Overview of the health benefits of fruit and vegetable consumption for the dietetics professional: Selected literature

MARY ANN S. VAN DUYN, PhD, MPH, RD; ELIZABETH PIVONKA, PhD, RD

ABSTRACT

Epidemiologic evidence of a protective role for fruits and vegetables in cancer prevention is substantial. The strength of this scientific base guides US national policymaking in diet and health issues and facilitates community and local programs that address national dietary goals to increase fruit and vegetable consumption. Current scientific evidence also suggests a protective role for fruits and vegetables in prevention of coronary heart disease, and evidence is accumulating for a protective role in stroke. In addition, a new scientific base is emerging to support a protective role for fruits and vegetables in prevention of cataract formation, chronic obstructive pulmonary disease, diverticulosis, and possibly, hypertension. This article provides an overview of the health benefits associated with fruit and vegetable consumption for each of these conditions, including brief discussions of underlying protective mechanisms, identifies key scientific findings regarding the health benefits of fruit and vegetable consumption, and outlines applications of these findings for dietetics professionals. The evidence reviewed provides additional support for increased consumption of a wide variety of vegetables, in particular, dark-green leafy, cruciferous, and deep-yellow-orange ones, and a wide variety of fruits, in particular, citrus and deep-yellow-orange ones. Continued attention to increasing fruit and vegetable consumption is a practical and important way to optimize nutrition to reduce disease risk and maximize good health. *J Am Diet Assoc. 2000;100:1511-1521.*

Dietetics professionals, along with other health professionals, have the responsibility of providing consumers with scientifically supported facts to help them make informed dietary decisions. The scientific base supporting the unique health benefits derived from eating fruits and vegetables is growing rapidly. Epidemiologic researchers find a strong link between increased fruit and vegetable consumption and decreased risk of chronic diseases such as cancer, heart disease, and stroke. Evidence is also emerging about a positive role for fruit and vegetable consumption in reducing the risk of cataracts, diverticulosis, chronic obstructive pulmonary disease, and hypertension. Through the understanding, interpretation, and application of scientific data, dietetics professionals can help clients not only to be more aware of the health benefits of eating more fruits and vegetables, but also to increase their intake of fruits and vegetables.

In this overview of the health benefits of consumption of fruits and vegetables, the focus is an examination of current research reported in the professional literature. Discussions are provided of proposed underlying protective mechanisms of action and of applications of this information to encourage increased fruit and vegetable consumption as part of disease risk reduction and healthful eating. Primary sources of information for this review were epidemiologic and review articles published in peer-reviewed professional journals from 1989 to 1999; articles were identified via MEDLINE database searches. Search terms included *diet, nutrition,* and *fruits and vegetables* and specific medical conditions such as coronary heart disease, stroke, cataracts, and diverticulosis. Current government reports and recent major books reviewing the research on the health benefits associated with fruit and vegetable consumption also were consulted and were identified via National Library of Medicine searches. Studies reviewed focused on fruit and vegetable intake rather than on nutrient intakes or serum levels of nutrients or biomarkers of fruit and vegetable intake. The epidemiologic studies selected were intervention, prospective, and to a limited extent, case-control and ecological studies.

M. A. S. Van Duyn is a nutrition consultant in the Office of Communications, with the National Cancer Institute, Bethesda, Md. E. Pivonka is president of the Produce for Better Health Foundation in Wilmington, Del.

Address correspondence to: Elizabeth Pivonka, PhD, RD, Produce for Better Health Foundation, 5301 Limestone Rd, Wilmington, DE 19808-1249.

Table 1
Summary of epidemiologic evidence related to protective effect of fruit and vegetable consumption against cancers

Cancer[a]	Vegetables		Fruits	
	AICR[b]	COMA[c]	AICR	COMA
Mouth and pharynx	⇓Convincing	Inconsistent	⇓Convincing	⇓Weakly consistent
Larynx	⇓Probable	⇓Moderately consistent, limited data	⇓Probable	⇓Moderately consistent, limited data
Esophagus	⇓Convincing	⇓Strongly consistent	⇓Convincing	⇓Strongly consistent
Lung	⇓Convincing	⇓Weakly consistent	⇓Convincing	⇓Moderately consistent
Stomach	⇓Convincing	⇓Moderately consistent	⇓Convincing	⇓Moderately consistent
Pancreas	⇓Probable	⇓Strongly consistent, limited data	⇓Probable	⇓Strongly consistent, limited data
Liver	⇓Possible			
Colon, rectum	⇓Convincing	⇓Moderately consistent		⇓Inconsistent, limited data
Breast	⇓Probable	⇓Moderately consistent	⇓Probable	⇓Weakly consistent
Ovary	⇓Possible	⇓Insufficient	⇓Possible	⇓Insufficient
Endometrium	⇓Possible	⇓Insufficient	⇓Possible	⇓Insufficient
Cervix	⇓Possible	⇓Strongly consistent, limited data	⇓Possible	⇓Strongly consistent, limited data
Prostate	⇓Possible	⇓Moderately consistent, especially raw and salad type		Inconsistent
Thyroid	⇓Possible		⇓Possible	
Kidney	⇓Possible			
Bladder	⇓Probable	⇓Moderately consistent, limited data	⇓Probable	⇓Moderately consistent, limited data

[a]No evidence found by AICR or COMA for nasopharynx or gallbladder cancers.
[b]AICR=American Institute for Cancer Research (1).
[c]COMA=Committee on Medical Aspects of Food and Nutrition Policy (British Department of Health) (3).
⇓=decreasing risk.

Table 2
Summary of results of studies examining associations between vegetable and fruit intake and coronary heart disease[a]

Study type	Vegetable or fruit category	Association		
		Protective	Null	Negative[b]
Ecological	Vegetables	7[c]	0	1
	Fruits	4	1	2
Case-control	Vegetables	3	0	0
	Fruits	3	0	0
Prospective	Vegetables	6	2	0
	Fruits	5	2	0

[a]Summary of findings reviewed by Klerk et al. (5) and Ness and Powles (6). Eight ecological, 3 case-control, and 9 prospective studies were reviewed.
[b]Negative for the absence (not eating) of vegetables or fruits.
[c]Number of studies.

CANCER

Some of the most convincing evidence for the health benefits of fruit and vegetable consumption relates to the risk of certain cancers. A report commissioned by the World Cancer Research Fund and the American Institute for Cancer Research (AICR), in which an exhaustive collection of worldwide research on this topic was reviewed, estimated that "diets high in vegetables and fruits (more than 400 g/day) could prevent at least 20% of all cancer incidence" (1). In the United States, cancer is the second leading cause of death after cardiovascular disease and is responsible for 1 of 4 deaths (2).

A second extensive review of research on the health benefits of fruit and vegetable consumption and cancer risk is the report of the Chief Medical Officer's Committee on Medical Aspects of Food and Nutrition Policy (COMA), British Department of Health (3). The majority of the research reviewed both by COMA and AICR is drawn from epidemiologic studies.

Table 1 summarizes the epidemiologic evidence related to vegetable and fruit intakes and cancer as assessed by AICR and COMA. The AICR panel classified the strength of evidence as convincing, probable, or possible. The COMA working group used classifications of strongly consistent, moderately consistent, and weakly consistent. In general, COMA tended to be more conservative in its judgment of the evidence than AICR.

Both AICR and COMA found the scientific base convincing (AICR) or strongly consistent (COMA) for a protective effect of vegetables and fruits against esophageal cancer. For a number of other site-specific cancers, AICR and COMA tended to differ somewhat in their assessments of the scientific base. For stomach and colorectal cancers, the evidence was judged convincing (AICR) or moderately consistent (COMA) for vegetables. However, for fruits in stomach cancer, AICR judged the evidence convincing, whereas COMA determined it to be only moderately consistent, and for fruits in colorectal cancer, AICR declined to comment, whereas COMA found the evidence limited and incinsistent. For cancers of the lung and mouth and pharynx, AICR found the evidence convincing for a protective effect of high intakes of vegetables and fruits.

However, COMA determined the evidence moderately consistent for fruits in lung cancer, only weakly consistent for fruits in cancers of the mouth and pharynx and for vegetables in lung cancer, and inconsistent for vegetables in cancers of the mouth and pharynx. For laryngeal cancer, the scientific base was determined to be moderately consistent (COMA) or probable (AICR) for a protective effect of fruits and vegetables.

AICR judged the evidence as probable for a protective effect of vegetables and fruits against breast cancer and as stronger and more consistent for a protective effect of vegetables, particularly green vegetables. COMA assessment of the evidence in breast cancer was similar to that of AICR for vegetables, but COMA determined the evidence only weakly consistent for fruits. The evidence is less strong for cancers of the prostate, ovary, endometrium, cervix, thyroid, kidney, bladder, and liver according to AICR and COMA.

Despite some differences in their assessments of the underlying science, summary recommendations by AICR and COMA for vegetable and fruit intake related to cancer focus on variety. AICR promotes year-round consumption of a variety of vegetables and fruits, which should provide 7% or more of total energy. COMA recommends increasing intakes of a wide variety of fruits and vegetables.

For cancer prevention, AICR established a goal of eating 400 to 800 g (15 to 30 oz) of a variety of vegetables and fruits, which translates to 5 to 10 servings of vegetables and fruits daily. COMA did not quantify an optimum level of fruit and vegetable intake. COMA did, however, recommend that fruit and vegetable consumption increase, and stated that any increases would be expected to confer benefit.

HEART DISEASE

Coronary heart disease, the major cause of death in the United States, is the most common and most serious form of cardiovascular disease. Despite a decline in deaths from coronary heart disease during the past 30 years, this disease still causes more than 700,000 deaths annually and contributes to another 250,000 deaths (4).

Epidemiologic evidence is growing for a protective role of fruits and vegetables in coronary heart disease. A report by Klerk and colleagues (5) reviewed findings from 4 ecological, 2 case-control, and 7 cohort studies conducted after 1994 that focused on foods rather than nutrients. They estimated risk reduction for coronary heart disease to be 20% to 40% (5). In another review, Ness and Powles (6) examined findings from 5 ecological, 2 case-control, and 6 cohort studies that focused on foods and reported, but did not quantify, a protective effect of fruits and vegetables against coronary heart disease (6).

Table 2 presents a summary of the findings reviewed by Klerk et al (5) and Ness and Powles (6) from studies in which fruit and vegetable intake, rather than nutrient intakes, were examined. Taken together, findings from the ecological, case-control, and prospective studies reviewed by these authors support a protective role for vegetables and fruits in coronary heart disease.

Examples, particularly from cohort studies, highlight the protective role of fruits and vegetables. Knekt and associates (7) reported a protective effect against death from coronary heart disease for both fruits and vegetables in a large group of Finnish men and women. These researchers controlled for some potential lifestyle confounders (age, gender, smoking status, obesity, and energy intake), which suggests that their finding is not explained by these factors and thereby, strength-

Table 3
Summary of results of studies examining associations between vegetable and fruit intake and stroke[a]

Study type	Vegetable or fruit category	Association		
		Protective	Null	Negative
Ecological	Vegetables	2[b]	0	1
	Fruits	2	0	1
Prospective	Vegetables	5	1	0
	Fruits	4	2	0

[a]Summary of findings reviewed by Klerk et al. (5) and Ness and Powles (6). Three ecological and 6 prospective studies were reviewed; no case control studies were reviewed..
[b]Number of studies.

Table 4
Phytochemicals: functions and presence in fruits and vegetables[a]

Phytochemicals	Function	Presence	
		Fruits	Vegetables
Sulfides (allium)			
Diallyl sulfide	Stimulates anticancer enzymes, detoxifies carcinogens; antibacterial activity may inhibit conversion of nitrate to nitrate, thereby reducing formation of nitrosamines which are thought to be carcinogenic		x
Allyl methyl trisulfide	Stimulates anticancer enzymes, detoxifies carcinogens; antibacterial activity may inhibit conversion of nitrate to nitrate, thereby reducing formation of nitrosamines which are thought to be carcinogenic		x
Dithiolthiones	Increases activity of enzymes involved in detoxification of carcinogens and other foreign compounds		x
Carotenoids			
α-Carotene	Antioxidant; precursor to vitamin A inhibits cell proliferation		x
Beta carotene	Antioxidant; precursor to vitamin A; helps in differentiation of normal epithelial cells; inhibits cell proliferation	x	x
Lutein	Antioxidant; protects against cataracts, macular degeneration		x
Lycopene	Antioxidant	x	x
Flavonoids			
Quercetin	Antioxidant; may reduce cell proliferation; extends action of vitamin C; inhibits blood clot formation; antiinflammatory action	x	x
Kaempferol	Antioxidant; may reduce cell proliferation; extends action of vitamin C; inhibits blood clot formation; antiinflammatory action	x	x
Tangeretin	Antioxidant; may reduce cell proliferation; extends action of vitamin C; inhibits blood clot formation; antiinflammatory action	x	
Nobiletin	Antioxidant; may reduce cell proliferation; extends action of vitamin C; inhibits blood clot formation; antiinflammatory action	x	
Rutin	Antioxidant; may reduce cell proliferation; extends action of vitamin C; inhibits blood clot formation; antiinflammatory action	x	
Glucosinolates/Indoles			
Glucobrassicin	Forms indoles		x
Indoles	Protects against estrogen-promoted cancers, induces protective enzymes		x
Phytoestrogens			
Genistein	Antioxidant; inhibits growth of cancer cells; lowers blood cholesterol level and platelet aggregation		x
Biochanin A	Antioxidant; inhibits growth of cancer cells; lowers blood cholesterol level and platelet aggregation		x
Lignans	Antioxidant; may block or suppress cancerous changes	x	x
Isothiocyanates			
Sulphorophane	Exceptionally potent inducer of detoxification enzyme		x
D-Limonene	Increases activity of glutathione transferase, a detoxification enzyme	x	
Phytosterols	Protects against hormone-dependent cancers, slows colon cancer and growth		x
Protease inhibitors	Anticancer agent; suppresses enzyme action of cancer cells		x
Saponins	Anticancer activity; possibly by preventing tumor cell division; binds bile acids and cholesterol to help reduce cholesterol level		x
Phenols			
Chlorogenic acid	Prevents cancer-causing nitrosamines	x	x
Ellagic acid	Antioxidant; protects DNA from damage by carcinogens	x	
Caffeic acid	Prevents formation fo carcinogens and blocks reaction of carcinogens with cells	x	
Coumarin	Increases activity of glutathione transferase, a detoxification enzyme	x	x
Catechin	Antioxidant	x	
Capsaicin	Antioxidant; prevents carcinogens from binding to DNA		x
Resveritrol	Antioxidant; protects against heart disease	x	
Anthocyanins	Antioxidant	x	x
Tannins	Prevents carcinogens from binding to target sites	x	x

Table 4 (cont'd)
Phytochemicals: functions and presence in fruits and vegetables[a]

Phytochemicals	Function	Presence	
		Fruits	Vegetables
Terpenes	Produces enzymes that deactivate carcinogens; prevents carcinogens from reacting with target sites; possibly prevents hormones that promote tumor growth	x	x
Dietary fiber	Binds to and dilutes carcinogenic substances; speeds carcinogens through digestive tract; helps control diabetes and high serum cholesterol level; may prevent diverticulosis	x	x
Vitamins/minerals			
Vitamin C	Antioxidant; reduces nitrite, thereby reducing formation of nitrosamines	x	x
Vitamin E	Antioxidant that protects polyunsaturated fatty acids in cell membranes from oxidation; assists with antioxidant capacity of selenium	x	x
Folic acid	Inadequate intake may lead to chromosomal damage at sites relevant to specific cancers; may also lead to reduced methylation of DNA, which may permit a loss of normal controls on the expression of genes	x	x
Potassium	May help prevent or control hypertension and reduce the subsequent risk of stroke and heart disease	x	x
Selenium	A cofactor for glutathione peroxidase, an enzyme that protects against oxidative tissue damage	x	x

[a]Sources: Coughlin C, DeBusk R. *Integrative Medicine, Your Quick Reference Guide.* 1998; Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc.* 1996;96:1027-1039; Nutrient Data Bank for Fresh Fruits and Vegetables. Produce Marketing Association; 1991; Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II Mechanisms. *Cancer Causes Control.* 1991;2:427-442; Beecher G. *Nutr. Rev.* 1999;57(9):S3-S6; Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: an evaluation of analytic data. *J Am Diet Assoc.* 1993;93:284-296.

ens their results. Additional strengths of this study were the large number of persons who were followed up and use of a diet history methodology (7). Key et al (8), who studied health-conscious individuals, found reductions of 21% to 32% in mortality from all causes, ischemic heart disease, and cerebrovascular disease among daily consumers of fresh fruits compared with those who ate less fruit. Rimm and colleagues (9) reported a protective effect of fruit and vegetable consumption on risk of heart attacks among male professionals. In another cohort study, La Vecchia et al (16) reported a high intake of vegetables associated with a decreased prevalence of heart attacks and angina pectoris. Klerk et al (5) also found a high intake of vegetables, particularly raw and leafy green vegetables, to be protective against heart attacks, and for intake of fruits, only citrus fruits were protective.

A study by Ornish et al (11) adds important new information. In a 5-year trial of 48 participants, Ornish et al demonstrated for the first time that a diet consisting mostly of vegetables, grains, beans, and fruits, with no animal products except for the occasional nonfat dairy product, in combination with other lifestyle changes can reverse heart disease without the need for medications or medical procedures, compared with an American Heart Association diet.

STROKE

Exciting new evidence is accumulating for a protective role for fruits and vegetables in stroke. Stroke is the third leading cause of deaths in the United States and each year kills about 160,000 of the 500,000 people who experience one (4).

Although the evidence is still limited, results of 1 ecological and 4 cohort studies suggested to Klerk and colleagues (5) that the high intake of fruits and vegetables may reduce the risk of stroke up to 25%. Ness and Powles (6), in their review of 3 ecological, 1 case-control, and 4 cohort studies, were particularly impressed with the protective effect of fruits and vegetables against stroke, which they found to be even stronger than in coronary heart disease. Table 3 provides a summary of the findings from these studies that focus on foods. Although limited in number, the studies suggest a protective effect of vegetables and fruits against stroke.

A recent prospective study by Joshipura et al (12) showed that consumption of 6 servings daily of fruits and vegetables was associated with a 30% reduction in the risk of ischemic stroke among men and women. This study, which controlled for known lifestyle confounders, found green leafy and cruciferous vegetables and citrus fruits and juice, in particular, to be protective.

PROPOSED ACTIVE COMPOUNDS IN FRUITS AND VEGETABLES THAT PROVIDE HEALTH BENEFITS

Cancer

The mechanism that explains the health benefits from vegetables and fruits in relation to cancer is yet to be determined but is likely to be multiple in origin. There are estimated to be more than 100 beneficial vitamins, minerals, fiber, and other dietary components (13). Some of these healthful substances are found in particular types of fruits and vegetables (14).

Tables 4 and 5 identify common phytochemicals and other potential anticarcinogenic compounds by their function and presence in fruits and vegetables (Table 4), then by their presence in specific types of fruits and vegetables (Table 5). Deep yellow-orange vegetables and fruits, such as carrots, sweet potatoes, winter squash, cantaloupe, and mango, are rich sources of beta carotene, a carotenoid, which as an antioxidant may protect cell membranes and DNA from oxidative damage. Vitamin C, which is found in citrus fruits, lutein, which is found in green leafy vegetables (such as collards and spinach), and lycopene, which is found in fruits and vegetables of deep-red color, are also antioxidants. Dark-green leafy vegetables and some citrus fruits are also good sources of folic acid, which may have a protective role at the molecular level in cancer development. Cruciferous vegetables, such as broccoli, cauliflower, and cabbage, are major sources of sulfur-contain-

Table 5
Phytochemicals in specific vegetables and fruits

Vegetable/fruit	Sulfides	Carotenoids	Flavonoids	Glucosinolates/indoles	Phytoestrogens	Isothiocyanates	Phenols	Other
Vegetables								
Allium vegetables								
Onion	x		x				x	Saponins
Garlic	x		x				x	Saponins
Green onion	x		x				x	
Leek	x		x				x	
Chive	x		x				x	
Artichoke			x				x	
Asparagus		x	x				x	
Beans								
Lima bean			x		x	x	x	Saponins, phytosterols
Pinto bean			x		x	x	x	Saponins, phytosterols
Chickpea			x		x	x	x	Saponins, phytosterols
Kidney bean			x		x	x	x	Saponins, phytosterols
Lentil			x		x	x	x	Saponins, phytosterols
Split pea			x		x	x	x	Saponins, phytosterols
Soybean			x		x	x	x	Phytosterols, saponins, lignans, protease inhibitors
Tofu			x		x	x	x	Saponins
Beet			x				x	
Belgian endive			x				x	
Bell pepper		x	x				x	Terpenes
Carrot		x	x				x	Terpenes
Celery		x	x				x	
Corn		x	x					
Cruciferous vegetables								
Broccoli		x	x	x		x	x	Dithiolthiones, tannins, terpenes
Bok choy			x	x		x	x	Dithiolthiones, tannins, terpenes
Cauliflower			x	x		x	x	Dithiolthiones, anthoxanthins
Brussels sprout		x	x	x		x	x	Dithiolthiones, anthoxanthins
Green cabbage		x	x	x		x	x	Dithiolthiones, anthoxanthins
Kale		x	x	x		x	x	Terpenes
Cucumber			x			x		Phytosterols, terpenes
Eggplant			x					Terpenes, anthocyanins
Ginger root			x					Gingerol
Green leafy vegetables								
Collard		x	x				x	
Endive		x	x				x	
Iceberg lettuce		x	x				x	
Leaf lettuce		x	x				x	
Mustard green		x	x	x			x	
Parsley		x	x				x	Terpenes
Romaine lettuce		x	x				x	
Spinach		x	x				x	
Green snap bean		x	x				x	
Hot chili pepper		x	x					Capsaicin
Mushroom			x					Terpenes
Okra			x					
Potato			x				x	
Pumpkin		x	x				x	
Radish			x				x	Anthocyanins

Table 5 (cont'd)
Phytochemicals in specific vegetables and fruits

Vegetable/fruit	Sulfides	Carotenoids	Flavonoids	Glucosinolates/indoles	Phytoestrogens	Isothiocyanates	Phenols	Other
Rutabaga			x	x			x	
Summer squash		x	x				x	Terpenes
Sweet potato		x	x				x	Terpenes
Tomato		x	x				x	Terpenes
Turnip			x	x			x	
Winter squash		x	x				x	
Fruits								
Apple			x				x	
Apricot		x	x					
Avocado		x	x					
Banana			x					
Berries								
Blueberry			x				x	Lignans, catechins, tannins
Cranberry			x				x	Catechins
Raspberry			x				x	Lignans, catechins, tannins
Blackberry			x				x	Lignans, catechins, tannins
Strawberry			x				x	Saponins, lignans, catechins, tannins
Cantaloupe		x	x					
Carambola			x					
Cherry		x	x					
Citrus								
Grapefruit			x			x	x	Terpenes
Red grapefruit		x	x			x	x	Terpenes
Lemon			x			x	x	Terpenes
Lime			x			x	x	Terpenes
Orange			x			x	x	Terpenes
Tangerine			x			x	x	Terpenes
Date			x					
Fig			x					
Grape			x				x	Anthocyanins, resveritrol
Honeydew melon			x					
Kiwifruit		x	x					
Mango		x	x					
Nectarine			x					
Papaya			x				x	
Peach		x	x					
Pear			x					
Pineapple			x				x	
Plum		x	x					
Prune		x	x					
Raisin			x					
Rhubarb		x	x					
Watermelon		x	x					

[a]Sources: Coughlin C, DeBusk R. *Integrative Medicine, Your Quick Reference Guide.* 1998; Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc.* 1996;96:1027-1039; Nutrient Data Bank for Fresh Fruits and Vegetables. Produce Marketing Association; 1991; Steinmetz KA, Potter JD. *Cancer Causes Control.* 1991;2:427-442; Beecher G. *Nutr. Rev.* 1999;57(9):S3-S6; Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: an evaluation of analytic data. *J Am Diet Assoc.* 1993;93:284-296.

ing compounds (for example, isothiocyanates and dithiolthiones), which help to increase enzyme activity involved in detoxifying carcinogens and other harmful foreign substances. Cruciferous vegetables are also rich sources of indoles, which have been shown to block tumor production in animal studies. Allium-containing vegetables, such as onions, garlic, scallions, and leeks, contain sulfur compounds known to activate enzyme detoxification systems in the body.

Other potential protective substances occur in a variety of fruits and vegetables rather than just a type of category of fruit or vegetable (14). Flavonoids, such as quercetin, are phenols that occur widely in most all vegetables and fruits and may help to remove carcinogens from body cells. Isoflavones, a phytoestrogen, are uniquely found in one category of food—legumes—and appear to exert their protective effect by blocking binding to cell receptors.

Heart Disease

A number of possible mechanisms have been put forward to explain the protective benefit of fruits and vegetables against heart disease. The antioxidants in fruits and vegetables, such as vitamin C, beta carotene and other carotenoids, and flavonoids may reduce the risk of heart disease by reducing the oxidation of cholesterol in the arteries. Antioxidant minerals, such as selenium and zinc, and other antioxidant compounds such as sulfur-containing compounds or the allium family may also help explain the protective effect. Another line of reasoning proposes that the folic acid, found widely in fruits and vegetables such as dried beans, green leafy vegetables, melons, and oranges, and vitamins B-6 and B-12 help to lower blood homocysteine, a known risk factor for cardiovascular disease (5). The soluble fiber in fruits and vegetables may help to control serum cholesterol level; a high level is a well-established risk factor for cardiovascular disease.

Stroke

Results of the Rancho Bernardo Study suggested that intake of potassium may be responsible for the association between high intake of fruits and vegetables and low mortality from stroke (15). Newer data from a Dutch prospective study on stroke, however, suggest that low levels of dietary flavonoids are associated with a higher risk of stroke (16). Previously this group found that intake of flavonoids was protective against the risk of coronary heart disease in elderly men (17). Fiber and folic acid have also been associated with protection against stroke. However, the evidence is extremely limited for fiber, and for folic acid the protection may be exhibited through lower levels of plasma total homocysteine levels (5).

DISEASE STATES FOR WHICH SOME EVIDENCE IS AVAILABLE FOR A PROTECTIVE ROLE FOR FRUITS AND VEGETABLES

A developing body of scientific evidence indicates that fruits and vegetables may play a preventive role in cataract formation, chronic obstructive pulmonary disease (COPD), diverticulosis, and, possibly, hypertension. This section provides an overview of each of these major diseases, and where appropriate and available, a brief description of proposed underlying protective mechanisms.

Cataracts

A unique, relatively newly identified protective role for fruits and vegetables is in cataract prevention. Cataracts are one of the world's major causes of blindness: an estimated 50 million people in the world are blind because of cataracts (5). Cataracts are most common among the elderly. Occurrence in the United States increases from 5% at age 65 to 40% for persons 75 years and older (18). Health care costs associated with cataracts among the elderly are significant. In the United States, age-related cataracts cost $5 billion per year, the largest single item in Medicare expenditures, and account for 1.2 million cataract extractions per year (19).

Substantial evidence suggests that consumption of high levels of antioxidants—vitamins C and E and carotenoids—is associated with delayed development of the various forms of cataracts (200). There is some epidemiologic evidence that the same beneficial relationship exists for fruits and vegetables.

The case for a protective role for fruits and vegetables in cataract development begins with case-control studies such as the one by Jacques and Chylack (21). They found high fruit and vegetable intake associated with lower risk of any form of cataracts. A significant 5-fold reduction in relative risk of cataracts was demonstrated among individuals who consumed more than 1.5 daily servings of fruits, vegetables, or both fruits and vegetables. In another case-control study of middle-aged and older residents of Beaver Dam, Wisconsin, dietary sources of folic acid, fiber, and carotenoids, particularly from vegetables, were associated with lower risk of cataracts, especially in men (22). In a cohort study of women 45 to 67 years of age followed for 8 years, Hankinson et al (23) found high dietary carotenoid intake, particularly from green vegetables, associated with a lower risk of cataract extraction. Women who consumed high levels of carotenoids were noted to have a 39% lower risk of cataract extraction than low consumers (23). Another cohort study of US male health professionals found foods rich in beta carotene (eg, spinach, broccoli, corn, and tomato sauce) associated with a significantly lower risk of cataracts (24).

Chronic Obstructive Pulmonary Disease

COPD is a collection of diseases that affect the airways in the mucous membranes of the respiratory tract and obstructions in the small bronchial tubes. In 1998 COPD was the fourth leading cause of death in the United States; it affected 10% to 20% of adults (4). Common examples of COPD are asthma and bronchitis, each of which affects approximately 15 million people in the United States, or about 5% of the population.

Five epidemiologic studies examined the role of fruits and vegetables in COPD. In a cross-sectional study Cook and colleagues (25) reported improved lung function in children who consumed fresh fruits more than once a day compared with those who did not. Consumption of salad and green vegetables in this group of British school-aged children (8 to 11 years old) was also associated with a beneficial effect on lung function, but it was weaker than the effect of fresh fruits (25). Strachan et al (26) found that consumption of winter fruits had a protective effect on lung function in British adults in comparison with those who never drank fruit juice and only ate fresh fruits less than once a week. This association was true across ages (participants ranged in age from 18 to 69 years) and among current nonsmokers and those who had never smoked. In the cohort Zutphen Study, consumption of fruit, in particular solid fruits, was found to be protective against COPD, including asthma, among a group of middle-aged Dutch men followed up for 25 years (27). Age, smoking habits, body mass index, and energy intake did not explain the protective effect,

as researchers controlled for these factors. La Vecchia et al (28) reported a high vegetable intake, but not fruit intake, to be protective against bronchitis and bronchial asthma. A study of more than 3,000 men in Finland, The Netherlands, and Italy showed that men with high fruit and vegetable intakes (median daily intakes of 3.5 to 5.3 oz of fruits and 1.5 to 5.8 oz of vegetables) had the highest lung function, as measured by forced expiratory volume (29).

The findings of these studies suggest that a high intake of fruits and vegetables enhances ventilatory function, thereby reducing risk of COPD. A possible explanation for the findings is the high level of flavonoids, such as quercetin, available widely in fruits and vegetables. Although flavonoids are found in high concentrations in most all fruits and vegetables, fruits generally contain greater amounts than vegetables. The outer layers of fruits and vegetables are the richest sources. Miedema et al (27) found that fresh fruits containing this quercetin-rich outer layer were the particular type of fruit found to be protective against COPD. Vitamin C intake has also been singled out as a possible dietary component to explain these results (30). Both flavonoids and vitamin C are strong antioxidants. Additionally, vitamin C is the main antioxidant substance found in the airway surface liquid of the lung; thus, it is conveniently located to protect the body from harmful oxidants (30).

Diverticulosis

Diverticulosis occurs predominantly in industrialized nations and is one of the most common medical conditions. It is clearly linked with aging: an estimated one third of people aged 50 years have diverticulosis, and this increases to two thirds in those older than 80 years (31). Diverticulosis occurs when small outpouches called diverticulum develop in the large intestine or colon. In most cases the condition is asymptomatic; only an estimated 10% to 25% of affected individuals develop symptoms (32). Diverticulitis occurs when the colonic diverticulum and surrounding tissues become inflamed, frequently as the result of obstruction by dietary products or stool.

High-fiber diets, which help to increase stool bulk and moisture and reduce travel time through the gastrointestinal tract, provide substantial defense against the development of diverticulosis. This role for diet in the prevention of diverticulosis was first identified from epidemiologic data (33) and subsequently from animal and clinical studies (34,35). Insoluble fiber may be the type of dietary fiber most responsible for this protective role.

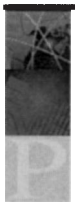
Prospective work by Aldoori and colleagues (36) found that insoluble fiber, particularly cellulose, was significantly associated with decreased risk of diverticulosis among a large group of male health professionals (n=43,881). Earlier work by these same researchers identified an association between fiber from fruits and vegetables, not cereal sources, and reduced risk of diverticulosis (37).

Fruits and vegetables are generally known to be higher in cellulose than cereals (38); Aldoori and colleagues (37) believe this fact may explain the association between the fiber from fruits and vegetables and lower risk of diverticulosis. These researchers suggest that, indeed, it is the insoluble fiber that is providing the protective benefit against diverticulosis, particularly the cellulose component in the insoluble fiber. Marlett (38) identified amounts of insoluble fiber in foods consumed frequently in the United States, including fruits and vegetables. Cellulose accounted for 30% of the insoluble fiber in fruits and 50% or more in vegetables. Most foods contain about a third or less of total fiber from cellulose, with the exception of legumes in which about half of total fiber is from cellulose.

Taken together, these results indicate that fruits and vegetables provide dietary fiber and that the insoluble fiber, especially the cellulose in fruits and vegetables, may be particularly important in helping to prevent diverticulosis.

Hypertension

Evidence from a clinical trial suggests a protective role for fruits and vegetables in hypertension, which is estimated to affect approximately 43 million Americans (39). Appel and colleagues (40) examined the effects of dietary patterns on blood pressure. Their randomized, controlled study of 459 men and women showed that a diet rich in fruits and vegetables (8 to 10 servings of fruits and vegetables daily) reduced blood pressure in individuals with and without hypertension. Combining a fruit- and vegetable-rich diet with consumption of low-fat dairy products, and with reduced intake of saturated and total fat, lowered blood pressure even further (40).



APPLICATIONS/CONCLUSIONS

A diet rich in fruits and vegetables offers the possibility of health benefits beyond that of a protective role against cancer. Large-scale adoption of a diet rich in fruits, vegetables, and low-fat dairy products, combined with reduced intake saturated and total fat, is estimated to reduce coronary heart disease by approximately 15% and stroke by approximately 27% (40). A diet rich in fruits and vegetables may be a low-cost and practical means to delay cataracts (18), may help prevent asthma and bronchitis, common forms of COPD, particularly among children (5), and may provide an additional approach for the prevention and treatment of hypertension (40).

The weight of scientific knowledge linking fruit and vegetable consumption with disease prevention and control, and an ever-increasing understanding of underlying protective mechanisms, provide enhanced support for dietetics professionals to encourage individuals to increase fruit and vegetable consumption. The evidence reviewed in this article supports the minimum goal of 5 servings of vegetables and fruits daily (1,3,5,40). The AICR set 400 g/day, or 5 servings per day, of vegetables and fruits as the low end of the range recommended and estimates that diets high in vegetables and fruits (>400 g/day could prevent at least 20% of all cancer incidence (1). A system designed to provide dietary guidance for individuals with low and high energy needs has also identified 5 servings of vegetables and fruits as the minimum number needed to ensure adequacy of select nutrients at low energy levels (41). At high energy levels, the system encourages consumption of larger or additional servings. In reference to an upper intake level, AICR recommends up to 10 servings of vegetables and fruits daily to reduce the risk of cancer (1); the Food Guide Pyramid encourages up to 9 servings of fruits and vegetables daily for general good health (42). More research is needed,

however, to enhance understanding of threshold levels for increased fruit and vegetable intake and to assess the relationship between quantity and quality of fruit and vegetable intake.

The evidence reviewed in this article also supports increased consumption of a wide variety of vegetables, particularly dark-green leafy, cruciferous, and yellow-orange ones, and a wide variety of fruits, particularly citrus and deep-yellow-orange ones. Microconstituents in vegetables and fruits likely to protect against cancers, cardiovascular disease, stroke, cataracts, and COPD are antioxidants such as carotenoids, flavonoids and vitamin C. Other microconstituents that may help explain the protective effect in cancer and heart disease are the sulfur-containing compounds in the allium family vegetables; for cancer, the dithiothiones, indoles, and isothiocyanates in cruciferous vegetables play a potentially protective role.

The scientific evidence supporting a role for fruits and vegetables in prevention of chronic diseases is expanding beyond that of a role in cancer and heart disease prevention

The evidence reviewed also identified fiber, of which fruits and vegetables are a rich source, as potentially helping to control high serum cholesterol levels and protecting against diverticulosis. Folic acid found in most fruits and vegetables, particularly in green leafy vegetables and some citrus fruits, may have a protective role in heart disease and hypertension, as well as in cancer. The potassium found in a variety of vegetables and fruits may also help control hypertension.

Applications of current research findings to clinical settings by dietetics professionals have several benefits. First, counseling of clients to increase fruit and vegetable intakes is facilitated because people know what fruits and vegetables are; in contrast, clients may not recognize some dietary sources of sodium or fat. Second, the addition of a behavioral criterion, such as eating 5 or more fruits and vegetables, facilitates goal setting and self-monitoring on whether a goal is reached. Additional behavioral strategies can help ensure effective dietary change by clients, for example, introducing a lifestyle approach that includes skill building, emphasizing the natural good taste of fruits and vegetables, exercising problem-solving skills, increasing fruit and vegetable availability and accessibility, and encouraging trial and error with provision of feedback. Education about the importance of increased fruit and vegetable consumption, even if it includes a discussion of the associated health benefits of increased fruit and vegetable intake, does not appear to be enough. Third, advice to increase fruit and vegetable intake is a positive message, and as such can aid in capturing a client's attention. In addition the message tells clients to eat more of something, thereby focusing in counseling on something people can do rather than on something they should avoid or limit. Finally, it is useful to inform clients that meeting the recommendations for fruit and vegetable intake can help reduce dietary fat intake. In an analysis of the diets of individuals participating in the 1989-1991 Continuing Survey of Food Intake of Individuals, percentage of energy from fat was at or below the population average when the fruit intake recommendation was met (43).

The 5 A Day for Better Health program, a nationwide nutrition initiative sponsored by the National Cancer Institute and the Produce for Better Health Foundation, combines research with a national dietary guidance program to increase fruit and vegetable consumption to a minimum of 5 servings by all Americans (44). The 5 A Day program, therefore, can provide a larger context in which individual counseling to increase fruit and vegetable consumption by dietetics professionals is supported and reinforced through a nationwide research and public health initiative. Through a combination of awareness and skill, building strategies, the program challenges individuals, families, schools, and communities to increase fruit and vegetable consumption to reduce risk of disease and achieve good health. In its 1996 nutrition guidelines the American Cancer Society stated that the best advice is to eat 5 or more servings of fruits and vegetables each day (13).

The message to eat more fruits and vegetables is in keeping with the US government's health promotion and disease prevention objectives (45) and readily fits within a broader message that a healthful diet is low in fat and high in fiber. Primary instruments with which dietitians can encourage increased intake of fruits and vegetables are the Food Guide Pyramid (42) and the US Dietary Guidelines for Americans (46). The Food Guide Pyramid supports consumption of fruits and vegetables and the Dietary Guidelines recommend to "eat plenty of grains, fruits and vegetables." The 2000 Dietary Guidelines for Americans contain a separate guideline for fruits and vegetables (47), which provides dietitians with a powerful counseling tool. As a cornerstone of US nutrition policy, a greater emphasis on fruits and vegetables in the Dietary Guidelines could have far-reaching effects in efforts by nutrition educators, in federal nutrition programs (eg, school lunch), and in refinement of educational tools such as the Food Guide Pyramid (42).

Dietary supplements are sometimes used as a substitute for increasing fruit and vegetable consumption, but scientific data suggest caution with this approach (48-50). Dietetics professionals need to reassure clients that a balanced diet which includes a variety of fruits, vegetables, and grains daily is still the optimal choice to reduce risk of certain chronic diseases. To date, clinical trials of dietary supplements have not successfully replicated the beneficial effects of fruit and vegetable intake. Three large clinical trials have shown either no effects or detrimental effects of supplements of beta carotene, vitamin A, and vitamin E (51-53).

The scientific evidence supporting a role for fruits and vegetables in prevention of chronic diseases is expanding beyond that of a role in cancer and heart disease prevention. A science base is developing to support a protective role for fruits and vegetables in the prevention of stroke, and potentially, cataracts, diverticulosis, COPD, and hypertension. Continued attention to increasing fruit and vegetable consumption is a

practical and important means for optimizing nutriture to reduce disease risk and maximize good health.

References

1. World Cancer Research Fund, American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* Washington, DC: American Institute for Cancer Research; 1997.
2. Ries LAG, Eisner MP, Kosary CL, Hanlcey BF, Miller BA, Clegg LX, Edwards, BK (eds). SEER Cancer Statistics Review, 1973-1997. National Cancer Institute. NIH Pub. No. 00-2789. Bethesda, MD, 2000.
3. Committee on Medical Aspects of Food and Nutrition Policy. Epidemiology of diet in relation to specific cancers. In: *Department of Health Report on Health and Social Subjects, No. 48: Nutritional Aspects of the Development of Cancer.* London, England: Stationery Office; 1998:80-153.
4. *Ten Leading Causes of Death in the U.S.* Hyattsville, Md: National Center for Health Statistics; 1997; 46: 32-33.
5. Klerk M, Jansen MCJF, Van't Veer P, Kok FJ. *Fruits and Vegetables in Chronic Disease Prevention.* Wageningen, The Netherlands: Grafisch Bedrijf Ponsen & Looijen BV; 1998.
6. Ness AR, Powles JW. Fruit and vegetables and cardiovascular disease: a review. *Int J Epidemiol.* 1997;26:1-13.
7. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol.* 1994;139:1180-1189.
8. Key TJA, Thorogood M, Appleby PN, Burr ML. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. *BMJ.* 1996;313:775-779.
9. Rimm EB, Ascherio A Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA.* 1996;275:447-451.
10. La Vecchia C, Decarli A, Pagano R. Vegetable consumption and risk of chronic disease. *Epidemiology.* 1998;9:208-210.
11. Ornish D, Scherwitz LW, Billings JH, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA Kirkeeide RL, Hogeboom C, Brand RJ. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA.* 1998;280:2001-2007.
12. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA.* 1999;282:1233-1239.
13. The American Cancer Society 1996 Advisory Committee on Diet, Nutrition, and Prevention. Guidelines on diet, nutrition and cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *Cancer J Clin.* 1996;46:325-341.
14. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc.* 1996;96:1027-1039.
15. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. *N Engl J Med.* 1987;316:235-240.
16. Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins and incidence of stroke: the Zutphen Study. *Arch Intern Med.* 1996;154:637-642.
17. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet.* 1993;342:1007-1011.
18. Taylor A, Jacques PF, Epstein EM. Relations among aging, antioxidant status, and cataracts. *Am J Clin Nutr.* 1995;62(suppl):1439S-1447S.
19. Ryan SJ. Congressional testimony, May 5, 1993. Washington, DC: US Government Printing Office.
20. Jacques PF, Chylack CT, Taylor A. Relationships between natural antioxidants and cataract formation. In: Frei B, ed. *Natural Antioxidants in Human Health and Disease.* New York, NY: Academic Press; 1994.
21. Jacques PF, Chylack LT. Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. *Am J Clin Nutr.* 1991;53:352S-355S.
22. Mares-Perlman JA, Brady WE, Klein BEK, Klein R, Haus GJ, Palta M, Ritter LL, Shoff SM. Diet and nuclear lens opacities. *Am J Epidemiol.* 1995;141:322-334.
23. Hankinson SE, Stampfer MJ, Seddon JM, Colditz GA, Rosner B, Speizer FE, Willett WC. Nutrient intake and cataract extraction in women: a prospective study. *BMJ.* 1992;305:335-339.
24. Brown L, Hankinson SE, Seddon JM, Rimm E, Willett WC. A prospective study of carotenoid intake and cataracts among US men [abstract]. *Am J Epidemiol.* 1998;147:213.
25. Cook DG, Carey IM, Whincup PH, Papacosta O, Chirico S, Bruckdorfer KR, Walker M. Effect of fresh fruit consumption on lung function and wheeze in children. *Thorax.* 1997;52:628-633.
26. Strachan DP, Cox BD, Erzinclioglu SW, Walters DE, Whichelow MJ. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. *Thorax.* 1991;46:624-629.
27. Miedema I, Feskens EF, Heederik D, Kromhout D. Dietary determinants of long-term incidence of chronic nonspecific lung diseases; the Zutphen Study. *Am J Epidemiol.* 1993;138:37-45.
28. La Vecchia C, Decarli A, Pagano R. Vegetable consumption and risk of chronic disease. *Epidemiology.* 1998;9:208-210.
29. Tabak C, Smit HA, Rasanen L, Fidanza F, Menotti A, Nissinen A, Feskens EM, Heederik D, Dromhout D. Dietary factors and pulmonary function: a cross-sectional study in middle aged men from three European countries. *Thorax.* 1999;54:1021-1026.
30. Hatch GE. Asthma, inhaled oxidants, and dietary antioxidants. *Am J Clin Nutr.* 1995;61(suppl3):625S-630S.
31. Roberts PL, Veidenheimn MC. Diverticular diseases of the colon. In: Bayless TM, ed. *Current Therapy in Gasterenterology and Liver Diseases.* Toronto, Ontario; Canada: DC Decker, 1990;3:416-419.
32. Kennedy MV, Zarling EJ. Answers to ten key questions on diverticular disease of the colon. *Compr Ther.* 1998;24:364-369.
33. Painter NS, Burkitt DP. Diverticular disease of the colon: a 20th century problem. *Clin Gastroenterol.* 1975;4:3-21.
34. Brodribb AJM, Humphreys DM. Diverticular disease: three studies, 1: relation to other disorders and fiber intake. *BMJ.* 1976;1:424-425.
35. Fisher N, Berry CS, Fearn T, Gregory JA, Hardy J. Cereal dietary fiber consumption and diverticular disease: a lifespan study in rats. *Am J Clin Nutr.* 1985;42:788-804.
36. Aldoori WH, Giovannucci EL, Rockett HRH, Sampson L, Rimm EB, Willett WC. A prospective study of dietary fiber types and symptomatic diverticular disease in men. *J Nutr.* 1998;128:714-719.
37. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr.* 1994;60:757-764.
38. Marlett JA. Content and composition of dietary fiber in 117 frequently consumed foods. *J Am Diet Assoc.* 1992;92:175-186.
39. Burt VL, Whelton P, Roccell EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-19991. *Hypertension.* 1995;25:305-313.
40. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin P-H, Karanja N, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;136:1117-1124.
41. Cronin FJ, Shaw AM, Krebs-Smith SM, Marsland PM, Light L. Developing a food guidance system to implement the dietary guidelines. *J Nutr Educ.* 1987;19:281-302.
42. *Food Guide Pyramid: A Guide to Daily food Choices.* Washington, DC: US Dept of Agriculture, Human Nutrition Information Service; 1992. Home and Garden Bulletin No. 232.
43. Krebs-Smith SM, Cleveland LE, Ballard-Barbash R, Cook DA, Kahle LL. Characterizing food intake patterns of American adults. *Am J Clin Nutr.* 1997;65(suppl):1264S-1268S.
44. Heimendinger J, Van Duyn MA, Chapelsky D, Foerster S, Stables G. The national 5 A Day for Better Health program: a large-scale nutrition intervention. *J Public Health Manage Pract.* 1996;2:27-35.
45. *Healthy People 2010* [conference ed in 2 vol]. Washington, DC: US Dept of Health and Human Services; 2000.
46. *Nutrition and Your Health: Dietary Guidelines for Americans.* 4th ed. Washington, DC: US Dept of Agriculture and Health and Human Services; 1995. Home and Garden Bulletin No. 232.
47. US Depatments of Agriculture and Health and Human Services. Nutrition and Your Health: Dietary Guidelines for Americans. 5th ed. Washington, DC: US Depts of Agriculture and Health and Human Services, 2000. Home and Garden Bulletin No. 232. Report also available from http://www.ars.usda.gov/dgac.
48. Yaffe SJ, Filer LJ Jr. Use and abuse of vitamin A. *Pediatrics.* 1971;48:655-656.
49. The use and abuse of vitamin A. *Can Med Assoc J.* 1971;104:521-522.
50. Stein HB, Hasan A, Fox IH. Ascorbic acid-induced uricosuria: a consequence of megavitamin therpay. *Ann Intern Med.* 1976;84:385-388.
51. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994;330:1029-1035.
52. Omenn GS, Goodman GE, Thornquist M, Grizzle J, Rosenstock L, Barnhart S, Balmes J, Cherniack M, Cullen M, Glass A, Geogh J, Meyskens F, Valanis B, Williams J. The beta-Carotene and Retinol Efficacy Trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos exposed workers. *Cancer Res.* 1994;54(suppl):2038S-2043S.
53. Gaziano JM, Henekens CH. The role of beta-carotene in the prevention of cardiovascular disease. *Ann N Y Acad Sci.* 1993;691:148-155.