, while the saturated fats from most meats and some of the Ω-6 unsaturated fats from many oilseeds may enhance the action of exogenous or endogenous carcinogens.

An additional fatty acid with antimutagenic and anticarcinogenic effects in animal systems is conjugated linoleic acid (CLA), a mixture of positional isomers of linoleic acid where the double bonds are in positions 9 and 11 or 10 and 12 along the carbon chain. Since the bonds can be in the cis or trans configuration, eight isomers are possible. CLA was originally identified in grilled ground beef, but it has also been found in meat from other ruminants, and in dairy products such as cheese. In animal experiments, CLA has been effective as an inhibitor of tumors from application of polycyclic aromatic hydrocarbons, in decreasing the action of tumor promoters, decreasing cell proliferation, reducing

**TABLE 49.1**

Typical Dietary Fatty Acids

| Designation | Structure | Name | | Melting Point(°C) |
|---|---|---|---|---|
| | | Systematic | Common | |
| 4:0 | $H_3C(CH_2)_2COOH$ | Butanoic | Butyric acid | -7.9 |
| 5:0 | $H_3C(CH_2)_3COOH$ | Pentanoic | Valeric | -34.5 |
| 6:0 | $H_3C(CH_2)_4COOH$ | Hexanoic | Caproic | -3.9 |
| 7:0 | $H_3C(CH_2)_5COOH$ | Heptanoic | Enanthoic | -7.5 |
| 8:0 | $H_3C(CH_2)_6COOH$ | Octanoic | Caprylic | 16.3 |
| 9:0 | $H_3C(CH_2)_7COOH$ | Nonanoic | Pelargonic | 12.4 |
| 10:0 | $H_3C(CH_2)_8COOH$ | Decanoic | Capric | 31.3 |
| 12:0 | $H_3C(CH_2)_{10}COOH$ | Dodecanoic | Lauric | 44.0 |
| 14:0 | $H_3C(CH_2)_{12}COOH$ | Tetradecanoic | Myristic | 54.4 |
| 15:0 | $H_3C(CH_2)_{13}COOH$ | Pentadecanoic | Pentadecylic | 52.1 |
| 16:0 | $H_3C(CH_2)_{14}COOH$ | Hexadecanoic | Palmitic | 62.9 |
| 17:0 | $H_3C(CH_2)_{15}COOH$ | Heptadecanoic | Margaric | 61.3 |
| 18:0 | $H_3C(CH_2)_{16}COOH$ | Octadecanoic | Stearic | 69.6 |
| 20:0 | $H_3C(CH_2)_{18}COOH$ | Eicosanoic | Arachidic | 75.4 |
| 22:0 | $H_3C(CH_2)_{20}COOH$ | Docosanoic | Behenic | 80.0 |
| 24:0 | $H_3C(CH_2)_{22}COOH$ | Tetracasonoic | Lignoceric | 84.2 |
| 26:0 | $H_3C(CH_2)_{24}COOH$ | Hexacosanoic | Cerotic | 87.7 |
| 18:1 (9) | $CH_3(CH_2)_7CH{=}CH{-}(CH_2)_7COOH$ | Oleic | | 13.4 |
| 22:1 (13) | $CH_3(CH_2)_7CH{=}CH{-}(CH_2)_{11}COOH$ | Erucic | | 34.7 |
| 18:2 (9,12) | $CH_3(CH_2)_4{-}(CH{=}CH{-}CH_2)_2(CH_2)_6COOH$ | Linoleic | | -5.0 |
| 18:3 (6,9,12) | $CH_3(CH_2)_4{-}(CH{=}CH{-}CH_2)_3(CH_2)_3COOH$ | γ-Linoleic | | |
| 20:4 (5,8,11,14) | $CH_3(CH_2)_4{-}(CH{=}CH{-}CH_2)_4(CH_2)_2COOH$ | Arachidonic | | -49.5 |
| 18:1 (tr 9) | $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ | Elaidic | | 46.0 |
| 18:3 (9,12,15) | $CH_3{-}CH_2(CH{=}CH{-}CH_2)_3(CH_2)_6COOH$ | α-Linolenic | | -11.0 |

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the activation of heterocyclic amine carcinogens for some organ sites but not others, and modulating the action of protein kinase C proteins involved in signal transduction.[8,9] CLA was effective at a dietary level of 0.1%, one-hundredfold less than the level of dietary fish oil needed to inhibit animal tumors. Despite the effectiveness in both animal and cell culture studies, CLA as such has not been investigated in any sizable population studies.

A controversial aspect of the fatty acid situation relates to trans fatty acids. These compounds, where the hydrogens are on opposite sides of the carbons in the double bonds, are linear, akin to the shape of saturated fatty acids. Although trans fatty acids occur in nature in plants and in milk and meat from ruminants, the main source of dietary intake is through partial hydrogenation of vegetable oils, which have been used in margarine, salad oils, shortenings, and cooking fats for most of this century. Animal studies have shown that diets with up to 35% trans fat had no effect on growth or reproduction, but like natural saturated fats, they increased blood cholesterol levels. Epidemiological studies are controversial, but they have not shown untoward effects of trans fatty acids if used prudently.[10,11]

Thus, monounsaturated dietary fatty acids and perhaps the Ω-3 unsaturated acids found in fish oils may have a suppressing action against certain human cancers. Nevertheless, even such advantageous fats should be used prudently.[12,13]

## Protein

Proteins are complex molecules comprising combinations of amino acids. They can be of plant or animal origin; for example, about 20 to 35% of legumes is protein, 8 to 25%

of nuts and seeds, 8 to 16% of cereals, 10 to 20% of meat and fish, 15% of eggs, 3.5% of milk, and 13% of vegetables. Proteins are important nutritionally, as they supply the necessary building blocks for protein biosynthesis in specific organisms, contribute to the physical properties of food, and are either part of the flavor of food or are the precursors for flavor components formed during thermal or enzymatic reactions occurring during food processing.

Protein intake usually varies between 10 and 18% of total energy in different countries, and the composition varies depending whether animal or vegetable proteins are consumed.[14] There are no definitive data in humans indicating an association between cancer risk and protein intake, due to the presence of other macroconstituents in protein sources and various micronutrients. Dietary use of soy products has been suggestive for a lower risk of breast and endometrial cancer in Asian women.[15-17] Whether this is due to the soy protein, or more likely, the flavonoids present in soy has not been exactly determined. In animal studies, however, low protein diets tend to inhibit cancer, probably due to slower growth, while a high intake tends to enhance cancer development at various sites.

Proteins themselves are hydrolyzed or split by proteases to the individual amino acids, some of which are essential for mammalian growth and development while others are not (Table 49.2). Proteins from animal sources (animals, birds, fish, shellfish) are considered complete proteins since all the essential amino acids are present. Proteins from plant sources are generally incomplete since one or the other of the essential amino acids is low. However, combinations of plant proteins can usually supply all the essential amino acids; for example, corn and beans or rice and beans.

Chemically, some of the amino acids have nonpolar uncharged side chains; others have uncharged polar side chains, while still others have charged polar side chains (Table 49.2). These side chains are involved in the reactions and configurations of amino acids and the proteins from them.

Of all the amino acids, only methionine appears to be involved in physiological processes which have a chemopreventive action against cancer. As its S-adenosyl derivative or SAM, it is important, in conjunction with folate, in methylation of nucleic acid bases. Under- or hypomethylation of these cell constituents has been associated with cancer in animal studies. In animal experiments, deficiencies of SAM and folate led to tumors in rats and mice. The data for the folate/SAM effect for decreasing colorectal cancer in humans are suggestive but not definitive.[18,19]

### Total Energy

Total energy denotes the sum of the kcalories from fats, proteins, and carbohydrates within the diet of an individual. Energy requirements for each person vary with weight, height, age, body mass, and physical activity. Persons involved in strenuous physical activity such as competitive sports or mountain climbing obviously require more kcalories than those with sedentary lifestyles. However, it is excess total energy that becomes a problem, for the caloric matter in excess food is converted to fat and stored as such in the body. Fat, besides being an energy storage depot, also serves as a repository for all lipid-soluble xenobiotics and leads to greater conversion of endogenous steroids to estrogen. Estrogen, in turn, is a risk factor associated with breast and endometrial cancers. Higher body mass index is linked to an increased risk for cancer of the kidney and possibly gallbladder, colon, pancreas, and prostate. Continued physical activity and a body mass index below average tend to a decrease in cancer risk. Thus, continued physical activity tends to decrease cancer risk.[20]

Recommendations on a diet for prevention of cancer emphasize the need to rely on a low-fat diet, since dietary fat contains more kcalories on a weight basis than other macro-

**TABLE 49.2**

Amino Acids

| Name | Formula | Essential | Non-essential | Non-polar, Uncharged Sidechain | Polar, Uncharged Sidechain | Charged Sidechain |
|---|---|---|---|---|---|---|
| Alanine | (Ala) $H_2N$-CH($CH_3$) COOH | | X | X | | |
| Arginine | (Arg) $H_2N$-C(=NH) NH($CH_2$)$_3$ CH($NH_2$) COOH | X | | | | X |
| Asparagine | (Asn) $H_2N$-CH (COOH) $CH_2$ $CONH_2$ | | X | | X | |
| Aspartic acid | (Asp) $H_2N$-CH (COOH) $CH_2$ COOH | | X | | | X |
| Cysteine | (Cys) $H_2N$-CH ($CH_2SH$) COOH | | X | | X | |
| Glutamic acid | (Glu) $H_2N$-CH (COOH) ($CH_2$)$_2$ COOH | | X | | | X |
| Glutamine | (Gln) $H_2N$-CH (COOH) ($CH_2$) $_2$ $CONH_2$ | | X | | X | |
| Glycine | (Gly) $H_2N$-$CH_2$ COOH | | X | X | | |
| Histidine | (His) $H_2N$-CH (COOH) $CH_2$ ($C_3N_2H_3$) | X (infant) | | | | X |
| Isoleucine | (Ile) $H_2N$-CH (COOH) CH($CH_3$) $CH_2$ $CH_3$ | X | | X | | |
| Leucine | (Leu) $H_2N$-CH (COOH) $CH_2$ ($CHCH_2CH_3$) | X | | X | | |
| Lysine | (Lys) $H_2N$-CH (COOH) ($CH_2$)$_4$$NH_2$ | X | | | | X |
| Methionine | (Met) $H_2N$-CH (COOH) ($CH_2$)$_2$ $SCH_3$ | X | | X | | |
| Phenylalanine | (Phe) $H_2N$ CH (COOH) $CH_2$ $C_6H_5$ | X | | X | | |
| Proline | (Pro) HN ($CH_2$)$_3$ CH (COOH) | | X | X | | |
| Serine | (Ser) $H_2N$-CH (COOH) $CH_2$ OH | | X | | X | |
| Threonine | (Thr) $H_2N$-CH (COOH) CH (OH) $CH_3$ | X | | | X | |
| Tryptophan | (Try) $H_2N$-CH (COOH) $CH_2$ $C_8H_6N$ | X | | X | | |
| Tyrosine | (Tyr) $H_2N$-CH (COOH) $CH_2$ $C_6H_4$ OH | | X | | X | |
| Valine | (Val) $H_2N$-CH (COOH) $CH_2$ CH ($CH_3$)$_2$ | X | | X | | |

nutrients. However, there is no clear association between dietary fat and cancer in all cases. In one study, a higher risk of prostate cancer was associated with higher energy intake, but there was no clear association between fat intake and the cancer risk.[21] Conversely, in a study of skin cancer patients, reducing the level of dietary fat from 37 to 40% to about 20% led to a significant reduction in the incidence of new actinic keratosis and nonmelanoma skin cancer.[22]

Numerous animal studies have shown an inverse relationship between cancer incidence and lower body weight due to a calorie-restricted diet.[23] Such results may not apply to humans, but it seems that obesity, a sign of excess total energy, should be avoided by matching energy intake with expenditure and increasing physical activity.[24,25]

## Vitamins and Minerals

### Vitamins

#### *Vitamin A*

Vitamin A or retinol is a fat-soluble vitamin with an unsaturated aliphatic chain. It has a role in cell differentiation, in the protein metabolism of cells originating from the ectoderm, and in formation of the chromosphere component of visual cycle chromoproteins. Lack of retinol causes night blindness and thickening of the skin; conversely, excess vitamin A is toxic. Except for the occurrence in milk fat, egg yolk, and liver of mammals, most vitamin A is usually obtained from carotenoids. These precursors to vitamin A occur in vegetables, mostly green, yellow, and dark green leafy vegetables, and many yellow or orange fruits.[26] They are converted to vitamin A in the intestinal tract. Investigations in different animal species have shown that retinol esters and beta-carotene can inhibit the effects of various carcinogens through modulating DNA stability and decreasing lipid peroxidation.[27]

As for humans, there have been many epidemiologic studies of retinol and carotenes, with conflicting results. There were no protective effects against melanoma of the skin, suggestive but insufficient evidence for a decreased risk of bladder cancer with higher dietary retinol, and no consistent protective effect for cancer of the lung, stomach, breast, and cervix. An IARC (International Agency for Research on Cancer) group concluded that there is little evidence that vitamin A intake has a substantial cancer-preventive effect.[28]

The situation differs for dietary carotenoids, where there is evidence for a modest to weak protective action against lung cancer[29-31] and a possible decreased risk for esophageal,[32] stomach, colorectal, breast, and cervical cancers,[33-35] as well as an effect against cancers of the thyroid[36] and salivary gland.[37] Some epidemiologic surveys showed no such protective action.[38-41] Conversely, supplemental beta-carotene or megadose vitamin supplementation did not lead to any benefit.[42]

The controversy about carotenoids was heightened when studies of Finnish smokers receiving supplemental beta-carotene showed a higher death rate from lung cancer in those receiving additional beta-carotene than in those who did not.[43] Likewise, a combination study of beta-carotene with retinol had a similar trend, leading to termination of these studies.[44]

Nevertheless, another carotenoid which is not a vitamin A precursor, namely lycopene, responsible for the color of tomatoes, has shown a protective action against chemical carcinogens in animals.[45] Furthermore, epidemiologic studies have indicated that con-

sumption of tomato products, along with a modest amount of fat to facilitate absorption, has been associated with a lower incidence of prostate[46] and digestive tract cancers.[47]

On balance, although dietary supplements do not seem efficacious, obtaining vitamin A or carotenoids through a diet with high levels of fruits and vegetables seems to afford modest protection against cancer.

### *Vitamin B*

Vitamin B actually consists of several water-soluble compounds without any apparent structural similarity. All are necessary for proper physiological function; the requirements for some are actually filled through synthesis by endogenous intestinal bacteria (Table 49.3). Riboflavin, one of the B vitamins, was shown relatively early to have a chemopreventive action in rats fed a carcinogenic aminoazo dye. In this situation, as part of the enzyme system that reductively split the dye to two non-effective groups, dietary riboflavin definitely was a preventive agent.[48] However, there are no epidemiologic studies that indicate a connection between riboflavin and the prevention of cancer.

The situation differs for the $B_6$, $B_{12}$, and $B_c$ vitamins, as these are involved in reactions of amino acids and one–carbon units. Methionine, an essential amino acid, combines with adenosine triphosphate to form S-adenosylmethionine (SAM); in turn, SAM transfers methyl groups to adjacent molecules, thereby regulating expression of genes, preservation of membranes, and the action of various hormones and neurotransmitters. After the transfer of the methyl group, methionine becomes homocysteine, which has toxic effects on the cardiovascular system and the developing fetus. In the presence of $B_{12}$ and $B_c$, homocysteine is remethylated to methionine, with folate being especially important. Vitamin $B_6$, in turn, is involved by converting homocysteine to glutathione, another protective body constituent.

Both hypo- and hypermethylation of DNA are markers of the early stages of carcinogenesis. By maintaining a normal methylation pattern, folic acid may aid in decreasing cancer risk. For example, high dietary folate intake was weakly associated with decreased risk of colon cancer.[18,19]

### *Vitamin C*

Vitamin C has been widely studied, both in animal systems and in epidemiologic trials. Vitamin C, or ascorbic acid, is involved in biological hydroxylation reactions and formation of collagen in connective tissues, is important in wound healing, and is necessary for the prevention of scurvy. Most animals, except for primates and guinea pigs, synthesize their daily requirements, but for species which do not, the following foods are excellent sources: citrus fruits, strawberries, currants, cabbages, and potatoes. A great excess of vitamin C is not especially beneficial, as it is metabolized to oxalic acid, which is harmful to the kidneys. The recommended daily intake is 175 to 400 mg.

In many animal experiments, vitamin C had a beneficial action against skin or mammary cancer with dimethylbenz(a)anthracene, benzo(a)pyrene, or against estrogen-induced kidney cancer in hamsters. The most effective action was against formation of N-nitrosamines *in vivo* by combined administration of nitrite and a secondary amine; in this case, ascorbic acid reacts preferentially with nitrite, yielding non-effective compounds. However, in other cases vitamin C had no beneficial action.[49,50]

Epidemiologic trials have been less definitive. Most studies have shown some possible decrease in cancers of many organ systems, but the effects were not dramatic. Thus, the question of whether any protection was due solely to vitamin C or to a combined action with other constituents of the diet cannot be answered definitely.[38,51]

**TABLE 49.3**

B Vitamins

| Vitamin | Name | Function | Dietary Sources | Result of Deficiency |
|---|---|---|---|---|
| $B_1$ | Thiamine | Component of enzymes catalyzing oxidative decarboxylation reactions in Krebs cycle. | Wheat germ, pork | Beri-beri |
| $B_2$ | Riboflavin | Occurs in flavin mononucleotides (FMN) and flavin adenine dinucleotide (FAD), prosthetic groups in flavoproteins which are respiratory enzymes. | Yeast , liver, egg yolk, milk, fish, green vegetables | Chellosis (cracking of lips) |
| $B_3$ | Niacin | Component of nicotinamide adenine dinucleotide (NAD) and its phosphate derivatives (NADP) which are electron carriers in respiratory systems. | Wheat germ, yeast, liver | Pellagra |
| $B_5$ | Pantothenic Acid | Constituent of coenzyme A, important in many physiological processes such as fatty acid metabolism. | Animal or plant tissue, produced by intestinal bacteria | Deficiency rare |
| $B_6$ | Pyridoxine | Pyridoxine and derivatives, pyridoxal, pyridoxamines and their phosphates are co-factors for enzymes involved in metabolism of proteins and amino acids | Fish, meat, poultry, grains, legumes, potatoes | Skin lesions, anemia, muscle cramps |
| $B_{12}$ | Cyanocobalamin | Essential growth factor, component of enzyme involved in reactions of one-carbon units. | Animal tissues, produced by intestinal bacteria | Pernicious anemia |
| $B_C$ | Folic Acid (pteroylglutamic acid) | Needed for amino acid metabolism and formation of red blood cells; involved in reactions of one-carbon units (methylation) | Yeast extract, green vegetables | Anemia, spina bifida in fetus |

Data from Kingston, R., Supplementary benefits, *Chem. Brit.*, 35, 29, 1999.

### *Vitamin D*

Vitamin D, a fat-soluble vitamin (cholecalciferol; $D_3$), is formed naturally from cholesterol in the skin through photolysis of 7-dehydrocholesterol under the influence of ultraviolet light. The active metabolites are the 1, 25-dihydroxy- and 1-α-hydroxy-forms. These are needed for intestinal resorption of calcium and for its deposition into the organic matrix of the bones, which then triggers the biosynthesis of calcium-binding proteins. Deficiency of vitamin D in children leads to increased excretion of calcium and phosphate, thus impairing bone formation due to inadequate calcification of cartilage and bones — the disease known as rickets. In adults, deficiency leads to softening and weakening of bones, or osteomalacia. Some foods, especially milk, are fortified with vitamin D. Biochemically, vitamin D interacts with the vitamin D receptor, a member of the steroid/thyroid/retinoic acid family of nuclear receptors, which either induce or repress the expression of specific genes. In turn, the protein products of these genes include calcium-binding proteins (calbindins), bone matrix proteins (osteocalcin, osteopontin), digestive enzymes such as alkaline phosphatase, and vitamin D-metabolizing enzymes.[52]

The effect of vitamin D is linked to the level of dietary calcium, while therapeutic use is limited due to the calcemic effect of vitamin D, which causes calcium carbonate or phosphate disorders in various organs.

Although vitamin D inhibits the growth of breast cancer cells *in vitro*, the exact mechanism has not been delineated; induction of apoptosis has been implicated.[53] There is some evidence from population studies that higher serum vitamin D was associated with lower risk of breast cancer; likewise vitamin D may possibly reduce the risk of colorectal and prostate cancer.[53-55] As with other protective factors, the effect of vitamin D alone is relatively small. Animal studies with vitamin D in the chemoprevention of cancer have been few, and the results were positive in some cases, but not in others.[50] However, both animal and human studies lend support to the concept that increased intake of calcium and vitamin D can reduce the risk of colon cancer associated with high dietary fat.[56]

### *Vitamin E*

Vitamin E occurs in vegetable oils, especially the germ oils of cereals as tocopherols; of all these, d-α-tocopherol has the greatest biological activity. Tocopherols are antioxidants, and thus retard the oxidation of lipids or stabilize vitamin A, ubiquinones, hormones, and various enzymes. Vitamin E protects polyunsaturated fatty acids against autooxidation, protects against the immune response, and decreases the adherence of platelets to blood vessel walls.[57] In experiments using the hamster buccal pouch or other animal systems, vitamin E had a protective action against chemical carcinogens, but the effect on colon cancer in model animal systems was inconsistent.[50] In humans, vitamin E possibly protects against cancer of the mouth and pharynx, esophagus, pancreas, stomach, colon and rectum, cervix, and prostate.[58] For breast cancer, the epidemiologic results have been inconclusive.[38,51,59] The mechanism of its action, apart from the antioxidant properties, has not been elucidated.

## Minerals

### *Calcium*

Calcium, one of the more abundant essential minerals of the body, has several roles in building and maintaining bones and teeth, in blood clotting, and in muscle contraction. The usual requirement is 500 to 700 mg daily, with more necessary during pregnancy and lactation, or in osteoporosis patients. The main dietary sources are milk and dairy products,

although some vegetables (watercress, kale, spinach, broccoli) have reasonable levels. Supplementation of fruit juices with calcium has also become popular.

As for any chemopreventive action against cancer, a number of studies show a beneficial effect, but conflicts remain. A protective association for pancreatic cancer was noted in one study,[60] and for colorectal cancer, the weight of the evidence points toward an inhibitory action, as do some animal tests.[61-65] However, conflicting results were also noted.[54] Higher intake of calcium may reduce breast cancer risks,[51] but the data on prostate cancer and calcium intake levels are conflicting.[55,66]

Thus, for continued good health and body function, sufficient calcium is necessary. Except for breast and colorectal cancer, the epidemiologic studies are not definitive on whether calcium protects against other cancers.

### *Chromium*

Chromium is an essential micronutrient for utilization of glucose, since it activates phosphoglucomutase and increases insulin activity. The daily intake varies depending on the region of the country, with most foods containing some chromium; brown sugar is a good source along with meat and seafood. Average intake is about 80 µg per day.[67] Few, if any, chemopreventive experiments have been done with chromium, since hexavalent chromium has been considered a human carcinogen by the IARC.[68] Animal tests with trivalent chromium were negative, and surveys on chromium levels in diets and cancer incidence are lacking. Nevertheless, a sufficient supply is needed for good health. Although no long-term toxicity studies have been done, the use of chromium picolinate as a dietary supplement has increased recently. Chromium thus represents a paradox — it is needed for proper body function, but it presents a hazard under certain conditions.[69]

### *Iodine*

Iodine is an essential element for the thyroid gland to biosynthesize the hormones thyroxine or tetraiodothyronine and triiodothyronine; the requirement is 100 to 200 µg/day. A deficiency of iodine is associated with goiter or thyroid enlargement, which in turn is associated with a higher risk of cancer. Many epidemiologic studies have confirmed such an effect.[1]

The opposite, excess intake of iodine (18 to 1000 mg/day) can block uptake of iodine by the thyroid, leading to elevated thyroid-stimulating hormone (TSH) levels and an increased risk of thyroid cancer, as confirmed by animal experiments.[1] Thus, a proper balance in iodine uptake is required to maintain thyroid hormone levels and to decrease the risk of thyroid cancer.

### *Iron*

The essential micronutrient iron is mostly present in the body in the hemoglobin of the blood and the myoglobin of muscle tissue. Iron also occurs in various oxidative enzymes such as the P450s, peroxidases, catalases, hydroxylases, and flavine enzymes. The daily requirement is about 1 to 3 mg, but an intake of about 15 to 25 mg is needed due to poor absorption of iron. Good sources of iron are egg yolks, liver, wheat germ, lentils, and spinach.[70]

Deficiency of iron leads to anemia and has been associated with cancer of the esophagus and Plummer-Vinson syndrome.[71] Conversely, the risk of various other types of cancer increases in association with higher body iron stores. High serum ferritin levels were associated with an increased risk of colorectal adenomas or cancer,[72] and a high concen-

tration of iron in the liver was linked to a greater risk of liver cancer.[73] The suggestion has been made that high dietary intakes of iron enhance the generation of free radicals, which are implicated in the initiation or promotion phases of carcinogenesis. As with other essential micronutrients, a balance between a deficiency and an excess of iron is needed to maintain good health.

### *Selenium*

Selenium was recognized only about 30 years ago as an essential micronutrient, with a recommended intake of 75 to 125 μg daily. It is a component of the glutathione peroxidase system and occurs in organ meats, seafood, and in cereals and seeds at levels proportional to those in the soil.[74] An excess of selenium is toxic, resulting in damaged hooves and hair in range animals. A deficiency leads to "white muscle disease" in calves and lambs; thus, a proper balance in selenium levels is needed.

A survey of soil selenium levels in the U.S. versus cancer incidence pointed toward a decreased risk in high selenium areas. Likewise, animal studies with selenium, mostly as the selenite salt, have shown an inhibitory action against tumor development in various organs.[75] In humans, the data are often conflicting. High blood levels of selenium were correlated with esophageal cancer in a Chinese population,[76] while in other studies, high body selenium was protective against stomach cancer. Data for liver and pancreatic cancer are somewhat conflicting, but overall there was some inhibitory effect. Evidence for a protective action against colorectal and breast cancer in humans is limited.

Consumption of high-selenium brewer's yeast did not prevent the appearance of new skin cancers in patients who already had developed basal cell and squamous cell skin cancers, but total cancer incidence and deaths were lower in the selenium-using group.[77] Furthermore, higher body stores of selenium were associated with reduced risk of advanced prostate cancer.[78] Accordingly, although selenium suppresses most types of cancer and has a beneficial action, the toxicity of selenium limits the amount that can be administered, and must be considered.

### *Zinc*

Zinc is an essential trace element, as it is a component of several enzymes, including alcohol, glutamate, lactate, and malate dehydrogenases, carboxypeptidases, and carbonic anhydrase. In addition, several other enzymes are activated by zinc. Zinc deficiency causes serious disorders, but high zinc intake is toxic. A normal diet usually provides the daily requirement of a little over 10 mg (6 to 22 mg).[79]

Many animal experiments have shown that dietary zinc deficiency as well as zinc supplementation can increase the incidence of some carcinogen-induced tumors and decrease the incidence of others.[80] However, there are no definitive epidemiologic studies that associate human cancers with either a deficiency or an excess of zinc.

## Nonnutritive Components

### Fiber

Of all the nonnutritive food constituents, dietary fiber has been the one most extensively investigated in humans. The evidence is suggestive that high dietary fiber decreases the

risk of stomach, pancreatic, and breast cancer, and is protective against colorectal (and possibly endometrial) cancer,[17,3981-83] although contradicting studies are also available.[84] Animal studies showing the preventive effects of fiber against intestinal cancer predated most epidemiologic studies by a decade or more.[34,85-87]

Several possible reasons exist for the beneficial action of dietary fiber. The fiber may physically trap or attach to various deleterious substances ranging from carcinogen metabolites to certain bile acids, and sweep them out of the intestinal tract. Fiber may also trap hormonal constituents and thus help decrease breast cancer. Further, some fiber is eventually fermented by intestinal bacteria to butyric acid, which regulates cell cycles.[88,89]

For continued good health and function of the digestive system, a reasonable level of fiber in the diet is needed. Generally, this can be attained by eating a diet with whole grain products and fruits and vegetables.

### Flavonoids, Isoflavones, and Polyphenols

Flavonoids and isoflavones are present in plants and their various parts in combination with sugars (glycosides). The common property of many chemopreventive plant products is the presence of several hydroxyl groups in the molecule; thus the designation as polyphenols is appropriate for a wide range of these substances.

Many polyphenols from foods have demonstrated preventive effects against chemical carcinogens in animal experiments. Examples include ellagic acid,[90] silymarin from the artichoke,[91] quercetin, found in most plant materials,[92] the flavones or epicatechins common in tea,[93] curcumin in tumeric and mustard, caffeic and ferulic acids, resveratrol from grapes, and lignans derived from plant phenolics through bacterial action in the intestinal tract. Further, several plant phenolics can inhibit nitrosamine formation *in vivo* and thus have a chemopreventive action. The beneficial effects of these polyphenols are difficult to delineate separately, since they occur in many fruits and vegetables. Epidemiologic studies definitely associating one or the other dietary polyphenol with a reduction in cancer incidence are lacking or inconclusive.

That is not the case with the soybean compounds genistein and daidzein, examples of isoflavones. Various surveys have indicated a lower risk of breast and possibly endometrial cancer in women who consume soybean products,[15,94] while animal studies have confirmed the chemopreventive action of genistein.[95,96] The mechanism probably resides in the weak estrogenic effect of these compounds which then bind to estrogen receptors, thus blocking the action of the more potent natural estrogens.[16] Plant lignans, which also are beneficial, appear to bind weakly to estrogen receptors. Furthermore, daidzein sulfoconjugates inhibit the enzymes involved in estrogen steroid activation.[97]

An additional benefit of soy, reported recently, was that a soy-based beverage had suppressed an increase in prostate specific antigen (PSA) in prostate cancer patients.[98]

Despite these beneficial aspects of soy consumption, soy should be used in moderation. Soy consumption is associated with a goitrogenic effect, as confirmed by mechanistic studies in animals.[99] Thus, moderation in use is a reasonable policy.

### Indole-3-carbinol

Indole-3-carbinol (I3C) was one of the first specific cancer chemopreventive compounds to be isolated from a cruciferous vegetable, namely Brussels sprouts.[100] Many animal studies have shown its ability to suppress the effects of chemical carcinogens, presumably through its induction of detoxifying enzymes.[101] There is a concern that under certain

conditions it may act as a promoting agent, and possible application of I3C as a chemopreventive agent in humans should be approached cautiously.[102]

### Isothiocyanates

Isothiocyanates occur naturally in the form of their glucosinolate conjugates in a variety of cruciferous vegetables. When the plant cells are damaged by cutting or chewing, the enzyme myrosinase is released, which causes hydrolysis of the glucosinolates followed by a rearrangement which affords the isothiocyanates. These are generally responsible for the sharp taste associated with cruciferous vegetables, mustard, horseradish, and watercress. Animal studies with isothiocyanates have shown definitive and often quite specific inhibition of the action of some carcinogens, largely through suppressing metabolism to an activated intermediate.[103]

Epidemiologic studies focused specifically on isothiocyanates are lacking. However, one trial showed that if confirmed smokers ate watercress, a source of phenethyl isothiocyanate, the oxidative action of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a carcinogen present in tobacco smoke, was suppressed and higher urinary levels of a detoxification product of NNK were observed.[104]

Another unique isothiocyanate, sulforaphane or 1-isothiocyanate-4-methylsulfinylbutane, has been isolated from broccoli.[105] Sulforaphorane induces P450 enzymes which tend to detoxify carcinogens.[106] It appears to be still another component of the protective substances present in cruciferous vegetables.

Methods have recently been developed to quantify the metabolic endproducts of isothiocyanates.[107,108] This should expedite the further application of these compounds in both metabolic and epidemiologic studies.[109]

### Sulfides

The chemical background for the numerous sulfides and their selenium analogs occurring in "Allium" vegetables has been presented in several reviews. The substances involved are various sulfur derivatives, and in series are: alkyl cysteine-S-oxides, sulfenic acids, and thiosulfinate esters, which in turn afford alkyl and allyl sulfides and the selenium analogs.[110]

Animal tests have shown an inhibitory action of garlic and onion constituents, especially diallyl sulfide, on experimental carcinogenesis of the skin, esophagus, and colon. Epidemiologic studies have noted the same trend — that Allium vegetables protect against stomach and colon cancer — but no such action was noted for breast and lung cancer.[111] In one animal trial, garlic enriched with selenium had a chemopreventive action against the effects of a mammary carcinogen.[112] However, application of these results to the human situation will require much further study.

### Terpenoids

The terpenoid substances which occur in foods generally are the monoterpenes; examples include carvone, p-cymene, geraniol, limonene, linalool, nerol, perillyl alcohol, pinene, and thymol, among others. These substances occur in the essential oils of fruits and plants, in citrus and other fruits, cherries, certain grapes, mint, dill, and caraway, and are largely responsible for the pleasant fragrances of the fruits and plants.

The inhibitory action of fruit oil containing a monoterpene on the effect of a potent chemical carcinogen was noted several decades ago. More recent efforts have confirmed

**TABLE 49.4**

Cancer Preventive Action of Vitamins

| Vitamin | Species | Organ/Tissue |
|---|---|---|
| A | Mouse | Skin |
| | Rat | Mammary gland |
| | | Urinary bladder |
| B (folate) | Mouse | Lung |
| | Human | Colon (weakly) |
| C | Mouse | Colon |
| | | Lung |
| | Rat | Mammary gland |
| | | Colon |
| | | Liver |
| | Hamster | Kidney |
| D | Mouse | Skin |
| | Rat | Colon |
| | Human | Breast |
| | | Colon/rectum |
| | | Prostate |
| E | Mouse | Skin |
| | | Colon? |
| | Rat | Mammary gland |
| | | Stomach |
| | | Colon? |
| | | Ear duct |
| | | Liver |
| | Hamster | Buccal pouch |
| | Human | Mouth (possibly) |
| | | Pharynx (possibly) |
| | | Esophagus (possibly) |
| | | Pancreas (possibly) |
| | | Stomach (possibly) |
| | | Colon/rectum (possibly) |
| | | Cervix and prostate (possibly) |

that d-limonene, the putative active component of sweet orange oil, has several inhibitory mechanisms.[113] It suppresses the activation of nitrosamines[114] and azoxymethane,[115] induces glutathione-S-transferase, and inhibits oncogene activation by depressing the isoprenylation of oncogene products. The benefits of consuming citrus fruits may lie not only in their vitamin C content, but also in the limonene contained therein. Another monoterpene, perillyl alcohol, also inhibits protein isoprenylation, thus suppressing eventual oncogene activation,[116] even in human-derived cell lines.[117]

Although other monoterpenes have not been investigated, it is gratifying to know that these compounds with a pleasant fragrance are beneficial for health.

The diversity of cancer chemopreventive substances in foods is noteworthy and allows the individual many choices in devising a healthful diet. The aim should be a varied diet with moderation in the amounts of any one constituent. Dietary supplements, in which the active factor has been isolated and administered in a concentrated form, are not as useful as the actual food. However, Tables 49.4 and 49.5 provide results from both animal and human studies with vitamins and nonnutritive food components. In an actual diet, synergism among food constituents may occur with the combination, as in foods, being better than the individual components. All the more incentive to follow a varied moderate diet with plenty of fruits, vegetables, and whole-grain products.

**TABLE 49.5**

Chemopreventive Action of Nonnutritive Principles of Foods

| Substance | Species | Organ/Tissue |
|---|---|---|
| Fiber | Human | Stomach |
| | | Pancreas |
| | | Breast |
| | | Colon/rectum |
| | | Endometrium |
| | Rat | Colon |
| Flavonoids, isoflavones, polyphenols | Human | Breast |
| | | Endometrium |
| | Rodents | Mammary gland |
| | | Skin |
| Indole-3-carbinol | Mouse | Forestomach |
| | Rat | Mammary gland |
| Isothiocyanates | Mouse | Lung |
| | | Forestomach |
| | Rat | Mammary gland |
| Sulfides | Human | Stomach |
| | | Colon |
| | Rat | Esophagus |
| | | Lung |
| | | Thyroid |
| | Mouse | Forestomach |
| | | Lung |
| | | Colon |
| Terpenoids | Mouse | Forestomach |
| | | Lung |
| | Rat | Mammary gland |

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