Section I

Vegetables and Health

1 Effect of Dietary Phytochemicals on Cancer Development

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CONTENTS

ABSTRACT

Fruits, vegetables, and common beverages as well as several herbs and plants, each having a variety of pharmacological properties, have been shown to be rich sources of microchemicals with the potential to prevent human cancers. Several epidemiological studies have suggested that microchemicals present in our diet could be the most desirable agents for the prevention and/or intervention of human cancer incidence and mortality due to stomach, colon, breast, esophagus, lung, bladder, and prostate cancer. Also, the consumption of vegetables and fruits often is lower in those who subsequently develop cancer. There are many biologically plausible reasons why consumption of plant foods might slow or prevent the appearance of cancer. The specific mechanisms of action of most phytochemicals in cancer prevention are not yet clear, but appear to be varied. Phytochemicals can inhibit carcinogenesis by induction of phase II enzymes and inhibiting phase I enzymes, scavenge DNA reactive agents, suppress the abnormal proliferation of early preneoplastic lesions, and inhibit certain properties of the cancer cell.

1.1 INTRODUCTION

Fruits, vegetables, and common beverages as well as several herbs and plants with diversified pharmacological properties have been shown to be rich sources of microchemicals with the potential to prevent human cancers.[1,2] About 30 classes of chemicals shown to have cancer-preventive effects that may have practical implications in reducing cancer incidence in human populations have been described.[3] Several epidemiological studies, supported by long-term animal tumor experiments, etc., have suggested that microchemicals present in our diet could be the most desirable agents for the prevention and/or intervention of human cancer incidence and mortality due to stomach, colon, breast, esophagus, lung, bladder, and prostate cancer.[4] Also, a diet rich in fruits and vegetables is associated with reduced risk for a number of common cancers. Food chemists and natural product scientists have identified hundreds of phytochemicals that are being evaluated for the prevention of cancer. These include the presence in plant foods of such potentially anticarcinogenic substances as carotenoids, chlorophyll, flavonoids, indoles, isothiocyanates, polyphenolic compounds, protease inhibitors, sulfides, and terpenes (Table 1.1). The specific mechanisms of action of most phytochemicals in cancer prevention are not yet clear, but appear to be varied. Considering the large number and variety of dietary phytochemicals, their interactive effects on cancer risk may be extremely difficult to understand. Phytochemicals can inhibit carcinogenesis by induction of phase II enzymes while inhibiting phase I enzymes, scavenge DNA reactive agents, suppress the abnormal proliferation of early preneoplastic lesions, and inhibit certain properties of the cancer cell (Figures 1.1 and 1.2).[6,7]

This chapter will help to elucidate the current knowledge on dietary phytochemicals in cancer prevention.

TABLE 1.1
Some Dietary Sources of Phytochemicals[5]

Phytochemical	Food Source
Carotenoids	Apricot, peach, nectarine, orange, broccoli, cabbage, spinach, pea, pumpkin, carrot, tomato
Flavonoids	Green tea, black tea, citrus fruits, onion, broccoli, cherry, wheat, corn, rice, tomatoes, spinach, cabbage, apples, olives, red wine, soy products
Polyphenols	Grapes, strawberry, raspberry, pomegranate, paprika, cabbage, walnut
Protease Inhibitors	Soy bean, oats, wheat, peanut, potato, rice, corn
Sulfide	Cabbage, chives, allium, onion, garlic
Terpenes	Grapefruit, lemon, lime, orange, lavender, mint, celery seed, cherry

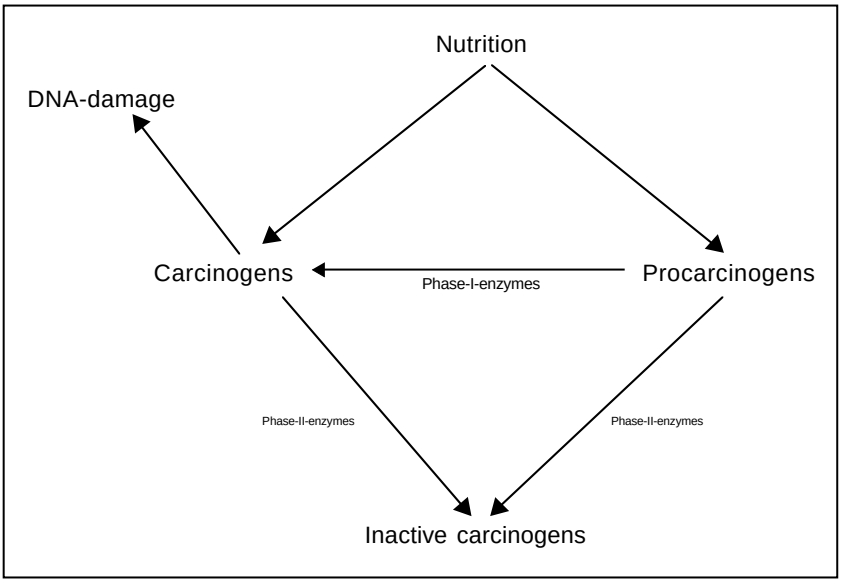

FIGURE 1.1 Effect of phase I and phase II enzymes.[6]

1.2 CAROTENOIDS

Carotenoids are a diverse group of over 600 structurally related compounds synthesized by bacteria and plants. The dietary carotenoids undergo a series of metabolic conversions, extracellularly in the lumen of the intestine and intracellularly in the intestinal mucosa.[8] Many carotenoids have the ability to quench singlet oxygen and thus function as antioxidants. Evolving evidence suggests that carotenoids may modulate processes related to mutagenesis, cell differentiation, and proliferation, independent of their role as antioxidants or precursors of vitamin A.[9,10] They also act on the differentiation and growth control of epithelial cells[11,12] and inhibit 1,2-diglyceride-induced growth and protease secretion.[13] Epidemiological data[14] show that increased consumption of beta carotene-rich foods and higher blood levels of β-carotene are associated with a reduced risk of lung cancer (Table 1.2).

1.3 CHLOROPHYLL

Chlorophyll is the ubiquitous pigment in green plants. Chlorophyllin, the food-grade derivative of chlorophyll, has been used historically in the treatment of several human conditions, with no evidence of human toxicity.[16] The potential carcinogenic activity of chlorophyll is of considerable interest because of its relative abundance in green vegetables widely consumed by humans. Chlorophyll and chlorophyllin have been shown to exert profound antimutagenic behavior against a wide range of potential

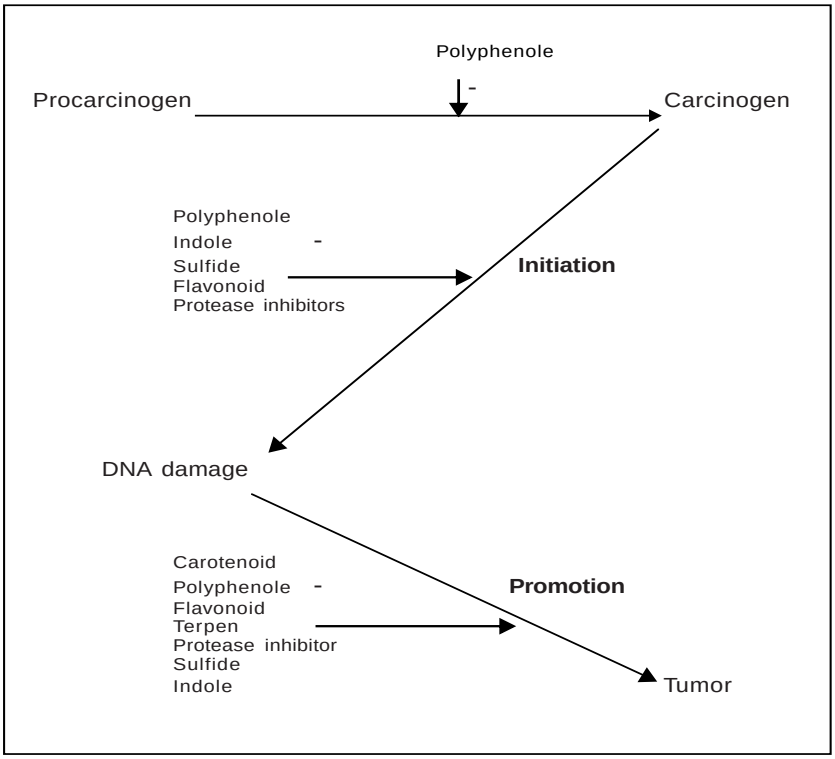

FIGURE 1.2 Relationship between phytochemicals and carcinogenesis.[7]

TABLE 1.2
Biological Behavior of Some Carotenoids[15]

Carotenoid	Anticarcinogenic activity	Inhibition of Lipid peroxidation
β-Carotene	++++	++
Canthaxanthin	++++	+++
Lutein	+	+++
α-Carotene	++	+
Lycopene	+	++

Note: weak = +, middle = ++, strong = +++, very strong = ++++.

human carcinogens.[17,18] In spectrophotometric studies mutagen-inhibitor interaction (molecular complex formation) was identified. *In vivo*, chlorophyllin reduced hepatic aflatoxin B1-DNA adducts and hepatocarcinogenesis when the inhibitor

and carcinogen were co-administered in the diet.[19] Also, the formation of a chlorophyllin:aflatoxin B(1) complex reduced systemic aflatoxin B(1) bioavailability.[20] Vibeke et al.[21] indicated that the chlorophyllin dosage required to give an overall protection against aflatoxin B1-induced hepatocarcinogenesis was less than 1500 ppm in animal experiments. By comparison, the reported concentration of chlorophyll in spinach isolates is in the range of 1500 to 600,000 ppm, depending on agronomic conditions.[22]

Further, chlorophyllin possesses free-radical scavenging properties. Recent studies suggest that chlorophyllin effectively protects plasmid DNA against ionizing radiation independent of DNA repair or other cellular defense mechanisms.[23]

Chlorophyll-related compounds pheophytin a and b have been recently identified as antigenotoxic substances in the nonpolyphenolic fraction of green tea.[24] They have potent suppressive activities against tumor promotion in mouse skin.[25]

1.4 FLAVONOIDS

Flavonoids are a group of polyphenolic compounds ubiquitously found in fruits and vegetables. The family includes monomeric flavanols, flavanones, anthocyanidins, flavones, and flavonols. In addition to their free-radical scavenging activity[26] flavonoids have multiple biological activities,[27] including vasodilatory,[28] anticarcinogenic, anti-inflammatory, antibacterial, immune-stimulating, anti-allergic, antiviral, and estrogenic effects, as well as being inhibitors of phospholipase A2, cyclooxygenase, lipoxygenase,[27,29,30] glutathione reductase,[32] and xanthine oxidase.[32]

Flavonoids are known to be good transition metal chelators; most lipid peroxidation inhibition assays measure a combination of transition metal (usually iron) chelation and radical scavenging. In animal experiments cyanidanol-3 led to a strong inhibition of lipid peroxidation.[33] Also, some flavonoids might regenerate the reducing agent, ascorbate.[34]

Increased levels of estrogens in blood and urine are high-risk markers for breast cancer.[35,36] In a large, prospective, case-control study there was a significant relationship between serum estrogen levels and the risk for breast cancer in women in New York.[36] Goldin et al.[37] reported 44% lower blood levels of estrogen and androgens in Asian women who emigrated to the U.S. from areas of low breast cancer risk, when compared to Caucasian Americans, who have a higher risk for breast cancer. Another studies indicated a 36% lower plasma estrogen level in women in rural China when compared to women in Britain, where breast cancer is more common.[38] Among premenopausal women in Singapore, breast cancer risk was inversely related to soy protein intake.[39] These epidemiological observations are supported by results of animal studies. Also, soy feeding is protective against experimentally induced mammary and other organ cancers.[40] Soy contains significant amounts of the isoflavones daidezein and genistein.[41] They may act as antiestrogens by competing with endogenous estrogens for receptor binding, and this may reduce estrogen-induced stimulation of breast cell proliferation[42] and breast tumor formation (Table 1.3).

TABLE 1.3
Some Dietary Sources of Flavonoids[43]

Flavonoid	Food Source
Flavanol	
Epicatechin	
Catechin	
Epigallocatechin	Green and black teas
Epicatechin gallate	Red wine
Epigallocatechin	
Flavanone	
Naringin	Peel of citrus fruits
Taxifolin	Citrus fruits
Flavonol	
Kaempferol	Endive, leek, broccoli, radish, grapefruit, black tea,
Quercetin	onion, lettuce, broccoli, cranberry, apple skin, berries, olive, tea, red wine
Myricetin	Cranberry, grapes, red wine
Flavone	
Chrysin	Fruit skin
Apigenin	Celery, parsley
Anthocyanidins	
Malvidin	Red grapes, red wine
Cyanidin	Cherry, raspberry, strawberry, grapes
Apigenidin	Colored fruit and peels
Phenyl propanoids	
Ferulic acid	Wheat, corn, rice, tomatoes, spinach, cabbage, asparagus
Caffeic acid	White grapes, white wine, olives, olive oil, spinach, cabbage, asparagus, coffee
β-Coumaric acid	White grapes, white wine, tomatoes, spinach, cabbage, asparagus
Chlorogenic acid	Apples, pears, cherries, plums, peaches, apricots, blueberries, tomatoes, anise

1.5 INDOLES

In ancient times, cruciferous vegetables were cultivated primarily for medicinal purposes.[44] The biologically active compound is glucobrassicin, a secondary plant metabolite that is abundant in cruciferous vegetables.[45] Glucobrassicin undergoes autolysis during maceration to indole-3-carbinol, which is known to undergo acid-condensation in the stomach following ingestion. Incubation of indole-3-carbinol under conditions that mimic the acid conditions in the stomach results in the production of multimeric derivatives of indole-3-carbinol.[46] *In vitro* acid-condensation of indol-3-carbinol may include cyclic and noncyclic tetramers, pentamers, and hexamers.[47,48]

Rabbits fed on cabbage leaves survived a lethal dose of uranium.[49] A series of 3-substituted indoles: indole-3-carbinol, 3-indoleacetonitrile, and 3,3'-diindolylmethane, are inhibitors of induced cancer.[50] Animals fed diets high in cruciferous

vegetables and then exposed to various carcinogens expressed lower tumor yields and increased survival rates.[51,52] Indole-3-carbinol administration is known to induce cytochrome P450 and glutathione *S*-transferase activities, resulting in increased metabolic capacity toward chemical carcinogens.[53] These properties of indole-3-carbinol are considered to contribute to the known anticarcinogenic properties of this compound, as well as to the reduced risk of cancer associated with diets rich in cruciferous vegetables.[54] Evidence from an epidemiological case-control study of diet and cancer also suggested that consumption of cruciferous vegetables are associated with a decreased incidence of cancer.[55]

Oligomeric acid-condensation derivatives of indol-3-carbinol inhibit P-glycoprotein-mediated cellular efflux by acting as competetive inhibitors of the pump by overloading its capacity to transport cytotoxic therapeutic agents from the cell.[56] So, inhibition of P-glycoprotein transport results in an increase in cellular accumulation of cytotoxic chemotherapeutic agents, thus increasing the efficacy of these agents.

1.6 ISOTHIOCYANATES

Organic isothiocyanates are widely distributed in plants. In addition to their characteristic flavors and odors, isothiocyanates have a variety of other pharmacological and toxic activities. Gluconasturtiin is a common isothiocyanate. Upon chewing of watercress, gluconasturtiin is hydrolyzed to phenylethyl isothiocyanate. It is responsible for the sharp taste of this vegetable. The consumption of 30 g of watercress will release a minimum of 2–5 mg of phenylethyl isothiocyanate (PEITC).[57] In smokers the consumption of watercress increases urinary excretion of NNK (4-methylnitrosamino-1-3-pyridyl-1-butanone) metabolites.[58] NNK is a potent pulmonary carcinogen in rodents. It is believed to be one of the causes of lung cancer in smokers.[59] NNK requires metabolic activation by α-hydroxylation to express its carcinogenic activity. The metabolic activation of NNK generates reactive intermediates that form a variety of DNA adducts that are involved in carcinogenesis. Inhibition of the α-hydroxylation pathways and other oxidative metabolic pathways of NNK by PEITC cause increased excretion of metabolites in urine.[58] Dietary administration of nontoxic doses of PEITC decreases NNK metabolic activation and lung tumor induction.[60] Recent studies indicate that dietary isothiocyanates have remarkable chemopreventive efficacy in the N'-nitrosonornicotine-induced esophageal tumor model.[61]

1.7 POLYPHENOLIC COMPOUNDS

The polyphenolic components of higher plants may act as antioxidants or as agents of other mechanisms contributing to anticarcinogenic or cardioprotective action.[43] Ellagic acid, a polyphenol generated from ellagitannins, is a most promising chemopreventive for reduction of risk of human cancers and it could potentially be introduced in human intervention trials.[62] Studies of the mechanism of action of ellagic acid have concluded that it could inhibit phase I enzymes involved in the activation of procarcinogens.[63] Ellagic acid induces hepatic glutathione *S*-transferase, a phase

II enzyme responsible for the detoxification of some carcinogen-generated electrophiles.[64] Ellagic acid may also scavenge oxygen radicals involved in oxidative destruction of membrane lipids and involved in tumor promotion.[65] Studies have shown that green tea affords cancer chemopreventive effects in a variety of animal model systems.[66] Green tea polyphenols have also been demonstrated to inhibit ornithine decarboxylase induction caused by tumor promoters in mouse skin and other tissues.[67,68] Epigallocatechin gallate (EGCG) is extracted from the leaves of the plant *Camellia sinensis*. A heavy drinker of green tea may consume 1 g/day.[69] EGCG, at 1 to 10 μ*M*, reduced inflammation-induced generation of mutagenic peroxynitrite radicals and nitrite.[70] Two epidemiological studies indicate that people who consume tea regularly may have a decreased risk of prostate cancer.[71] EGCG has been shown to cause growth inhibition and regression of human prostate and breast tumors in athymic nude mice.[72]

Curcumin is a phenolic compound widely used as a spice and coloring agent in food. Curcumin possesses potent antioxidant, anti-inflammatory, and antitumor promoting activities. Previous studies have shown that topical application of curcumin inhibits TPA (12-*o*-tetradecanoylphorbol-13-acetate) epidermal DNA synthesis, tumor promotion in mouse skin, and edema of mouse ears.[73] In mice, dietary administration of 5000 to 20,000 ppm curcumin reduced the incidence of intestinal tumors.[74] Further, curcumin induced apoptotic cell death in promyelocytic leukemia HL-60 cells at concentrations as low as 3.5 μg/ml;[75] recent studies demonstrated an inhibitory effect of dietary curcumin when administered continuously during the initiation and postinitiation phases.[76,77] Administration of curcumin may retard growth and/or development of existing neoplastic lesions in the colon.[76]

1.8 PROTEASE INHIBITORS

A variety of studies have made it clear that protease inhibitors (PI) can inhibit transformation *in vitro*, as well as development of both benign and malignant lesions *in vivo*.[78,79] The content of two prominent PI (Bowman-Birk inhibitor BBI and Kunitz trypsin inhibitor KTI) varies considerably with species of soy,[80] and PI content of several soy protein isolates can vary by as much as 20-fold. In many models, dietary administration of exogenous PI is effective in reducing cancer incidence.[78,79] Also, their ability to diminish the occurrence of a variety of cancers in organs where the inhibitor is not present points to an indirect role for PI.[79] Recent studies indicate that BBI and BBI concentrate prevent and suppress malignant transformation *in vitro* and carcinogenesis *in vivo*, without toxicity.[81] Further, BBI concentrate could be a useful agent for the potentiation of radiation- and cisplatin-mediated cancer treatment without significant adverse effects on surrounding normal tissues.[82]

A number of clinically important PI are found in serum, including α2-protease inhibitor, α2-macroglobulin, α1-antichymotrypsin, α1-acid glycoprotein, etc. Many of these PI are referred to as acute-phase reactants and are active against serine proteinases.[83] Other potentially important effects of dietary PI may occur via hormonal modulation and inactivation of trypsin and chymotrypsin in the duodenum. For example, potato carboxypeptidase inhibitor is an antagonist of human epidermal growth factor. It competed with epidermal growth factor for binding to epidermal

growth factor receptor and inhibited EGFR activation and cell proliferation induced by this growth factor. Potato carboxypeptidase inhibitor suppressed the growth of several human pancreatic adenocarcinoma cell lines, both *in vitro* and in nude mice.[84] A number of studies have documented, for instance, that dietary PI stimulates secretion of pancreatic enzymes, presumably via modulation of cholecystokinin levels.[85] Cholecystokinin release is of additional interest because cholecystokinin acts as a cocarcinogen in various models.[86]

Among other effects, PI block release of oxygen radicals and H_2O_2 from polymorphonuclear leukocytes and activated macrophages,[87] which may protect DNA from oxidative damage or from single-strand breaks. Hydroxyl radicals also appear to be involved.[88] Further, PI inhibit influx of polymorphonuclear leukocytes.[87]

1.9 SULFIDES

Sulfides have been shown to inhibit a variety of tumors induced by chemical carcinogenesis. In rat liver, supernatant ajoene and diallyl sulfide affected aflatoxin B1 metabolism and DNA binding by inhibiting phase I enzymes, and may therefore be considered as potential cancer chemopreventive agents.[89] In mice the oral application of diallyl sulfide suppressed the activity of ornithine decarboxylase.[90] In the murine model, topical application of diallyl sulfide and diallyl disulfide (DAS), oil-soluble constituents of garlic and onions, significantly inhibited skin papilloma formation from the ninth week of promotion and significantly increased the rate of survival.[91]

Animal studies indicate that dietary intake of DAS has chemopreventive potential during the time corresponding to the initiation phase on 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced mammary carcinogenesis.[92] Upon examining specific P450 enzymes, the 7-pentoxyresorufin-*O*-dealkylase (PROD) activity, which was low in untreated rat liver microsomes, was greatly increased by DAS, reaching a plateau of 100-fold increase at 24 to 48 h. Subsequent studies indicated that this increase in PROD activity was due to the induction of the CYP 2B1 gene at the transcriptional level.[93] On the other hand, the P450 2E1-dependent *N*-nitrosodimethylamine demethylase activity was lowest (20% of the control) at 15 h and gradually returned to the control level after 2 days. DAS has also been shown to slightly decrease 16β-testosterone hydroxylase activity.[94]

1.10 TERPENES

Monoterpenoids are commonly produced by plants and found in many fruits and vegetables. Pharmacokinetic studies in dogs and rats revealed that oral administration of perillyl alcohol is rapidly absorbed from the gastrointestinal tract and metabolized to perillic acid and dihydroperillic acid.[95,96] Several monoterpenes induce phase II enzymes.[97] With regard to the mode of the chemopreventive action of perillyl alcohol, monoterpenes exhibit a diverse array of metabolic, cellular, and molecular activities, including inhibition of activation of carcinogen metabolism, inhibition of cellular proliferation, and the induction of differentiation and apoptosis.[98,99] Limonene has been studied in animal models as an anticarcinogen.[100] Limonene caused regression of DMBA-induced mammary tumors.[101] Limonene is also capable of inhibiting the

development of upper digestive tract carcinomas in *N*-nitrosodiethylamine-treated mice.[102] In humans, the three metabolic derivatives detected in plasma after single oral doses of limonene 100 mg/kg are perillic acid, dihydroperillic acid, and limonene-1,2-diol.[103] The metabolic precursors to perillic acid and dihydroperillic acid are likely perillyl alcohol and perillyl aldehyde, both of which have potent antiproliferative activities in cell culture systems.[104–106] Limonene impairs DNA synthesis in the human-derived myeloid leukemia cell line THP-1 and in the lymphoid leukemia cell line RPMI-8402 in a concentration-dependent manner.[106] In addition, *d*-limonene inhibits carcinogen activation to produce an inhibitory effect in carcinogenesis. Animal studies indicated that *d*-limonene administered in the diet at the 1 to 5% levels inhibited both DMBA- and MNU-induced rat mammary carcinogenesis in female rats.[107]

1.11 CONCLUSION

Review of the epidemiological data, including both cohort and case-control studies of all cancer sites as well as a variety of animal studies, strongly suggest that plant foods have preventive potential and that consumption of vegetables and fruits is lower in those who subsequently develop cancer. Other data suggest that foods high in phytoestrogens are plausibly associated with a lower risk of sex hormone-related cancers.

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