Annu. Rev. Nutr. 1992. 12:139–59

DIETARY CAROTENES, VITAMIN C, AND VITAMIN E AS PROTECTIVE ANTIOXIDANTS IN HUMAN CANCERS[1]

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KEY WORDS: nutrition, diet, prevention, β-carotene

CONTENTS

INTRODUCTION

A massive research effort over the last decade has improved our understanding of the role of antioxidants in protecting the human body against cancer.

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Consequently, cancer chemoprevention through supplementation and fortification of the diet with micronutrient antioxidants could become an effective strategy for cancer control before the close of this century (7, 63). The scientific literature on antioxidants and cancer is extensive and spans many disciplines, from basic chemistry to experimental research and epidemiology. Therefore, an exhaustive examination of the literature on the role of antioxidants in preventing cancer is beyond the scope of this short review. In 1989, an expert committee of the National Research Council (NRC) published an extensive review of the relationship between diet and health, including the relationship between antioxidants in the diet and cancer risk (65). Our review focuses principally on the research reported since 1987, the year before the NRC panel concluded its work. Selected major reviews published since 1987 on the topic of antioxidants and cancer prevention are listed in Table 1.

DIETARY ANTIOXIDANTS: THEORETICAL ROLES IN CANCER PREVENTION

Some dietary factor, or set of factors, apparently plays an important part in the etiology of cancer (65). Cancer rates vary considerably between countries, and migrants tend to acquire the cancer risk of persons in their new country within a generation or two. One of the most important changes in the experience of migrants is a change in dietary practices. Factors in the changing diet of migrants hypothesized to be related to cancer risk include carcinogens found in foods, cancer-promoting factors such as high levels of dietary fat, and factors in the diet that may be anticarcinogenic as well (4). Such protective factors might include dietary fiber, trace minerals, and other micronutrients, including many of the vitamins, provitamins, and other compounds that have chemical properties of antioxidants (95).

The human body is under constant assault by reactive oxygen molecules. Reactive oxygen molecules (free radicals and singlet oxygen) are formed as a natural consequence of normal biochemical activity. Reactive oxygen can damage the body in many ways: by denaturing proteins, by damaging nucleic acids, and by saturating the double bonds of fatty acids in lipid membranes, thereby altering membrane structure and function (95). Because oxidative damage can be life threatening, the body has many overlapping defense mechanisms to protect against oxidation (28). These defenses include both mineral-dependent enzymes and small molecules that act as scavengers of reactive oxygen species. One such mineral-dependent enzyme is glutathione peroxidase, the selenium-dependent free radical scavenger. Small molecules that act as antioxidants include water-soluble compounds such as vitamin C, glutathione, and uric acid, as well as lipid-soluble molecules such as the carotenoids and vitamin E. This review focuses on the antioxidant properties

Table 1 Selected major reviews of dietary antioxidants and cancer risk

Author (Ref.)	Dietary antioxidants reviewed[a]				Description
	Carot.	Vit. C	Vit. E	Others	
NRC (65)	X	X	X	X	Comprehensive review by expert panel of both animal and human studies through 1987
Bertram et al (7)	X	X	X	X	Thorough discussion of the scientific basis for chemo prevention trials
Ziegler (116)	X				Review of the epidemiologic evidence regarding carotenoids and cancer
Moon (64)	X			X	Review of the animal experimental evidence regarding carotenoids and cancer
Schneider & Shaw (83)	X	X		X	Cervical cancer epidemiology review, including dietary factors
Vogel & McPherson (102)	X	X		X	Colon cancer epidemiology review, including dietary factors
London & Willet (55)	X	X	X		Review of dietary factors in breast cancer epidemiology
Henson et al (38		X			Comprehensive review of cancer-relevant vitamin C physiology
Ziegler (115)	X			X	Review of epidemiologic evidence regarding fruits and vegetables, emphasizing carotenoids
Knekt et al (49)			X		Review of animal and epidemiologic studies on vitamin E and cancer
Block et al (10)		X			Comprehensive review of epidemiology regarding vitamin C and cancer
Krinsky (51)	X				Comprehensive review of carotenoids and cancer in laboratory experiments
Weisburger (105)	X	X	X	X	Review of mechanisms that might explain epidemiologic findings on antioxidants
Dorgan & Schatekin (29)	X	X	X	X	Review of epidemiologic studies regarding cancer and several micronutrients
Byers (18)	X	X	X		Review of dietary antioxidants in lung cancer epidemiology

[a] Carot. = carotenoids; vit. C = vitamin C; vit E = vitamin E; others = various other antioxidants.

of the three most intensively studied antioxidant compounds found in the diet: carotenoids, vitamin C, and vitamin E.

The carotenoids are a set of several hundred pigmented, fat-soluble antioxidants found in fruits and vegetables (64). Approximately 10% of the carotenoids are convertable to vitamin A (retinol) by enzymatic cleavage in the body. Because vitamin A is essential for the maintenance of normal epithelial cellular differentiation, the carotenoids are important in cancer prevention, in part because of their provitamin A activity. Perhaps more importantly, the carotenoids may reduce cancer risk because of their role as antioxidants in the body (73). Antioxidation may be the most important effect of carotenoids in cancer prevention.

Vitamin C is an essential nutrient that likely protects against cancer by several mechanisms (38), including its role in promoting the formation of collagen in the body and in inhibiting the formation of *N*-nitroso compounds in the stomach. Perhaps more importantly, vitamin C is the most abundant water-soluble antioxidant in the body (32). Recently it has become apparent that both vitamin C and the carotenoids may also have beneficial effects on immune function, thereby reducing cancer risk by enhancing tumor surveillance by the immune system (6, 38, 78).

Vitamin E is a fat-soluble compound found in a wide variety of foods and serves many physiologic functions (9). Vitamin E may protect against cancer by several mechanisms (49). Like Vitamin C it may inhibit the formation of *N*-nitroso compounds in the stomach. Vitamin E also protects selenium against reduction (40) and protects polyunsaturated fatty acids in lipid membranes from oxidative damage (39). Vitamin E is thought to be the most important antioxidant found within lipid membranes in the body (74).

LABORATORY ANIMAL RESEARCH

Animal experimentation has played an important role in the development of our understanding of the role of antioxidants in preventing cancer. Animal experiments have enabled researchers to demonstrate the biologic plausibility of a preventive role for several antioxidants compounds. Animal experiments have also been designed to examine the efficacy of antioxidants at various stages of the development of cancer. Because oxidative damage to nucleic acids can lead to genetic damage, and hence to the initiation of cancer, it is reasonable to hypothesize that antioxidants are most likely to be protective at the initiation stage. The results of animal experiments have clearly shown, however, that antioxidants are most protective during the later promotional phases of cancer development (51, 64). Animal experiments have demonstrated beneficial effects of antioxidants on cellular membrane integrity and on immune system function. These observations have helped to direct

epidemiologic research on the effects of antioxidants in the later promotional phases of cancer.

Animal experimental models have many limitations, however. Many animal tumors in experimental systems are either induced by high doses of strong carcinogens or they occur sporadically only in particular genetic strains of animals. In addition, findings from one animal tumor model are often not generalizable to other species, and the behavior of animal tumors often differs in significant ways from the behavior of human cancer. In most cases, for instance, animal tumors used to model human cancer do not metastasize. Nonetheless, many laboratory animal experiments have been conducted. Following is a brief summary of findings from experimentation with antioxidant supplementation in animal tumor models.

Carotenoids

Many investigators have demonstrated the ability of β-carotene, independent of its role in the formation of vitamin A, to protect against cancer in animals (51). The effectiveness of β-carotene has been confirmed in different animal species, at different cancer sites, and in several different cancer model systems using different inducing agents (8, 51). Carotenoids have been shown to be protective against the development of skin tumors in rats after the administration of 7,12-dimethylbenz (α)anthracene (DMBA) (85), and in mice after the administration of benzo(α)pyrene (81). High levels of carotene in the diet of mice prior to their irradiation with ultraviolet light prolonged the time to appearance of tumors (58), while β-carotene supplementation after the stage of initiation reduced the incidence of tumor development (59).

Nevertheless, the effects of β-carotene in experimental tumor models can be sensitive to experimental conditions. For example, salivary gland tumors initiated by DMBA appeared less frequently and were of lower weight in rats fed high levels of β-carotene in one study (2), but the same investigators were later unable to replicate those findings (3). They speculated that subtle effects owing to different amounts of DMBA used in initiation may have made a difference in the β-carotene effect. β-Carotene has been shown to have a protective effect against colonic tumors induced by 1,2-dimethylhydrazine (DMH) in mice (97). Gastric dysplasia was altered by β-carotene supplementation in rats whose tumors were initiated with *N*-methyl-*N*'-nitro-*N*-nitrosaguanidine, but supplementation did not affect the subsequent rate of cancer development (82).

The effects of β-carotene in animal tumor model systems are therefore varied. Animal experiments have shown the plausibility of an anticancer role for β-carotene in the later promotional and progression phases. However, effects appear to be sensitive to experimental conditions and are not universally seen at all cancer sites.

Vitamin C

The ability of ascorbic acid to inhibit the formation of carcinogenic nitrosamines is the best documented cancer-protecting effect of vitamin C (10, 21). Vitamin C may have additional cancer-preventing effects that are independent of this mechanism, however. Like β-carotene, vitamin C has been shown to reduce the rate of tumor development in mouse skin cancer models employing either ultraviolet light (30) or DMBA-croton oil models (86).

As is true for β-carotene, however, findings in other organ systems are mixed for vitamin C. Investigators reported that ascorbate supplementation did not affect tumor development in chemical-induced bladder (90) or mammary cancers (1). Colon tumors induced by DMH were shown to be inhibited in rats in one study (76), but were enhanced in another (87). DMH-induced colon cancers were unaffected by ascorbate (46, 87). Some experiments have demonstrated the possibility of adverse effects of ascorbate supplementation. In rats treated with *N,N*-dibutylnitrosamines, ascorbate increased bladder tumor yield (34). When both nutrients were supplemented together, vitamin C was found to nullify the beneficial effects of selenium in mammary tumorigenesis (44).

Vitamin E

Vitamin E shares with vitamin C the ability to inhibit nitrosamine formation in the stomach (21). Vitamin E has also been shown to have cancer-preventing effects in several other animal tumor model systems. Skin cancer induced by DMBA is inhibited by vitamin E supplementation in mice (72). Likewise, vitamin E has been shown to reduce the incidence of DMBA-induced cancers of the oral cavity (88) and mammary gland (104). This effect may be modified by the level of fat in the diet (47, 60). Experimental diets extremely deficient in vitamin E have been shown to increase tumor initiation of DMH-induced colon tumors (96) and DMBA-induced mammary tumors (43), but the relevance to the human condition of states of very extreme vitamin E deficiency is unclear.

EPIDEMIOLOGIC STUDIES

The literature on the epidemiology of antioxidants in cancer is complex, largely because of the complexity of the human diet (17, 37). Ecologic studies are inquiries in which the average diet of a set of populations is correlated with cancer rates. Typically, ecologic studies are conducted by comparing diet and cancer across different countries. Although these studies are useful for generating hypotheses, they are susceptible to the ecologic fallacy: the appearance of spurious associations between diet and cancer that are due to truly causal correlated factors. Because of this limitation, ecologic studies are not reviewed in detail here. Instead, we review those studies in which

researchers have investigated cancer risk as related to dietary or supplemental antioxidant intake in individual study subjects. Epidemiologic studies of individuals include case-control studies, cohort studies, and randomized controlled trials.

Dietary Assessment

The greatest limitation of case-control and cohort studies is the difficulty of accurately ascertaining dietary intake. The only practical method for estimating a person's usual intake of foods and nutrients over a period of time is the food frequency method (107). By asking subjects to report their usual frequency of intake of selected foods that are key indicators of nutrients of interest, one can create "nutrient indices," quantitative estimates of intake that are useful for establishing the rank-order of intake in the study group. Correct ranking of study subjects is essential in order to accurately estimate relative risks for the extremes of intake (for example, the lowest compared with the highest quartiles of intake) in case-control and cohort studies. Several validation studies have shown that food frequency techniques can be used to accurately classify people into extreme quantiles of intake of antioxidant micronutrients. The validity of food frequency techniques has been established by comparing food frequency estimates of dietary intake with intake estimates from multiple diet records (109) and with nutrient levels circulating in the blood (111).

The major sources of carotenes, vitamin C, and vitamin E in the American diet are listed in Table 2. The twenty top contributors for these three nutrients are listed along with the cumulative percent of the total nutrient intake in the diet contained in the listed foods. Approximately two thirds of the nutrient content of the diet is contained in only five foods for carotene and in ten foods for vitamin C. However, more than twenty foods are needed to account for two thirds of the vitamin E in the diet. In many studies, investigators have not specifically computed nutrient indices, but they have ascertained and reported many of these key indicator foods. Therefore, many studies are useful for elucidating the role of antioxidant micronutrients in cancer, even though their findings are not described in those terms. This is particularly true for vitamin C and carotenes, which are highly concentrated in a relatively short list of fruits and vegetables. Because the types of foods that contain vitamin E are less distinct and less discernible in the diet (for example, vegetable oils and margarines), inferring vitamin E intake in the diet from a limited set of foods in a food frequency interview may be more difficult.

Case-Control and Cohort Diet Studies

Case-control studies compare diets of individuals having cancer with those of individuals without cancer, when both are sampled from the same population. The major problem with case-control studies is the possibility of bias, either

Table 2 Major sources of carotenes, vitamin C, and vitamin E in the American diet

Carotenes[a]		Vitamin C[b]		Vitamin E[a]	
Food	*Cumulative %[c]*	*Food*	*Cumulative %[c]*	*Food*	*Cumulati %[c]*
1. Carrots	37.8	1. Orange juice	26.5	1. Mayonnaise	14.6
2. Tomatoes	51.0	2. Grapefruit (and juice)	33.7	2. Potato chips	18.8
3. Sweet potatoes	56.7	3. Tomatoes (and juice)	39.9	3. Apples	22.9
4. Yellow squash	62.3	4. Fortified fruit drinks	45.7	4. Nuts	27.0
5. Spinach (cooked)	67.9	5. Oranges	50.6	5. Peanut butter	30.9
6. Cantaloupe	71.7	6. Potatoes (not fried)	54.8	6. Oil and vinegar	34.2
7. Mixed vegetables	75.4	7. Potatoes (fried)	58.9	7. Tomatoes	37.4
8. Romaine lettuce	78.3	8. Green salad	62.4	8. Margarine	40.5
9. Broccoli	80.6	9. Other fruit juices	65.2	9. Sweet roll	43.2
10. Spinach (raw)	83.0	10. Broccoli	67.2	10. Tomato sauce	45.9
11. Tomato sauce	84.4	11. Coleslaw, cabbage	69.1	11. Sweet potatoes	48.3
12. Margarine	85.7	12. Spaghetti and sauce	71.0	12. Eggs	50.4
13. Orange juice	87.0	13. Orange juice substitute	72.8	13. Cold cereal	52.5
14. Iceberg lettuce	88.1	14. Cold cereal	74.6	14. Shrimp	54.6
15. Pizza	89.1	15. Hot dogs, lunch meat	76.3	15. Cake	56.6
16. Cheese	90.1	16. Cantaloupe	77.9	16. Cabbage	58.5
17. String beans	91.0	17. Whole milk	79.4	17. Iceberg lettuce	60.3
18. Peas	91.9	18. Greens	80.8	18. Tuna	62.2
19. Oranges	92.6	19. Strawberries	82.1	19. Cheese	63.9
20. Whole milk	93.4	20. Fortified cold cereal	83.0	20. Whole milk	65.1

[a] From Romieu et al (79).
[b] From Block et al (11).
[c] The cumulative percent of total nutrient intake in the diet provided by the listed foods.

in the selection of participants or in the estimation of diet. Although several validation studies have shown that people can accurately report their diets, the possibility of biased error in dietary reports related to the recent experience of cancer diagnosis and treatment has not been thoroughly studied. An additional problem with case-control studies is that either cancer or its treatment can affect levels of biologic markers of nutrients, thus rendering them virtually useless for drawing causal inference. Prospective studies, in which diet or biological markers of nutrition are ascertained years before diagnosis, have many advantages over case-control studies. However, prospective studies are often plagued by small numbers of incident cases and/or by very cursory measures of diet.

Findings from selected case-control and cohort studies that have examined the relationship between dietary antioxidants and cancer risk are listed in Table 3 (carotenes), Table 4 (vitamin C), and Table 5 (vitamin E). Only those studies published since 1987 that specifically presented findings according to indices of nutrient intake and that included at least 100 cases (or 30 cases if a cohort study) are included in these tables.

The risk of lung cancer is generally elevated for those with lower levels of carotene intake (Table 3). This is consistent with findings from many earlier studies (18). All of these studies have been adjusted for tobacco exposures. Findings are more mixed for dietary vitamin C (Table 4), though there may be more consistency in the observation of higher risk at lower levels of intake in men than in women. Because cigarette smoking lowers levels of both circulating carotenes and vitamin C, low dietary intake may be a risk factor for low circulating levels of antioxidants, compounds in high demand after tobacco use. The observation of higher risk of lung cancer with infrequent intake of fruits and vegetables has been made in several studies (18, 25, 50, 66). Of note is the finding from a cohort study of over one million Americans that those reporting infrequent intakes of fruits were at higher risk of subsequent lung cancer mortality (56).

Breast cancer is less consistently related to carotene intake than is lung cancer, though there may be a weak relationship. Low intakes of vitamin C were associated with elevated breast cancer risk in only two studies. Those two studies were conducted in the Soviet Union (113) and China (53). This suggests that vitamin C deprivation might increase breast cancer risk, but only at a lower threshold of intake than is commonly seen in the United States or Western Europe. Other studies have shown evidence of a protective effect of fruit and vegetable consumption (77), but this finding is not universal (66).

Several studies have examined dietary antioxidants and cancers of the gastrointestinal tract. Stomach cancer is associated with low intakes of vitamin C, as is cancer of the pancreas. The mechanism for the effect of dietary antioxidants may well be the inhibition of nitrosamine formation by ascorbate

Table 3 Selected[a] case-control and cohort studies of the relationship between dietary caroten and cancer risk

Author (Ref.)	Cancer site	Study design (n:N)[b]	Extremes compared by relative risk[c]	Relati risk
Byers et al (19)	Lung (M)	C:C (296:587)	Quartiles	1.8
	Lung (F)	C:C (154:315)	Quartiles	1.3
Kromhout (52)	Lung (M)	Cohort (63:878)	Quartiles	1.5
Bond et al (12)	Lung (M)	C:C (308:308)	Tertiles	1.2
Wu et al (112)	Lung (F)	C:C (220:220)	Quartiles	2.5
Fontham et al (31)	Lung (M)	C:C (866:982)	Tertiles	1.2
	Lung (F)	C:C (287:292)	Tertiles	1.0
Le Marchand et al (54)	Lung (M)	C:C (230:597)	Quartiles	2.0
	Lung (F)	C:C (102:268)	Quartiles	2.9
Mettlin (62)	Lung (M,F)	C:C (569:569)	Quintiles	2.0
Jain et al (45)	Lung (M,F)	C:C (839:772)	Quartiles	1.1
Hsing et al (42)	Prostate (M)	Cohort (149:17,633)	Quartiles	1.1
Paganini-Hill et al (70)	Prostate (M)	Cohort (92:10,433)	Tertiles	1.0
	Breast (F)	Cohort (123:10,473)	Tertiles	1.2
Howe et al (41)	Breast (F)	C:C (12 studies)	Quartiles	1.2
Zaridze et al (113)	Breast (F)	C:C (139:139)	Quartiles	4.8
Lee et al (53)	Breast (F)	C:C (200:420)	Tertiles	3.4
Van'T Veer et al (100)	Breast (F)	C:C (133:289)	Below vs above 2 mg	1.1
Richardson et al (77)	Breast (F)	C:C (409:515)	Tertiles	1.0
Maclure & Willett (57)	Kidney (M,F)	C:C (203:207)	Quintiles	1.2
Brock et al (14)	Cervix (F)	C:C (117:196)	Quartiles	1.0
Verreault et al (101)	Cervix (F)	C:C (189:227)	Quartiles	1.7
vanEenwyk et al (99)	Cervix (F)	C:C (102:102)	Quartiles	2.8
Shu et al (89)	Ovary (F)	C:C (172:172)	Quartiles	1.0

Table 3 *(Continued)*

Author (Ref.)	Cancer site	Study design (n:N)[b]	Extremes compared by relative risk[c]	Relative risk[c]
Ghadirian et al (35)	Pancreas (M,F)	C:C (179:239)	Quartiles	1.4
Bueno de Mesquita et al (15)	Pancreas (M,F)	C:C (164:480)	Quintiles	1.7
Stryker et al (93)	Skin (M,F)	C:C (204:248)	Quintiles	1.4
Nomura et al (68)	Bladder (M)	C:C (195:390)	Quartiles	1.4
Paganini-Hill et al (70)	Colon (M)	Cohort (52:10,473)	Tertiles	1.1
	Colon (F)	Cohort (58:10,473)	Tertiles	0.9
Freudenheim et al (33)	Colon (M)	C:C (205:205)	Quartiles	1.2
	Colon (F)	C:C (223:224)	Quartiles	1.5
	Rectum (M)	C:C (293:277)	Quartiles	2.9
	Rectum (F)	C:C (151:146)	Tertiles	2.1
Buiatti et al (16)	Stomach (M,F)	C:C (923:1159)	Quintiles	1.4
Sturgeon et al (94)	Vulva (F)	C:C (201:343)	Quintiles	0.8

[a] Only includes studies published since 1987 that present findings by nutrient indices and have at least 100 cases (or 30 if it is a cohort study).

[b] C:C = case-control, (n:N) = the number of cases:controls or the number of incident cases:cohort size.

[c] Relative risk is the ratio of risk for persons in the lowest category of intake compared to those in the highest category of intake.

in the low-pH gastric environment. The dramatic decline in gastric cancer incidence in the past eighty years in developed countries may be due in large part to better vitamin C nutrition year-round (65, 67). Little association has been found between vitamin C and colon cancer, but rectal cancer risk was increased in persons with low intakes of carotenes and/or vitamin C in one study (33). Several investigators have examined the risk of stomach and colon cancers as related to fruit and vegetable intake. In general, these studies tended to indicate elevated risk for those who ate fruits and vegetables infrequently (22, 66, 106), though such effects are not always seen (110). Whether this is an effect of deficiencies in fiber (98), micronutrients, and/or due to the higher fat content of diets of those who infrequently eat fruits and vegetables, is not clear.

Studies of cervical cancer have been generally consistent in demonstrating higher risk at lower levels of intake of carotenes, vitamin C, and vitamin E

Table 4 Selected[a] case control and cohort studies of the relationship between dietary vitamin C and cancer risk

Author (Ref.)	Cancer site	Study design (n:N)[b]	Extremes compared by relative risk[c]	Relativ risk[c]
Byers et al (19)	Lung (M)	C:C (296:587)	Quartiles	1.2
	Lung (F)	C:C (154:315)	Quartiles	1.1
Kromhout (52)	Lung (M)	Cohort (63:878)	Quartiles	2.8
Jain et al (45)	Lung (M,F)	C:C (839:772)	Quartiles	0.9
Le Marchand et al (54)	Lung (M)	C:C (230:597)	Quartiles	2.3
	Lung (F)	C:C (102:268)	Tertiles	0.7
Fontham et al (31)	Lung (M)	C:C (866:982)	Tertiles	1.6
	Lung (F)	C:C (287:292)	Tertiles	0.9
Zatonski et al (114)	Pancreas (M,F)	C:C (110:195)	Quartiles	2.7
Ghadirian et al (35)	Pancreas (M,F)	C:C (179:239)	Quartiles	1.8
Bueno de Mesquita et al (15)	Pancreas (M,F)	C:C (164:480)	Quintiles	1.2
Howe et al (41)	Breast (F)	C:C (12 studies)	Quartiles	1.5
Zaridze et al (113)	Breast (F)	C:C (139:139)	Quartiles	3.1
Nomura et al (68)	Bladder (M)	C:C (195:390)	Quartiles	0.8
Freudenheim et al (33)	Colon (M)	C:C (205:205)	Quartiles	1.2
	Colon (F)	C:C (223:224)	Quartiles	0.9
	Rectum (M)	C:C (293:277)	Quartiles	2.3
	Rectum (F)	C:C (151:146)	Tertiles	5.0
Buiatti et al (16)	Stomach (M,F)	C:C (923:1159)	Quintiles	2.0
Brock et al (14)	Cervix (F)	C:C (117:196)	Quartiles	1.7
Verreault et al (101)	Cervix (F)	C:C (189:227)	Quartiles	2.0
Sturgeon et al (94)	Vulva (F)	C:C (201:324)	Quartiles	0.9
Shu et al (89)	Ovary (F)	C:C (172:172)	Quartiles	1.1

[a] Only includes studies published since 1987 that present findings by nutrient indices and have at least 10 cases (or 30 if it is a cohort study).

[b] C:C = case-control, (n:N) = the number of cases:controls or the number of incident cases:cohort size.

[c] Relative risk is the ratio of risk for persons in the lowest category of intake compared with those in the highest category of intake.

Table 5 Selected[a] case control and cohort studies of the relationship between dietary vitamin E and cancer risk

Author (Ref.)	Cancer site	Study design (n:N)[b]	Extremes compared by relative risk[c]	Relative risk[c]
Byers et al (19)	Lung (M)	C:C (296:587)	Quartiles	1.3
	Lung (F)	C:C (154:315)	Quartiles	1.1
Lee et al (53)	Breast (F)	C:C (200:420)	Tertiles	1.7
Richardson et al (77)	Breast (F)	C:C (409:515)	Tertiles	0.8
Verreault et al (101)	Cervix (F)	C:C (189:227)	Quartiles	2.5
Ghadirian et al (35)	Pancreas (M,F)	C:C (179:239)	Quartiles	0.8
Stryker et al (93)	Skin (M,F)	C:C (204:248)	Quintiles	1.4
Buiatti et al (16)	Stomach (M,F)	C:C (923:1159)	Quintiles	2.0

[a] Only includes studies published since 1987 that present findings by nutrient indices and have at least 100 cases (or 30 if it is a cohort study).

[b] "C:C" = case-control, (n:N) = the number of cases:controls or the number of incident cases:cohort size.

[c] Relative risk is the ratio of risk for persons in the lowest category of intake compared with those in the highest category of intake.

(Table 5). However, cervical dysplasia, the premalignant phase of cervical cancer, was not affected by β-carotene supplementation in a therapeutic trial (27). Too few studies of diet and cancers of other sites have been conducted to support any general conclusions.

Studies of Blood Nutrients

In many cohort studies, blood was collected and assayed for nutrients either at the time of the baseline examination or later, using frozen serum sampled in nested case-control designs. Findings from those cohort studies that have examined antioxidant levels in the blood as related to subsequent cancer risk are presented in Table 6. Only those studies with 30 or more incident cancers are included. A general pattern of increased risk with low levels of circulating antioxidants is observed. This pattern is particularly apparent for β-carotene in lung cancer, whereas findings for vitamin C and vitamin E in lung cancer are less convincing. Blood levels are only weakly and inconsistently associated with cancers of the breast, colon, and rectum.

Though studies of blood nutrient markers are useful, they also have important limitations. Dietary intake is just one of many determinants of circulating blood nutrient levels. A single determination of the level of any antioxidant micronutrient at a point in time may therefore be a poor indication of

Table 6 Selected[a] cohort studies of the relationship between antioxidant levels in the blood a subsequent cancer risk

Author (Ref.)	Cancer site	Years of follow-up (n:N)[b]	Dietary anti-oxidants	Categories compared by relative risk[c]	Relati risk[c]
Willett et al (108)	All	5 (111:210)	Total carotene	Quintiles	1.5
	All	5 (111:210)	Vitamin E	Quintiles	1.2
Salonen et al (80)	All	4 (51:51)	Vitamin E	Below vs above 33rd percentile	1.6
Wald et al (103)	All	10 (271:533)	β-Carotene	Quinitiles	1.7
Nomura et al (69)	Lung	10 (74:302)	β-Carotene	Quintiles	2.2
Connett et al (24)	Lung	10 (66:131)	Total carotene	Quintiles	1.8
	Lung	10 (66:131)	β-Carotene	Quintiles	2.3
Stahelin et al (91)	Lung	12 (68:2421)	Carotene	Below vs above 25th percentile	1.8
	Lung	12 (68:2421)	Vitamin E	Below vs above 25th percentile	1.5
	Lung	12 (68:2421)	Vitamin C	Below vs above 22.7 mmole/liter	0.8
Menkes et al (61)	Lung	8 (99:196)	β-Carotene	Quintiles	2.2
	Lung	8 (99:196)	Vitamin E	Quintiles	2.5
Comstock et al (23)	Breast	8 (30:59)	β-Carotene	Quintiles	0.9
	Breast	8 (30:59)	Vitamin E	Quintiles	0.6
	Rectum	8 (34:68)	β-Carotene	Quintiles	0.8
	Rectum	8 (34:68)	Vitamin E	Quintiles	0.6
Schober et al (84)	Colon	8 (72:143)	β-Carotene	Quintiles	1.2
	Colon	8 (72:143)	Vitamin E	Quintiles	1.5
Knekt et al (50)	Stomach	10 (48:841)	Vitamin E	Quintiles	1.6
	Lung	10 (144:841)	Vitamin E	Quintiles	1.4
	Prostate	10 (37:841)	Vitamin E	Quintiles	2.3
	Skin	10 (49:841)	Vitamin E	Quintiles	1.9

[a] Only studies with 30 or more incident cases are included.
[b] (n:N) = the number of incident cases per number of matched cohort members assayed for comparison.
[c] Relative risk is the ratio of risk for persons in the lowest category of intake compared with those in the highest category of intake.

long-term dietary exposures. Nonetheless, cohort study findings based on blood levels of antioxidant micronutrients are generally consistent with the findings from dietary epidemiology studies, which suggest that fruit and vegetable intake can prevent many cancers in humans.

Randomized Controlled Trials

Randomized controlled trials, in which antioxidants are administered blindly to individuals at risk for cancer, are the most definitive means of testing hypotheses related to specific antioxidant compounds. Trials have their own limitations, however. If the protective effects of antioxidants found in foods are dependent on the complex chemical mixtures of whole foods, then supplementation with only a single antioxidant may be an insufficient test of the hypothesis that food-borne antioxidants are cancer-preventive. In addition, randomized controlled trials are often conducted over a relatively short period of time in individuals at high risk for cancer. Trials now underway will therefore be very useful if they yield positive findings, but if they yield negative findings, interpreting the role of food-borne antioxidants over a lifetime for individuals at average risk may be difficult.

Table 7 lists the randomized controlled trials that have been designed to investigate the potential of reducing cancer risk by daily antioxidant supplementation (13). Only two trials have been completed. β-Carotene supplementation had no effect on the rate of new basal cell skin cancers in patients who had previously had a basal cell excised (36), and the rate of recurrence of rectal polyps was unaffected by combined supplementation with vitamins C and E in a small trial on patients who had previously undergone total colectomies for familial polyposis (26). Results from the other trials listed in Table 7 may not be reported for several years. Of special note is the National Cancer Institute trial of increasing fruit and vegetable intake to prevent adenomatous polyps in individuals who have had a polyp resection. This is the first randomized controlled trial in which researchers are using a fundamental modification of the diet as the intervention (seven servings of fruits and vegetables per day) rather than a nutritional supplement.

CONCLUSIONS AND RECOMMENDATIONS

Antioxidant micronutrients, especially carotenes, vitamin C, and vitamin E, appear to play many important roles in protecting the body against cancer. They block the formation of chemical carcinogens in the stomach, protect DNA and lipid membranes from oxidative damage, and enhance immune function. Nevertheless, many important questions need to be answered before either micronutrient supplementation or food fortification can be recommended as a cancer prevention strategy to the general population. Why do micronutrient effects differ by organ site, what are the optimal doses at which

Table 7 Randomized controlled trials of antioxidants in cancer prevention

Cancer site	Antioxidants	Study populations	Investigator/results
Lung	β-Carotene	Cigarette smokers	Lewis Kuller, University of Pittsburg
Lung	β-Carotene	Asbestos workers	Jerry McLarty, University of Texas
Lung	β-Carotene (and retinol)	Asbestos workers	Gilbert Omenn, Fred Hutchinson Center, Washington
Lung	β-Carotene (and retinol)	Cigarette smokers	Gary Goodman, Fred Hutchinson Center, Washington
Lung	β-Carotene and vitamin E	Cigarette smokers	Demetrius Albanes, National Cancer Institute
Colon	Fruits and vegetables	Patients with adenomatous polyps	Arthur Schatzkin, National Cancer Institute
Colon	β-Carotene and vitamins C & E	Patients with adenomatous polyps	Robert E. Greenberg, Dartmouth, New Hampshire
Rectum	Vitamins C & E (and fiber)	Patients with familial polyposis	Jerome DeCosse, Memorial Hospital, New York (26): There was no benefit of combined Vitamin C and E on rectal polyp recurrence after colectomy
Skin	β-Carotene	Albinos in Africa	Jeff Luande, Muhimbili Medical Center, Tanzania
Skin	β-Carotene	Patients with basal cell carcinoma	Robert E. Greenberg, Dartmouth, New Hampshire (36): There was no benefit of β-carotene on basal cell cancer recurrence
Skin	β-Carotene and vitamins C & E	Patients with basal cell carcinoma	Bijan Safai, Memorial Hospital, New York
All sites	β-Carotene	Physicians	Charles Hennekens, Harvard School of Public Health
Esophagus	β-Carotene and vitamin E (and minerals and multivitamins)	Residents in high risk area in China	Philip Taylor, National Cancer Institute

risk is reduced, and are there potential adverse effects are questions that need to be answered. Animal experiments can help us to better understand possible dose-response relationships and to study potential toxicities, but firm answers to important questions about the effects of micronutrients in humans will emerge only from human studies. Randomized controlled trials will be helpful, but they cannot answer questions about the effects of diet on individuals at average risk for cancer. Prospective studies that include better measures of diet need to be designed. Repeated questioning of cohort members using a combination of food frequency questionnaires, interviews, and diet recalls could be employed to construct a set of dietary indicators that would more accurately classify cohort members according to their usual dietary habits.

Although many important questions remain before dietary supplementation and/or food fortification can be recommended to the population, there is a strong scientific basis for current US recommendations that emphasize frequent fruit and vegetable consumption (5, 92). Fruits and vegetables seem to protect the human body against cancer, perhaps because they protect the body against oxidative damage. Achieving the current US Year 2000 goal of doubling the frequency of consumption of fruits and vegetables to five servings per day (75) is therefore likely to have an important effect on the cancer risk of Americans. To achieve this goal will require the cooperation of many in our society to make significant positive changes in the diet of the population (71).

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