Supplements

Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies[1,2,3]

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ABSTRACT

Epidemiologic data support the association between high intake of vegetables and fruits and low risk of chronic disease. There are several biologically plausible reasons why consumption of vegetables and fruit might slow or prevent the onset of chronic diseases. Vegetables and fruit are rich sources of a variety of nutrients, including vitamins, trace minerals, and dietary fiber, and many other classes of biologically active compounds. These phytochemicals can have complementary and overlapping mechanisms of action, including modulation of detoxification enzymes, stimulation of the immune system, reduction of platelet aggregation, modulation of cholesterol synthesis and hormone metabolism, reduction of blood pressure, and antioxidant, antibacterial, and antiviral effects. Although these effects have been examined primarily in animal and cell-culture models, experimental dietary studies in humans have also shown the capacity of vegetables and fruit and their constituents to modulate some of these potential disease-preventive mechanisms. The human studies have relied on intermediate endpoints related to disease risk. Design methodologies used include multiple-arm trials, randomized crossover studies, and more compromised designs such as nonrandomized crossovers and pre- and posttreatment analyses. Length of treatment ranged from a single dose to years depending on the mechanism of interest. Stringency of dietary control varied from addition of supplements to a habitual diet to provision of all food for the duration of a treatment. Rigorously conducted experimental dietary studies in humans are an important link between population- and laboratory-based research.

Key Words: Fruit • vegetables • phytochemicals • antioxidants • diet • human • cancer • atherosclerosis • prevention • epidemiologic studies • randomized trials • vegetarians

INTRODUCTION

Thousands of biologically active phytochemicals have been identified in plant foods, eg, grains, nuts, legumes, vegetables, and fruit. Of these plant food groups, vegetables and fruit are the most botanically diverse. In a Western diet alone, vegetables and fruit include roots, leaves, stems, fruit, and seeds from >40 botanical families. Thus, they have the potential to contribute significant variety and complexity to the human diet.

A diet rich in vegetables and fruit may provide protection against cardiovascular disease (1), several common cancers (2), and other chronic diseases. The associative evidence comes from case-control and cohort studies as well as ecologic studies. Analytic, epidemiologic studies also contribute evidence of a possible causal relation; however, in some cases, these studies may provide more evidence that a dietary or lifestyle pattern, rather than an individual constituent, plays a role in disease prevention. For example, Serdula et al (3) showed that the frequency of intake of fresh fruit and vegetables increased as the level of physical activity increased, and that consumption of fruit and vegetables was lower in those who reported that they were sedentary, heavy smokers, or heavy drinkers. Human intervention studies with disease as the endpoint would be the ideal test of causality, but we do not have the luxury of conducting placebo-controlled, randomized trials to examine the effect of endless doses and permutations of phytochemicals and dietary factors on disease outcomes.

Extensive study of phytochemicals in cell-culture systems and animal models has provided a wealth of information on the mechanisms by which a diet high in fruit and vegetables may lower the risk of chronic disease in humans. However, it is not always clear whether the effects in animals, often observed with high doses of single compounds, can be readily extrapolated to humans. It is not clear whether the biology that appears to influence disease risk in animals fed compounds, often at high levels, is functional to the same degree or in the same manner in humans consuming realistic doses as part of a habitual diet. Furthermore, studies in cell culture are often conducted before it is known how the phytochemicals are processed in vivo, how they are absorbed and metabolized in the body, or whether they are even available to tissues of interest. For example, some phytochemicals are fermented by colonic bacteria so that the compound absorbed from the gut and circulating in the blood is different from what was consumed (4) and the original phytochemical may not even be detectable in the blood.

Experimental dietary studies in humans serve as important links between nutritional epidemiologic studies and studies conducted in cell-culture systems and animal models. They rely on intermediate endpoints related to disease risk by using biological markers that also help provide insight into the modes of action of fruit and vegetable constituents in humans. At the same time, they are limited by the sensitivity and specificity of the biological markers, access to biological samples, and the logistics of conducting studies in humans.

The objective of this article is to present human experimental studies that examine the capacity of vegetables and fruit—and their nutrients and phytochemicals—to modulate biological processes related to the protective effects of these plant foods (Table 1⬇). The studies presented were chosen because they were human studies that tested the effects of vegetables, fruit, or both, or a component of vegetables, fruit, or both, on biological markers associated with disease risk. The studies were identified by: 1) using MEDLINE subject headings (ie, fruit, vegetables, allium, ß-carotene, ascorbic acid, and bioflavonoids), limiting the selection to human studies, and reviewing the selected titles and abstracts to identify experimental studies; 2) surveying journals that frequently publish experimental nutrition studies (eg, The American Journal of Clinical Nutrition; Cancer Epidemiology, Biomarkers and Prevention; Carcinogenesis; Journal of Nutrition; and Nutrition and Cancer); and 3) checking the reference lists of other publications. This third approach was used mainly to try to access studies published in journals not indexed in MEDLINE. Published studies with negative results were included, although it is often unclear whether the negative results are due to a true lack of effect or to lack of statistical power. The discussion excludes studies of legumes, which are reviewed elsewhere in this supplement.

TABLE 1. Potential disease-preventive mechanisms of vegetables and fruit and their constituents as identified in human dietary studies

MECHANISMS OF ACTION

Antioxidant activity

Oxidative damage can result when the critical balance between free radical generation and antioxidant defenses is unfavorable. It has been hypothesized to play a key role in cardiovascular disease, cancer initiation, cataract formation, the aging process, inflammatory diseases, and a variety of neurologic disorders (5). Free radicals—molecules that carry one or more unpaired electrons—are formed endogenously as a result of normal oxidative metabolic reactions; exogenously as components of tobacco smoke, diet, drugs, and other environmental pollutants; and indirectly through metabolism of certain solvents and by radiation. If not quenched by antioxidants, these highly reactive compounds will react with and potentially alter the structure and function of several cellular components, such as lipid-containing cell membranes, lipoproteins, proteins, carbohydrates, RNA, and DNA. The antioxidant defense system has both enzymatic and nonenzymatic components that prevent radical formation, remove radicals before damage can occur, repair oxidative damage, eliminate damaged molecules, and prevent mutation (6).

Several of the antioxidant enzymes are metalloenzymes, which contain trace minerals for which vegetables and fruit are significant sources. Mitochondrial superoxide dismutase is a manganese-containing enzyme. Glutathione peroxidases are selenium-dependent enzymes. Vegetables and fruit are rich sources of manganese, are but not typically significant sources of selenium. However, selenium is found in plant tissues in amount proportional to the mineral concentration of the soil in which the plant grows (2). Thus, depending on the location, vegetables and fruit can be sources of selenium for some populations. Certain patients (eg, organ transplant patients and those receiving chronic hemodialysis) tend to be selenium deficient and to have compromised antioxidant systems as a result of their diseases and treatments (7, 8). Results of studies conducted in these patients show that selenium supplementation improves the oxygen radical scavenger system, decreases the susceptibility of plasma lipids to peroxidation, lowers oxidized glutathione content of erythrocytes, and increases erythrocyte selenium-dependent glutathione peroxidase activity (7, 8).

Nonenzymatic components of the antioxidant defense system interrupt the free radical–initiated chain reaction of oxidation or scavenge and disable free radicals before they react with cellular components. The antioxidant capacity of constituents of vegetables and fruit has been documented in several human intervention studies, although most of the work has been directed toward effects detectable in blood samples. Typically, the antioxidant vitamins C and E and ß-carotene have received the most attention (9–11). Ten weeks of 280 mg *all-rac-α*-tocopherol acetate daily, compared with placebo, reduced erythrocyte susceptibility to hydrogen peroxide–induced lipid peroxidation and lowered plasma concentrations of lipid peroxides, thiobarbituric acid–reactive substances (TBARS), and conjugated dienes in both smokers and nonsmokers (10). A randomized, double-blind controlled trial with either 20 mg ß-carotene or placebo daily for 4 wk showed a significant reduction in breath pentane output and a trend toward lower breath ethane output with the ß-carotene supplement in smokers; this effect was not observed in nonsmokers (9). (Breath pentane and ethane are end products of the peroxidation of n–6 and n–3 fatty acids, respectively, and are useful, noninvasive measures of lipid peroxidation.)

The antioxidant effects of several other substances in plants such as flavonoids, which are even more potent antioxidants than vitamins C and E (12), have not been studied closely in humans. One study tested the effect of 4-wk of supplements of vegetable and fruit extracts, including sources of flavonoids, on lipid peroxide concentrations (13). The supplement included dried vegetable juice extracts from carrots, parsley, beets, broccoli, kale, cabbage, spinach, and tomatoes and fruit juice extracts from apples, oranges, pineapples, papayas, cranberries, and peaches. Plasma lipid peroxide concentrations in the 15 subjects decreased from 16.85 to 3.13 μmol/L within 1 wk and remained in this range through the additional 3 wk of treatment.

A variety of sulfur-containing compounds and precursors in garlic also have antioxidant activity. In a randomized, placebo-controlled, double-blind, crossover design study in 10 healthy volunteers, 2-wk of supplements of 600 mg garlic powder/d resulted in a 34% reduction in ex vivo susceptibility of apolipoprotein B–containing lipoproteins to oxidation (14).

Some of the same factors that contribute to oxidative damage and the production of reactive oxygen species can also lead to the production of reactive nitrogen species. A wide range of nitrogen-containing compounds and nitrosating agents to which humans are exposed can react in vivo to form potentially carcinogenic *N*-nitroso, *C*-nitroso, and reactive diazo compounds (15). Nitrosating agents can also be synthesized endogenously by bacteria and activated macrophages.

Ascorbic acid, α-tocopherol, polyphenols, and fruit and vegetable extracts inhibit *N*-nitroso compound formation by destroying nitrosating agents (15). Nitrosation in humans can be estimated quantitatively by monitoring urinary excretion of *N*-nitrosoproline (NPRO; a noncarcinogenic *N*-nitroso compound) (16). 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 (17–19). Similarly, in a controlled dietary study conducted in China, doses of ≤60 mL of fruit juices [*Actinidia chinensis* (kiwi), *Rosa roxburghii Tratt* (cili), *Rosa laevigata*, and *Phylantus emblica*] administered for 2 d reduced mean NPRO excretion by ≈70%; 75 mg ascorbic acid as a supplement reduced mean NPRO excretion by 44% (20). A 300-mL dose of processed vegetable juice prepared by high-temperature sterilization increased NPRO excretion by 56%. The authors postulated that the destruction of ascorbic acid and other antioxidants and the production of nitrite that occurs during processing and storage could explain this result, and proposed that consumption of fresh, rather than canned, vegetables should be encouraged to minimize nitrosation.

Interaction of reactive oxygen or nitrogen species with DNA bases can result in the formation of DNA adducts which, during the course of attempted repair or replication, can lead to DNA mutations. Accumulation of DNA mutations (specifically in crucial genes) contributes to the development of neoplastic cells. To test whether the antioxidant scavenging of free radicals reduces the production of DNA adducts, several studies measured oxidative damage to DNA in humans in relation to various nutrient treatments. In a double-blind, placebo-controlled trial in smokers and nonsmokers, Duthie et al (21) showed a significant decrease in endogenous oxidative base damage in the lymphocyte DNA of both smokers and nonsmokers with a 20-wk daily supplement of vitamin C (100 mg), α-tocopherol (280 mg), and ß-carotene (25 mg). In addition, lymphocytes from the antioxidant-supplemented individuals showed increased resistance to oxidative damage when challenged with hydrogen peroxide in vitro.
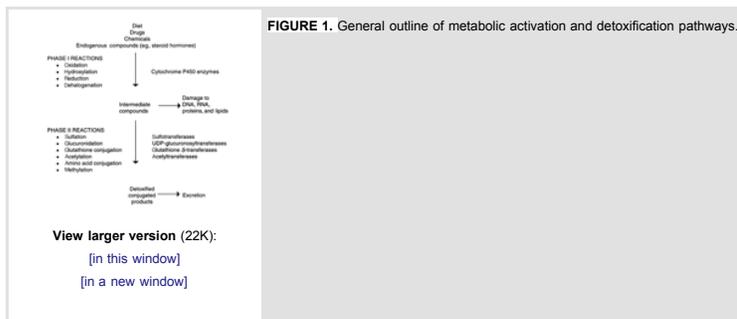
The effect of ß-carotene and ascorbic acid supplementation on lymphocyte micronucleus frequencies as an indicator of chromosomal damage has also been examined in healthy volunteers. Lymphocytes cultured after being irradiated with low-dose X-rays in vitro contained fewer X-ray–induced micronuclei in the ß-carotene–treated group, but not in the ascorbic acid–treated group, compared with the placebo group (22). In another study, carrot and tomato juices (330 mL/d), and spinach powder (10 g/d), added separately to a low-carotenoid diet for 2 wk all decreased endogenous lymphocyte DNA strand breaks in 23 healthy men (23). The carrot juice intervention also reduced DNA base oxidation; therefore, α- and ß-carotene may be more effective than lycopene and lutein at quenching free radicals in vivo (23).

The direct effect of diet on DNA adduct formation has been tested with use of supplemental garlic. Hageman et al (24) examined the effect of garlic consumption on ex vivo production of benzo[*a*]pyrene adduct production in lymphocytes. In a nonrandomized pilot study of 9 men, isolated lymphocytes from the blood of participants eating garlic (3 g raw garlic/d for 8 d) developed fewer adducts when incubated with benzo[*a*]pyrene. A cucumber-and-yogurt salad was the vehicle used to deliver the garlic. Interestingly, consumption of the salad alone (control) also resulted in significant reduction in benzo[*a*]pyrene DNA adducts (although not as markedly as with garlic). There was also a decrease in oxidized DNA as measured by 8-oxo- deoxyguanosine with the salad alone that was not reduced further by garlic, suggesting that some component of the control vehicle may also have protective properties.
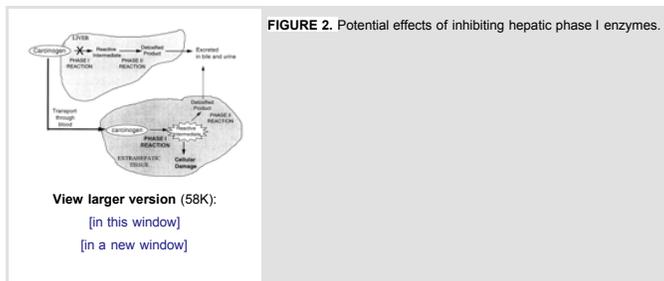
Residues of 8-oxodeoxyguanosine can also be measured in urine as a result of excision, repair, and excretion of the damaged DNA. Typically, urinary concentrations of 8-oxodeoxyguanosine are associated with the level of DNA oxidation, and thus, lower concentrations would suggest reduced risk of DNA damage. However, by nature, urinary 8-oxodeoxyguanosine is a biomarker of both oxidation and excision repair capacity. Greater excretion of urinary 8-oxodeoxyguanosine by smokers compared with nonsmokers of similar age does suggest that it is a useful marker of oxidative stress within a defined group (25). In a study of 5 men and 5 women, a 3-wk supplementation with 300 g Brussels sprouts decreased urinary 8-oxodeoxyguanosine excretion in 4 of the men but in only 2 of the women (26). The study was too small to yield any conclusions about sex differences in response to cruciferous vegetables; whether women do not reap the same benefits from these vegetables as men is intriguing and should be addressed in a larger study.

Modulation of detoxification enzymes

Detoxification, or drug-metabolizing, enzymes are essential for the biotransformation of many important endogenous compounds and in the detoxification of numerous xenobiotics (27) (**Figure 1**↓). Phase I enzymes such as cytochrome P450 (CYP)-dependent monooxygenases—which catalyze oxidation, hydroxylation, and reduction reactions—convert hydrophobic compounds to reactive electrophiles in preparation for their reaction with water-soluble moieties to improve excretion. Phase II enzymes, such as UDP-glucuronosyltransferases, sulfotransferases, and glutathione transferases, catalyze these conjugation reactions.

FIGURE 1. General outline of metabolic activation and detoxification pathways.

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Most chemical carcinogens require metabolic activation by phase I enzymes before exerting their carcinogenic effects. Thus, in theory, chemical carcinogenesis could be prevented by blocking the metabolic activation process. Unfortunately, in reality it is not so straightforward. Most carcinogen metabolism occurs in the liver. Inhibition of phase I metabolism may result in reduced first-pass clearance of many xenobiotics by the liver and hence result in greater delivery of a carcinogen to potentially more vulnerable extrahepatic tissues that may not have the same detoxification capacity as the liver (**Figure 2**). Based on this scenario, the question of whether it is beneficial to lower some of these enzyme concentrations by dietary manipulation must be addressed (27).

FIGURE 2. Potential effects of inhibiting hepatic phase I enzymes.

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Much of the research has been carried out with use of liver microsomes from rats and mice and, more recently, humans. These results provide an understanding of the mechanisms by which a dietary factor may influence carcinogen metabolism; however, extrapolating these findings from hepatic to nonhepatic tissues and from animals to humans is difficult (28). Furthermore, conducting metabolic studies of this type in humans and measuring CYP enzyme concentrations and activities in most tissues are not viable options because of the inaccessibility of the tissues of interest. Nonetheless, irrespective of the model used, interactions between inhibitory and stimulatory effects and substrates, in various concentrations and in the presence of other dietary compounds as they exist in vivo, need to be understood.

Numerous constituents of plant foods, including flavonoids (29), isothiocyanates (30), and allyl sulfides (31), have been found to be potent modulators of the CYP monooxygenases in vitro and in animal models. However, the effects of some of these phytochemicals on CYPs are complex. They have the capacity to inhibit certain enzymes at high concentrations of the compound and to activate moderately the same enzyme at lower concentrations (32). Furthermore, others may be competitive inhibitors of CYPs; even when present at low concentrations and in combination with other compounds, their actions can be significant (28).

In an attempt to clarify the pathways of metabolic activation, the emphasis has been on the CYP monooxygenase system. However, a report of concomitant inhibition and induction of the 2 major monooxygenase systems, CYP monooxygenase and flavin-containing monooxygenases, by a single compound (33) suggests another potential layer of complexity in response to the mixture of compounds in a typical diet. Flavin-containing monooxygenases, not thought to be modulated by xenobiotics, were recently shown in rats to be inhibited by indole-3-carbinol (I3C), the precursor of which is found in cruciferous vegetables, coincident with induction of CYP1A1 (33). Whether a similar phenomenon occurs in humans and how these types of effects may influence metabolism of the variety of xenobiotics to which humans are exposed are questions that also need to be explored.

The capacity to conjugate metabolically activated intermediates and excrete them from the body is critical in protecting against many potential mutagens. Thus, efforts have focused on determining how vegetable and fruit constituents can influence the phase II conjugating enzymes. A series of small studies in which subjects' diets were supplemented with 300 g Brussels sprouts showed the capacity of this cruciferous vegetable to affect specific glutathione transferase isoenzymes, increase plasma concentrations (reflecting hepatic concentrations) of glutathione transferase α but not π (34), and increase both glutathione transferase α and -π concentrations in rectal epithelium (35). Typically, induction of these enzyme systems is rapid and enzymatic activity rises and plateaus within 5 d of continued daily ingestion of a food with inducing capacity (36). Similarly, enzyme activities drop rapidly when the food is removed from the diet.

Xenobiotics share many of the same metabolic pathways with drugs, relying on the same enzyme systems for their biotransformation; therefore, drug metabolites can be monitored in experimental studies to examine the effects of plant-food constituents on the detoxification enzyme systems. This is especially useful in human studies in which it is often difficult to access particular tissues or organs to directly measure enzyme activities. For example, compounds in cruciferous vegetables can alter drug metabolism by both inhibiting and inducing certain CYPs and possibly by inducing select conjugating enzymes. Pantuck et al (37) showed in 1979 that feeding individuals a diet of cruciferous vegetables enhanced their ability to metabolize phenacetin and antipyrine oxidatively. They showed subsequently that consuming a diet containing Brussels sprouts and cabbage for 1 wk could also influence select conjugating enzyme systems, stimulating the conjugation of acetaminophen with glucuronide but not with sulfate (38). Coupled with the increase in acetaminophen glucuronide was a small decrease in the proportion of cysteine-acetaminophen conjugate, a product of the oxidative pathway for acetaminophen metabolism. This effect also was observed with a single 50-g dose of watercress, a rich source of phenethyl isothiocyanate (39). Chen et al (39) postulated that phenethyl isothiocyanate inhibition of CYP2E1 was the most likely mechanism, but that other CYPs may also be affected. Vistisen et al (40) showed that ingestion of broccoli (500 g/d for 10 d) also increased the CYP1A2-related caffeine metabolite ratio by an average of 12%. In another study, a single dose of watercress did not inhibit CYP2D6 in humans, as measured by metabolism of the drug debrisoquin (41).

The identification of phytochemicals that selectively metabolize known carcinogens is important to the development of chemoprevention strategies. Hecht et al (42) showed that phenethyl isothiocyanate can inhibit metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific lung carcinogen, in smokers. Watercress consumption (57 g, 3 times/d for 3 d) increased urinary excretion of detoxified metabolites by ≈30%. It appears that phenethyl isothiocyanate inhibits hepatic CYP1A2, resulting in more NNK undergoing reduction and conjugation to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNL) and its glucuronide (NNL-Gluc), and hence more excretion of these metabolites in the urine (42). I3C, a metabolite of glucobrassicin (found in cruciferous vegetables), may also protect against carcinogenesis by altering carcinogen metabolism. Five-day supplementation with I3C (400 mg/d) altered NNK metabolism in women who smoked (43). Unlike phenethyl isothiocyanate, I3C decreased conversion of NNK to NNL and NNL-Gluc. Both phenethyl isothiocyanate and I3C protect against NNK-induced lung tumorigenesis in rodents (44, 45); however, their effects on the NNK pathway, and therefore their mode of protection, are probably different.

Grapefruit juice also inhibits the biotransformation and increases the half-lives of several drugs in humans, including caffeine (46), and felodipine and nifedipine (47). This is presumably due to the inhibitory effects of flavonoids, particularly naringenin, on CYP1A2 (48) and enzymes in the CYP3A family (49).

Numerous oil- and water-soluble organosulfur molecules generated by enzymatic breakdown of precursor compounds in allium vegetables (onion and garlic family) have been studied for their effects on detoxification enzymes (27), but little of this work has been conducted in humans. In one study in 9 men, consumption of 3 g raw garlic/d for 8 d resulted in a 25% increase in *N*-acetyltransferase activity without significant changes in CYP1A2, CYP2A6, or xanthine oxidase (24). In another study, a 12-wk supplement of aged garlic extract given to 16 men had little effect on oxidative metabolism or glutathione conjugation of acetaminophen; however, sulfate conjugation increased slightly (50). These studies suggest that garlic may not influence CYP oxidation significantly in humans.

The studies to date of detoxification systems in humans have been short-term; chronic effects of vegetable and fruit constituents on regulation of these enzymes have not been examined. Normal ranges of expression or activity of these enzymes in human populations also need to be identified. Several other factors, including variation in environmental exposures and the influence of genetic polymorphisms on phenotype, are just beginning to be studied systematically.

Stimulation of the immune system

The human immune system has a central role in protecting against various external disease-promoting factors and perhaps against malignant cells. It is a complex and highly interactive network of cells and their products. A subset of immune cells recognizes and responds to external stimuli (*specificity*) and another component is capable of mounting a more vigorous and effective response the next time it receives a particular stimulus (*memory*). The immune system regulates itself by means of helper and suppresser cells and soluble products. Nutrients and other constituents of fruit and vegetables have the potential to affect almost all aspects of the immune system (51).

The relation of single nutrients to immune function (52), as well as the effect of nutrient-nutrient interactions (51) in humans and in animal models, has been reviewed comprehensively. Several of the vitamins associated with diets high in fruit and vegetables have been shown to improve immune status, particularly in older individuals. In a placebo-controlled, double-blind trial, 12 mo of supplementation with an over-the-counter multivitamin-and-mineral supplement improved delayed-type hypersensitivity skin responses in subjects aged 59–85 y, an effect that was not detected after 6 mo of supplementation (53). This effect was associated with significant increases in serum concentrations of ascorbate, ß-carotene, folate, vitamin B-6, and α-tocopherol at 6 mo, 12 mo, or both. Vitamin E supplementation alone also improves response to delayed-type hypersensitivity tests in healthy individuals >65 y of age (54). Subjects received either a placebo or 60, 200, or 800 mg *all-rac*-α-tocopherol/d for 235 d. The group given 200 mg/d had the greatest percentage increase in delayed-type hypersensitivity and antibody titer to hepatitis B compared with the placebo and the other 2 α-tocopherol doses. The optimal response detected at 200 mg/d suggests that there might be a threshold level for the immunostimulatory effect of α-tocopherol (54).

Natural killer (NK) cells, one of the types of immune cells, play an important function in immune surveillance, and NK cell activity is a component of the antitumor host defenses during tumor growth (55) and metastasis (56). It appears that nutrients and phytochemicals tend to affect NK cell activity without influencing cell number. Supplementation for 10–12 y with ß-carotene (50 mg on alternate days) resulted in 1.6-fold greater NK cell activity in elderly men (aged 65–85 y) relative to placebo without an increase in the percentage of NK cells or an increase in interleukin 2 (IL-2) receptor expression or IL-2 production; no effects of supplementation were observed in middle-aged men (aged 51–64 y) (57). Similarly, in healthy male college-student volunteers aged 20–25 y, 9 mo of ß-carotene supplementation (60 mg/d) did not alter NK cell numbers or virgin T cell, memory T cell, or cytotoxic T cell numbers (58). Two small human studies of garlic and immune function have produced encouraging results. A 12-wk garlic supplementation study (*n* = 7) significantly increased percentage NK cell activity from 5 ± 4% to 36 ± 15% in AIDS patients (59). In a 3-wk feeding study by Kandil et al (60; *n* = 7) using raw garlic (0.5 g/kg body wt) and aged garlic extract [1800 mg/d (allicin-free)], NK cell activity approximately doubled at 3 different effector-to-target cell ratios with both garlic treatments. The positive effect of the raw garlic, as well as the aged garlic extract that does not contain allicin, suggests that both allicin and other unidentified compounds may be responsible for the effects.

Peripheral blood mononuclear cells produce cytokines [eg, ILs and tumor necrosis factor (TNF)-α] that assist in the activation of T cells and enhance NK cell activity (51). Supplementation with vitamins C and E results in a transient increase in cytokine production (61). Vitamin C (1 g ascorbic acid), vitamin E (400 mg *all-rac*-α-tocopheryl acetate), vitamins C and E, or placebo were provided for 28 d as part of a randomized trial. On day 14, the combination of vitamins C and E increased IL-1ß and TNF-α production 1.8- and 1.5-fold, respectively; small increases were also detected with vitamin E, but vitamin C alone had no effect. However, by day 28, there was no difference in response among the supplement and placebo groups. Other cytokines not measured in this study may be influenced by sustained vitamin supplementation to modulate immune balance, resulting in the transient changes in IL-1ß and TNF-α that were observed (61).

Decreased platelet aggregation

Blood platelet aggregation is fundamental to a wide range of physiologic processes, ie, normal blood coagulation, thrombosis, atherosclerosis, and tumor formation and metastasis. Activated platelets adhere to altered blood vessel walls, aggregate, and release mitogenic factors that stimulate endothelial cell proliferation and a subsequent cascade of events leading ultimately to occluded vessels (62). The aggregation of host platelets by circulating tumor cells has been recognized as an important step for successful metastasis by some types of tumor cells (63). Platelets also play an important role in enhancing tumor cell–vasculature interactions (64). Thus, capacity to prevent excess and abnormal platelet aggregation is likely of issue in several chronic diseases.

Numerous pharmacologic studies have been conducted on the inhibition of the adhesion or aggregation of platelets by garlic preparations, garlic compounds, and products of enzymatic metabolism of these compounds [reviewed by Reuter et al (65)]. This inhibitory activity may also be the physiologic basis for some of the reported anticancer and antiatherogenic, effects of garlic. Human studies, albeit small ones, have helped to substantiate in vitro results of garlic's inhibition of platelet aggregation. Two studies reported reductions in platelet aggregation of 16.4% (66) and 58% (67), with 18 mg garlic oil (from 9 g fresh garlic) and 10 g fresh garlic cloves, respectively. These effects are attributed to the allylpropyldisulfide, diallyldisulfide, and other sulfur compounds contained in the essential oil (66). The specifics of the mechanism by which these compounds may alter platelet aggregation are not clear. Data from in vitro studies suggest that garlic extract inhibits platelet aggregation by altering both platelet lipoxygenase and cyclooxygenase activities and suppressing thromboxane B synthesis (68). Similarly, some of the flavonoids may act by inhibiting 5-lipoxygenase and cyclooxygenase pathways by a mechanism not related to their antioxidant capacities (69). Effects of phytochemicals on these pathways in humans have yet to be studied.

Attempts to identify dietary constituents that may explain the cardiovascular benefits of the Mediterranean diet and explain the so-called "French paradox" have focused in part on the phytochemicals in red wine and its precursor, grape juice. Working under the hypothesis that these beverages may contain bioactive polyphenols in sufficient concentrations to favorably modulate platelet aggregation and eicosanoid production, the antiaggregatory actions of the polyphenols resveratrol and quercetin on platelets from humans were first shown in vitro (70–72). Seigneur et al (73) reported that red wine was more effective than white wine in reducing platelet aggregation and plasma thromboxane B_2 concentrations in human volunteers. However, a follow-up study by Pace-Asciak et al (74), testing whether grape juice or grape juice enriched with resveratrol had effects similar to those of red wine, failed to show any significant antiaggregatory effect of the polyphenols.

Mitogenic factors released by platelets, such as platelet-derived growth factor (PDGF), are thought to be important in the initiation and progression of atherosclerotic lesions and to respond to alterations in diet (75). Ross et al (75) detected increases in serum PDGF-AB concentrations (adjusted for platelet concentrations) when study participants consumed diets high in carotenoid-rich vegetables (carrots and spinach) and soyfoods (tofu and textured soy protein). Cruciferous vegetables (broccoli and cauliflower) did not increase PDGF-AB above baseline, and none of the diets changed mitogenic activity. Until the complex feedback mechanisms that regulate growth factors have been worked out more completely in humans, the biological significance of these observed effects is not clear; however, this may be an additional mechanism by which vegetables may influence disease risk (75).

Alterations of cholesterol metabolism

Elevated serum total cholesterol, LDL-cholesterol, and triacylglycerol concentrations, as well as reduced HDL-cholesterol concentrations, are identified risk factors for coronary artery disease (76, 77). Treatment of hypercholesterolemia has focused on increasing fecal excretion of cholesterol and bile acids and reducing hepatic cholesterol synthesis through diet modification and use of pharmacologic agents. The hypocholesterolemic effects of vegetables and fruit and their constituents have been examined in some detail.

Isolated dietary fibers from vegetable and fruit sources, particularly pectins, have been shown to have hypocholesterolemic action in humans (78, 79). The addition of pectin- and fiber-containing foods to experimental diet also lowers plasma cholesterol to varying degrees as follows: a variety of vegetables (570 g/d) and fresh apples (600 g/d) by 4% (80), fresh carrots (200 g/d) by 11% (81), apples (350–400 g/d) by 8–11% (82), guava fruit (0.5–1 kg/d) by 8% (83), and prunes (100 g/d) by 5% (84). Another carrot feeding study reported no change in cholesterol after a 3-wk trial (85). The mechanisms for the hypolipidemic action in humans remain unclear. Results from animal studies that used isolated fibers suggest that the reductions in cholesterol are probably due to different mechanisms specific to each fiber source and to different dietary fiber intake amounts (86). On the basis of the physiologic effects observed in humans, possible mechanisms include *1*) increased excretion of fecal bile acids and neutral steroids, *2*) altered ratios of primary to secondary bile acids, *3*) increased fecal cholesterol and fatty acid excretion, *4*) and indirect effects, such as high-fiber foods replacing fat- and cholesterol-containing foods in the diet (87). However, the contribution of vegetable and fruit fibers to these effects have not been studied stringently.

Garlic and garlic extracts reduce cholesterol and triacylglycerol concentrations in a variety of conditions, including induced alimentary hyperlipidemia and normo- and hypercholesterolemia. A meta-analysis of 16 trials reported a mean difference in reduction of total cholesterol of 0.77 mmol/L (12% reduction) between garlic-treated groups and control subjects who avoided garlic or received a placebo—without a significant change in HDL cholesterol (88). Similarly, a recent placebo-controlled trial in hypercholesterolemic subjects reported a reduction in mean total and LDL cholesterol of 11.5% and 14.2%, respectively, with 900 mg garlic/d for 12 wk (89). These LDL-cholesterol lowering effects of garlic may be due to inhibition of hepatic cholesterol biosynthesis via inhibition of hydroxymethylglutaryl-CoA reductase (NADPH) (EC 1.5.1.20) (90).

Modulation of steroid hormone concentrations and hormone metabolism

Consumption of a vegetarian diet is associated with lower circulating concentrations of sex steroid hormones, increased fecal excretion of estrogens, and different hormonal profiles than those observed with consumption

of an omnivorous diet (91). In the past, much of the response to such a diet has been attributed to the physiologic effects of dietary fiber, either alone (92) or in tandem with effects of a low-fat diet (93, 94). However, other constituents of vegetables and fruit also may influence metabolism of endogenous steroid hormones.

Certain of the CYP enzymes that metabolize phytochemicals, are modulated by phytochemicals, or both, contribute to the inactivation of endogenous steroid hormones. They alter the potency of testosterone, estrogen, and their derivatives via oxidation and hydroxylation reactions (95). Thus, induction or inhibition of these enzyme systems in vivo also has the potential to modify substantially the biological impact of hormones in humans.

Metabolism of estrogen includes hydroxylation at various sites on the molecule, producing numerous hydroxylated metabolites with varying degrees of biological activity. Excess production of certain metabolites, particularly 16α-hydroxyestrogens, has been postulated to increase breast cancer risk (96); conversely, 2-hydroxylation, at the expense of 16α-hydroxylation, may reduce the risk of disease (97). There is much interest in how diet may influence the total-body estrogen load through modulation of the CYP enzymes involved in estrogen metabolism. Effects of I3C, a constituent of cruciferous vegetables, on estrogen metabolism have been observed in men and women. In men, 500 mg I3C/d (equivalent to 300–500 g cabbage) for 7 d increased estrone 2-hydroxylation from 29% to 46% (98). A randomized clinical trial compared the effects of 400 mg I3C, 20 g cellulose, and placebo daily on 2-hydroxylation of estrogen in women (97). The mean ratio of 2-hydroxyestrone-to-estriol, a measure of 2-hydroxylation, increased 1.6-fold in the first month and remained at that level for the 3 mo of the study; no change from baseline was observed in the cellulose or placebo group. A study in an Israeli kibbutz reported a similar response to a cruciferous diet calculated to contain 400 mg I3C/d (97). More recently, Michnovicz et al (99) showed that I3C supplementation significantly increased urinary excretion of 2-hydroxylated estrogens in men and women.

Like sex steroids, corticosteroids are also hypothesized to be influenced by plant-food intake. Lee et al (49) showed, in a preliminary study, that 946 mL (1 quart) grapefruit juice/d over a 7-d period resulted in a decrease in urinary cortisone-cortisol ratios in only 2 of 6 men. The men were free-living; thus, it is not clear whether the lack of response in two-thirds of the sample was due to a biological difference or lack of adherence to the juice intervention. In the 2 men who responded to the 946-mL dose (the investigators), subsequent consumption of grapefruit juice at doses of 1 and 2 L/d resulted in a dose-dependent decrease in urinary cortisone-cortisol ratios. A separate 3-wk trial conducted in 2 other men admitted to a clinical research center also showed a shift in cortisone-cortisol ratios, suggesting that under controlled conditions that promote adherence, grapefruit juice may have an effect. The authors postulated that the decrease in urinary cortisone-to-cortisol ratios was due to inhibition of 11ß-hydroxysteroid dehydrogenase.

Blood pressure reduction
Blood pressure control is important for the prevention of heart disease, kidney disease, and stroke, and can be influenced by numerous factors. Hypertension can be caused by atherosclerosis, imbalances in the renin-angiotensin system, and hyperinsulinemia, which increases sodium retention in the body and speeds atherosclerosis. Consequently, a general nutritional plan to minimize hypertension risk has included attaining and maintaining a healthy body weight; consuming a diet rich in calcium, phosphorus, and magnesium; and consuming alcoholic beverages and sodium in moderation (100).

Replacing animal products with vegetable products in vegetarian-diet trials reduces blood pressure in normotensive and hypertensive individuals (101, 102). Lower intakes of fat and higher intakes of dietary fiber and minerals, such as potassium and magnesium, are aspects of a high-vegetable, high-fruit diet believed to reduce blood pressure. However, results of trials testing these nutrients, usually as dietary supplements, have been inconsistent (103). One crossover study took a more holistic, rather than supplement-based, approach toward examining the effect of fiber from fruit and vegetables. Men consumed a high-fiber diet of fruit and vegetables and a lower-fiber diet of fruit and vegetable juices in a randomized cross-over study by Kelsay et al (104). Each diet was consumed for 26 d. Men who had diastolic blood pressures of ≥80 mm Hg when consuming the lower-fiber diet had lower blood pressures when consuming the high-fiber diet.

In a large, randomized, controlled trial of diet and blood pressure that provided a diet for 8 wk that included 8.5 or 3.6 (control) servings of vegetables and fruit daily, the participants who consumed the higher vegetable-and-fruit diet had a greater reduction in systolic and diastolic blood pressure than did the control subjects (103). In addition, the hypertensive subjects had greater reductions in blood pressure than did the normotensive subjects. The diets were designed to be isoenergetic and maintain body weight; to have similar distributions of carbohydrate, protein, and fat; and to have the same amounts of calcium and sodium. Dietary fiber, magnesium, and potassium intakes were 2–3 times higher with the vegetable and fruit diet. Under these conditions, changes in blood pressure could be attributed to the increased vegetable and fruit intakes. A third study arm with vegetables and fruit plus low-fat dairy products reduced blood pressure even further.

Few studies have examined the effect of feeding individual vegetables or fruit on blood pressure in humans. Garlic is probably the most studied vegetable. Reported reductions in systolic and diastolic blood pressures in response to garlic supplementation have been on average of the order of 6.7% and 7.9%, respectively (65). The mechanism for this hypotensive effect of garlic constituents in humans is not clear. Results of animal and in vitro studies suggest several possible mechanisms, including a direct relaxant effect on smooth muscle, increased blood adenosine concentrations via inhibition of adenosine deaminase and angiotensin-converting enzyme (EC 3.4.15.1), and production of nitric acid; the prostaglandin system does not seem to play a significant role (65). Addition of guava, a potassium-rich fruit, to the diet of patients with essential hypertension, was associated with net decreases in mean systolic and diastolic pressures of 7.5 and 8.5 mm Hg, respectively (83).

Antibacterial and antiviral activity
Plants have developed sophisticated active defense systems against pathogens, one being the production of antibiotic compounds. Centuries of folk wisdom have identified certain fruits or vegetables as having antibacterial or antiviral potential; however, randomized, placebo-controlled clinical trials to test the effects of these plant foods and their phytochemicals are sorely lacking. Considering that *1*) viruses are now recognized as the second most important known cause of human cancer (105), *2*) several bacterial infections are associated with risk of certain cancers (106), and *3*) microbial drug resistance is becoming a persistent problem (107), efforts are needed to identify constituents of diet that could be part of a global scheme of primary prevention of infection.

Garlic has long been used as an antibiotic, antiviral, and antifungal agent, and in countries where modern medicines are scarce, it remains a treatment for infection (65). Before the era of sulfonamides and modern antibiotics, garlic preparations were used in epidemics of typhus, paratyphus, cholera, dysentery, amebic dysentery, diphtheria, tuberculosis, influenza, and poliomyelitis [reviewed by Reuter et al (65)]. During World War I, soldiers whose diets included garlic suffered less frequently from dysentery than those who did not eat garlic (65). In vitro, garlic juice and garlic extracts are effective against a broad spectrum of Gram-negative and Gram-positive bacteria (108). Even at low concentrations, they are especially potent inhibitors of *Helicobacter pylori*, the bacteria implicated in development of gastric and duodenal ulcers (109). Whether the in vitro effects are translatable to humans remains to be tested.

Cranberry juice has long been advocated as a treatment for urinary tract infections in women, although its effects were only just recently tested in a double-blind, randomized, placebo-controlled trial. Avorn et al (110) showed that 300 mL cranberry juice/d for 6 mo can influence bacterial flora in the urinary tract: bacteriuria and pyuria were found in 28% of urine samples from the placebo group compared with only 15% of the samples from the cranberry-beverage group. Effects appeared only after 4–8 wk, a time course, the authors noted, that could be compatible with modification of gut flora, the typical pathogens in urinary tract infections in women. There was no evidence that urinary acidification was responsible for the observed effect.

▶ INTERVENTIONS WITH DISEASE ENDPOINTS

Human dietary intervention studies using disease endpoints provide the strongest evidence for an effect of vegetables and fruit on disease risk. The disadvantages are that dietary intervention studies typically need to be large to have adequate statistical power, and consequently they are very expensive. Because such studies run only for a limited time and disease is the end result, typically they only give information about late-stage events. In addition, issues such as time of intervention, dose of intervention, compliance with the intervention, and choice of study populations influence interpretation of the results.

Nutrient supplement studies
Vegetables and fruit are rich sources of vitamins C and E, folic acid, and the vitamin A precursor ß-carotene. Epidemiologic studies often report an inverse association between these specific vitamins, as well as vegetable and fruit intake, and disease risk (2, 3). Observational studies cannot establish whether the vitamins themselves are protective or whether they are serving as markers of vegetable and fruit consumption; randomized trials are needed to test this. Clinical trials of vitamin supplementation with cancer and coronary heart disease incidence and mortality as outcomes, as recently reviewed by Patterson et al (111), Duell (112), and Boeing and Rausch (113), suggest that supplements of vitamins C and E and ß-carotene have varying degrees of success. Trials of cancer incidence did not show significant protective effects of ß-carotene in a healthy population (114) and were associated with increased risk of lung cancer in 2 high-risk populations (115, 116). Protective effects were found for α-tocopherol against prostate cancer; combinations of retinol and zinc and ß-carotene, α-tocopherol, and selenium against stomach cancer; and selenium against total, lung, and prostate cancers [described in (111)]. Large-scale trials examining effects of supplementation on cardiovascular and cerebrovascular disease risk reported increased mortality from cardiovascular disease (115, 116) and stroke (115) with ß-carotene supplementation and a nonsignificant 10% reduction in cerebrovascular mortality with a combination of ß-carotene, α-tocopherol, and selenium (117). Several other large, randomized trials are in progress to test the efficacy of vitamin and mineral supplementation in prevention of coronary heart disease and cancer (113).

Dietary interventions

To date, intervention studies of disease prevention using vegetables, fruit, or both are rare. In a 1-y randomized trial, consumption of a low-fat diet enriched with fruit and vegetables compared with a standard low-fat diet was associated with an apparent 40% reduction in cardiac events and a 45% reduction in mortality in 406 men with myocardial infarction (118).

CONCLUSION

Vegetables and fruit and their constituents are potent effectors of biological systems in humans. Experimental dietary studies in humans show the capacity of these plant foods and some of their constituents to modify antioxidant pathways, detoxification enzyme profiles, and the immune system, as well as alter cholesterol and steroid hormone concentrations and metabolism (Table 1♦). Many phytochemicals have overlapping mechanisms of action, and within the context of a plant food, or even a plant-based diet, may have synergistic, additive, or inhibitory effects on each other. These aspects have barely begun to be addressed in human experimental studies.

A wide range of experimental approaches has been taken to test the effects of vegetables and fruit on risk factors for disease in humans (**Table 2♦**). Design methodologies used include multiple-arm trials, randomized crossover studies, and more compromised designs such as nonrandomized crossovers and pre- and posttreatment analyses. Duration of treatment varies from a single dose to years, depending on the mechanism of interest; however, study periods are a typically 2 wk to 1 mo in length and long-term effects are not well studied. Stringency of dietary control ranges from addition of supplements to a habitual diet to provision of all food for the duration of a treatment. Studies of this type, especially ones providing a controlled diet, are time and labor intensive. They can require a significant commitment by study participants. As a result, sample sizes are often small and may lack the statistical power to detect an effect. Despite the challenges, human experimental dietary studies must be rigorously designed and executed to provide meaningful data and a useful link between population- and laboratory-based studies.

View this table: [in this window] [in a new window]	**TABLE 2.** Summary of human studies that tested the effects of vegetables and fruit and their constituents on biological markers associated with disease risk[1]

The protective effects of vegetables and fruit observed in epidemiologic studies are not observed with pharmacologic doses of plant foods or their constituents, but with intakes constituting part of a usual diet. Although we often operate under the premise that "if some is good, more is better," the epidemiologic data show that consumption of vegetables and fruits within a range that is behaviorally possible and culturally normative is in itself beneficial; thus, conducting experimental studies using reasonable intakes of

a variety of plant foods is important in helping to elucidate the mechanisms by which humans are protected. Research on the effects of pharmacologic doses of individual plant food constituents may identify particular use for selected compounds, but considering that *1*) it is unlikely that any one compound will be a magic bullet preventing a whole myriad of chronic diseases, and *2*) humans will still continue to eat food to nourish body and soul, we must remain committed to consuming a variety of vegetables and fruit as part of a plant-food–based diet.

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