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Antioxidant Micronutrients in Cancer Prevention

*Joanne F. Dorgan, MPH, PhD,**
and Arthur Schatzkin, MD, DrPH†

Diet has been implicated as a risk factor for cancer in humans. Diet, however, is not a single entity but is comprised of numerous nutritive and nonnutritive components that could influence cancer risk in different ways. Some dietary components, such as fat, may exert a causative effect on cancer risk. Conversely, other dietary components, such as fiber and antioxidant micronutrients, may exert preventive effects. This article reviews the evidence for a preventive effect of antioxidant micronutrients on cancer risk. An accompanying article in this issue reviews the evidence on fat and fiber.

Antioxidant micronutrients, including the carotenoids, vitamin C, vitamin E, selenium, zinc, copper, iron, and manganese, are one of the body's primary defenses against free radicals and reactive oxygen molecules. Free radicals and reactive oxygen molecules are generated endogenously as a result of metabolic reactions. There are also numerous exogenous sources of these molecules, including tobacco smoke, pollutants, organic solvents, and pesticides. Free radicals react with unsaturated bonds of membrane lipids, denature proteins, and attack nucleic acids. Reactive oxygen molecules also initiate cellular damage by these mechanisms. Carotenoids, vitamin C, and vitamin E trap free radicals and reactive oxygen molecules, whereas selenium, zinc, copper, iron, and manganese are essential components of antioxidant enzymes.[97]

Although other antioxidant micronutrients may also play a role in cancer prevention, only the carotenoids, vitamin C, vitamin E, and selenium are discussed in this article. The relationships of these micronutrients to cancer risk have been studied most extensively. For each micronutrient, results of selected animal studies are briefly summarized. A more compre-

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hensive summary of results of human studies is provided. To assist the reader in interpreting results, a brief overview of epidemiologic methods used to assess micronutrient intake is provided before results of human studies on the association of that micronutrient to cancer risk are described.

Results of both cohort and case-control diet studies are summarized. In cohort studies, individuals are asked about their diets and followed to determine who subsequently develops cancer. Because of the large number of individuals who do not develop cancer, investigators frequently compare findings on cases with a sample of controls in a nested case-control analysis. For simplicity, studies of cohorts, whether the entire cohort was included in the analysis or a nested case-control analysis was performed, are referred to as *cohort studies* in this review. *Case-control studies,* in this review, refer to retrospective case-control studies in which individuals with cancer are identified from registries or hospital records and noncancer controls are selected from the community or hospital. In these studies, patients with cancer are asked to recall what they ate prior to diagnosis, and controls are asked to recall what they ate at a comparable time and responses are compared. Cohort and case-control designs are also used in serum studies of micronutrients and cancer. However, because cancer at many sites can affect levels of micronutrients in blood, only cohort serum studies, including those in which a nested case-control analysis was conducted, are reviewed. These studies use blood collected prior to diagnosis, and micronutrient levels are less likely to be affected by the presence of cancer.

Even in studies of large cohorts, sufficient numbers of site-specific cancers frequently do not occur for meaningful comparisons to be made. Results based on fewer than 10 cases are not included in this review. Although this cut-off is arbitrary, it allows inclusion of the majority of findings. For many of the rarer cancers, only data from retrospective diet studies are available.

CAROTENOIDS

Carotenoids comprise a group of more than 500 naturally occurring pigments that are powerful antioxidants and efficient scavengers of reactive oxygen molecules. Carotenoids also stimulate the immune system, although the mechanism for this action is unclear. Approximately 10% of carotenoids, including β-carotene, can be metabolized to retinol and have effects that are not intrinsic to carotenoids but are due to their provitamin A activity.[5]

Animal Studies

Carotenoids have been found to protect against tumorigenesis in a number of animal studies. Dietary carotenoids decreased the incidence (percent of animals with tumors)[154] and multiplicity (number of tumors per animal)[105] of skin tumors and the incidence of mammary tumors[153] in mice exposed to ultraviolet light and chemical carcinogens. Carotenoids also inhibited chemical induction of salivary gland tumors in rats[2] and oral,[161] but not respiratory,[4] tumors in hamsters. Although dietary carotenoids have been reported to decrease the incidence and multiplicity of chemically

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induced colon tumors[176] and the total number of gastric tumors,[155] carotenoids have also been reported to have no effect on gastrointestinal carcinogenesis.[73] In mice, dietary carotenoids delayed the appearance and decreased the incidence of virally induced tumors[162] and inhibited the growth of transplanted tumors.[141]

Human Studies

A protective role for carotenoids in the etiology of cancer in humans has been investigated in numerous epidemiologic studies. In some studies, the frequencies of intake of foods that are good sources, primarily dark yellow fruits and vegetables and dark green leafy vegetables, have been used as an indirect measure of dietary carotenoids. In other studies, carotenoid indexes have been calculated based on the nutrient composition of foods consumed. Food composition tables used in most epidemiologic studies provide a composite value of several, but not all, carotenoids. Therefore, carotenoid indexes are an approximate measure of dietary intake.[206] Blood carotenoid levels have also been used in epidemiologic studies to estimate dietary intake. Blood levels are very sensitive to dietary carotenoids and are a useful index of exposure.[199]

Cohort studies have yielded inconsistent results on the relationship of carotenoids to risk of cancer at all sites combined. Although a significant protective effect has been reported by some,[22, 43, 191] others have failed to detect an association.[24, 32, 85, 130, 197] There is considerable evidence for a protective effect of carotenoids on lung cancer risk in humans. For other sites, such as esophagus, oral cavity and pharynx, stomach, pancreas, bladder, colon, breast, cervix, ovary, and prostate, the relation is less clear. Because of differences in reported associations of carotenoids with site-specific cancers in humans, results of epidemiologic studies are reviewed by site.

Lung. Strong support for a preventive effect of carotenoids in relation to lung cancer risk is provided by a cohort study of 2107 men followed for 19 years.[165] Relative risks of lung cancer in the lowest to the highest quartile of carotenoid intake were 7.0, 5.5, 3.0, and 1.0. Additional support is provided by results of three other cohort studies. Kvale et al[87] reported that total vitamin A intake, including vitamin A from vegetable sources, was associated with a significantly decreased risk of lung cancer, particularly squamous cell carcinoma, in a cohort of 16,713 men and women. Protective effects of green and yellow vegetable consumption[59] and fruit consumption[96] have also been reported. However, a protective effect of dietary carotenoids on lung cancer risk has not been detected in all cohort studies.[85, 130]

Six of eight large case-control studies reported inverse associations between dietary carotenoids and lung cancer.[8, 17, 38, 58, 69, 94, 152, 208] In studies that reported an association, smoking-adjusted relative odds for the lowest compared to the highest category of intake ranged from 1.3 to 2.7. When frequency of consumption of dark green and yellow vegetables was considered, slightly stronger associations were observed; relative odds ranged from 1.5 to 3.9.[94, 99, 136, 208] Analyses by histologic type indicate a protective effect of carotenoids and vegetables for squamous[17, 38, 94, 136, 208] and small cell[38, 94, 136] carcinoma. Results for adenocarcinomas are less consistent, but protective effects have been reported.[17, 94, 201]

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Sex differences in the association of carotenoids with lung cancer have been observed in some studies.[17, 58] However, significant protective effects have been reported for both men[8, 17, 55, 94, 208] and women.[94, 201] Cigarette smoking has been observed to modify associations of dietary carotenoids and vegetable consumption with lung cancer risk in a number of studies, but results are inconsistent. In a large cohort study, Shekelle et al[165] found that the protective effect of carotenoids was strongest for men who smoked cigarettes for 30 or more years. Some case-control studies indicate a stronger protective effect of carotenoids in nonsmokers and former smokers,[17, 152] but others indicate a stronger protective effect in current smokers.[136, 208] In one study, a stronger protective effect of dietary carotenoids was observed in men who were current smokers but in women who were nonsmokers and former smokers.[94]

Serum studies also support a role for carotenoids in the prevention of lung cancer. Total serum carotenoids were significantly inversely associated with risk of developing lung cancer in one of two studies that measured total carotenoids.[24, 197] Four studies that specifically measured β-carotene also found significantly lower levels in individuals who subsequently developed lung cancer,[43, 110, 124, 191] and in a fifth study β-carotene was marginally significantly lower.[24] The smoking-adjusted relative odds of developing lung cancer ranged from 2.0 to 2.3 for those with the lowest versus highest serum β-carotene levels.[24, 110, 124, 191] Menkes et al[110] and Nomura et al[124] performed analyses by histologic type and found that the risk of squamous cell carcinoma was significantly inversely associated with serum β-carotene. Nomura et al[124] also reported a protective effect for small cell carcinoma; protection was afforded at all smoking levels, but the effect was greatest in heavy smokers.

Esophagus. Infrequent consumption of fruits and vegetables[61] and low plasma β-carotene levels[202] have been noted in populations with high esophageal cancer incidence rates. Studies of individuals, however, provide only limited support for a protective effect of carotenoids on esophageal cancer risk. Several case-control studies have reported a decreased risk of esophageal cancer in relation to consumption of fruits or vegetables.[11, 29, 30, 113, 121, 183, 205, 209] Decarli et al[30] and Ziegler et al[209] investigated the association of different types of vegetables with esophageal cancer risk. Although individuals with cancer ate fewer yellow and green vegetables than controls, differences were not statistically significant. Brown et al[11] also failed to detect an association of esophageal cancer with consumption of fruits that are good sources of β-carotene. Of four studies that estimated dietary carotenoids, two reported a significant inverse association with cancer of the esophagus,[30, 183] but two others did not detect an association.[11, 209] In a fifth study, Graham et al[48] reported a significant inverse trend in risk of esophageal cancer associated with vitamin A from vegetable sources but not for total dietary carotenoids.

Oral Cavity, Pharynx. Case-control studies also provide limited support for a protective effect of dietary carotenoids on risk of oral and pharyngeal cancers. Winn et al[200] and McLaughlin et al[107] observed significant protective effects of fruit, including dark yellow fruit,[107] on oral and pharyngeal cancer risk. Winn et al[200] also reported a marginally significant

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inverse association of green leafy vegetable consumption with cancer risk. Although green leafy vegetables were not associated with oral and pharyngeal cancers in the study by McLaughlin et al,[107] yellow vegetables were protective for men. Ning et al[122] also observed a protective effect of carrots, but not green leafy vegetables, on nasopharyngeal cancer risk. However, the association with carrots was only significant for childhood consumption. Rossing et al[148] failed to detect an association of dietary carotenoids with pharyngeal cancer. McLaughlin et al[107] also found no association between oral and pharyngeal cancers and carotenoids from vegetables but a significant protective effect of carotenoids from fruit.

Stomach. In the one cohort diet study with a sufficient number of stomach cancers to allow a site-specific analysis, consumption of green and yellow vegetables was associated with a significantly decreased risk of stomach cancer.[59] The standardized mortality ratio was 1.5 for individuals who did not eat green and yellow vegetables, as compared to those who ate these foods daily. Case-control studies further support a protective effect of fruits or vegetables on stomach cancer risk.[27, 50, 71, 84, 93, 144, 180, 203] Of four case-control studies that investigated the relation of a dietary carotenoid index to stomach cancer, three reported significant protective effects.[93, 144, 203] The fourth study found a marginal protective effect of dietary carotenoids that was limited to whites.[27] Lower levels of β-carotene in the serum of individuals who subsequently developed stomach cancer were reported in three studies,[43, 124, 191] and in one, differences were statistically significant.[43]

Pancreas. Green and yellow vegetable consumption was not associated with pancreatic cancer in two cohort studies.[60, 116] However, fruits or vegetables were protective in five case-control studies.[36, 44, 98, 125, 128] In the study by Norell et al,[125] there was a significant protective effect of carrots, whereas in the study by Olsen et al,[128] the effect was limited to cruciferous vegetables. Falk et al[36] failed to detect an association of dietary carotenoids with pancreatic cancer. Burney et al[13] also failed to detect an association of β-carotene in prediagnostic serum with risk of pancreatic cancer. However, low levels of lycopene, another carotenoid, were significantly associated with an increased risk of developing pancreatic cancer after 12 years of follow-up. The relative odds for individuals in the lowest versus the upper two terciles of lycopene was 6.4 (95% confidence interval: 1.8 to 24.2).

Colon and Rectum. Fruit or vegetable consumption has been associated with decreased risks of cancers of the colon and rectum in several case-control studies.[45, 86, 92, 100, 133, 170, 194, 204] In a meta-analysis of six studies, Trock et al[182] calculated a relative odds of colorectal cancer for individuals with low versus high consumption of vegetables of 2.1 (95% confidence interval: 1.8 to 2.4). However, it is unclear whether carotenoids or another component of fruits and vegetables, such as fiber, is protective. Three cohort studies failed to detect an association between dietary carotenoids and cancers of the colon and rectum.[55, 130, 165] Although these studies had only limited power to detect an association because of small numbers of cases, results of case-control studies on the relation of carotenoids and colorectal cancer risk are inconsistent. Kune et al[86] present data that suggest an inverse association between dietary carotenoids and cancer of the colon and rectum combined. Two of four studies of colon cancer[47, 92, 137, 194] and two of

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three studies of rectal cancer[39, 92, 137] also reported an inverse association with dietary carotenoids. However, in one study, the protective effect of carotenoids on rectal cancer risk was significant for men only.[39] Prospective serum studies also provide only limited support for a role of carotenoids in prevention of colorectal cancer. Four of five studies of prediagnostic serum observed lower levels of β-carotene in individuals who subsequently developed colorectal cancer, but even in studies with fairly large sample sizes, the association was not statistically significant.[23, 24, 124, 156, 191]

Bladder. In a cohort of residents living in a retirement community, there was a decreasing trend in risk of bladder cancer with increasing β-carotene intake that was significant in women.[130] However, only 13 women developed bladder cancer and only one of them was in the highest tercile of β-carotene intake. In a second cohort of men, there was no evidence of a protective effect of dietary carotene in relation to bladder cancer risk.[165] Three case-control studies reported a decreased risk of bladder cancer in relation to consumption of fresh fruits and vegetables,[20] green vegetables,[91] and carrots.[91, 112] The protective effect, however, was limited to men in one study[20] and women in another study.[112] Dunham et al[33] found no association between consumption of leafy and yellow vegetables and risk of bladder cancer. Although La Vecchia et al[91] observed a significant inverse association between dietary carotenoids and bladder cancer, Risch et al[143] failed to detect an association with β-carotene or other carotenoids. There also was no association of β-carotene with development of bladder cancer in three serum studies.[56, 124, 191] Helzlsouer et al,[56] however, reported a marginally significant protective effect of serum lycopene.

Cervix. An inverse association of carotenoid intake and cervical cancer risk was reported in a case-control study by Marshall et al.[103] Brock et al[10] also present data that suggest a possible protective effect of dietary carotenoids on in-situ cervical cancer risk. La Vecchia et al,[88] however, failed to detect an association of dietary carotenoids or green and yellow vegetables with in-situ cervical cancer. In the latter study, significant inverse associations of dietary carotenoids and green and yellow vegetables were observed for risk of invasive cervical cancer. Inverse associations of these dietary components with risk of invasive cervical cancer were also reported by Verreault et al,[186] but results were not significant after adjustment for other risk factors. Ziegler et al[207] did not find an association of dietary carotenoids with risk of invasive cervical cancer.

Breast. In a cohort of residents of a retirement community, carotenoid intake was not associated with the development of breast cancer.[130] Although vegetables,[74, 89] including leafy green vegetables,[68] and carotenoids[68, 75, 145] were reported to be protective in some case-control studies of breast cancer, no association was reported in others.[104, 178] Howe et al[63] reanalyzed combined data from eight case-control studies of breast cancer. The relative odds of breast cancer for postmenopausal women in the lowest compared to the highest quintile of carotenoid intake was 1.2, which was statistically significant. However, there was no association of breast cancer with carotenoid intake in premenopausal women. Three cohort studies failed to detect a significant association of serum carotenoids with breast cancer risk.[23, 188, 197] In one of these studies, women who developed breast cancer

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had lower levels of β-carotene,[188] but this may have been due to differences in storage conditions for serum from cases and controls.[189]

Ovary. Slattery et al[169] and Byers et al[15] observed significantly lower levels of dietary carotenoids in women with ovarian cancer in case-control studies. In the study by Byers et al,[15] however, the association was restricted to women 30 to 49 years of age. Two additional case-control studies found no association of dietary carotenoids with ovarian cancer after adjustment for other risk factors,[90, 168] but consumption of green vegetables remained protective in one study.[90]

Prostate. Hirayama[59] reported an inverse association of green and yellow vegetable consumption with risk of dying of prostate cancer in a cohort of Japanese men. Mills et al[117] also found that a variety of fruits and vegetables were associated with a decreased risk of developing prostate cancer in a cohort of Seventh Day Adventist men. However, no association of prostate cancer with intake of fruits and vegetables[171] or carotenoids[130, 165] was reported in three other cohort studies. Case-control studies on the association of carotenoids and prostate cancer have also yielded inconsistent results. In a study by Ohno et al,[126] a significant protective effect of green and yellow vegetables was observed for prostate cancer. Consumption of greens and carrots was also associated with decreased risks of prostate cancer in blacks and whites, respectively, in a study by Ross et al.[147] Relative odds of prostate cancer greater than or equal to 2.0 for rare versus frequent consumers of green and yellow fruits and vegetables were reported in two additional studies, but in neither were results statistically significant.[120, 160] In another study, there was no association of green vegetable consumption with prostate cancer.[175] Dietary carotenoids were associated with a decreased risk of prostate cancer in studies by Mettlin et al,[114] Oishi et al,[127] and Ohno et al.[126] The effect was significant for younger men only in the study by Mettlin et al[114] and for older men only in the study by Ohno et al.[126] Results of another study suggested a protective effect of dietary carotenoids on prostate cancer in blacks but not in whites.[147] In contrast to other findings, Kolonel et al[83] reported a marginally significant enhancement of risk of prostate cancer by dietary carotenoids in older men. Two studies of prediagnostic serum showed no association between carotenoids and prostate cancer.[23, 197]

In summary, results of human studies support a protective effect of fruit and vegetable consumption on risk of cancer at several sites. However, whether the effect is due to dietary carotenoids or to other components of fruits and vegetables is unclear. The consistency with which infrequent consumption of dark green and yellow fruits and vegetables and low levels of dietary carotenoids and serum β-carotene are associated with an increased risk of lung cancer provides strong support for a protective effect at this site. Studies also support a protective effect of consumption of dark green and yellow fruits and vegetables and possibly carotenoids on stomach cancer risk. However, no firm conclusions can be drawn on the association of fruits and vegetables and carotenoids with oral cancer and cancers of the esophagus, pancreas, colon and rectum, bladder, cervix, breast, ovary, and prostate.

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VITAMIN C

Vitamin C is a water-soluble antioxidant. In addition to trapping free radicals and reactive oxygen molecules, vitamin C reduces nitrite. This reaction blocks the formation of nitrosamines and nitrosamides, compounds that induce tumors in experimental animals and possibly in humans. Vitamin C also stimulates the immune system and may protect against the development of cancer by enhancing immune surveillance.[118]

Animal Studies

Animal studies support a role for vitamin C in prevention of some cancers. Vitamin C supplementation delayed the appearance and decreased the incidence of skin tumors in mice exposed to ultraviolet light.[34] It also decreased the incidence of nasal tumors in hamsters exposed to cigarette smoke and a chemical carcinogen but accelerated the appearance of tracheal tumors in these animals.[53] Vitamin C decreased the multiplicity of lung adenomas in mice exposed to one chemical carcinogen, but it enhanced the effect of another carcinogen on tumorigenesis.[119] Vitamin C decreased the incidence of kidney tumors in hamsters exposed to estrogens[95] and rats exposed to single, but not multiple, doses of a chemical carcinogen.[138] In rats, vitamin C at lower doses also decreased the incidence of colon tumors following exposure to single, but not multiple, doses of a chemical carcinogen.[138] Conversely, at higher doses it increased the incidence of adenomas and the multiplicity of all colon tumors in rats.[166] Vitamin C supplementation had no effect on colon tumors in mice.[72] Vitamin C also had no effect on chemical induction of mammary[1] or bladder tumors in rats.[41] Although an increased incidence of bladder tumors in rats fed high doses of vitamin C has also been reported,[40] this effect has been attributed to the sodium salt of ascorbic acid fed to animals rather than to an effect of vitamin C per se.[42]

Human Studies

Dietary vitamin C is estimated in epidemiologic studies by determining the frequency of consumption of foods that are good sources and by calculating the vitamin C content of the diet using nutrient composition data. The primary dietary sources of vitamin C are fruits and vegetables, especially citrus fruits, dark green leafy vegetables, tomatoes, and potatoes. Although blood levels can also be used to assess short-term vitamin C intake, vitamin C deteriorates rapidly during frozen storage unless blood samples are acid stabilized.[195] Because samples in serum banks generally have not been acid stabilized prior to storing, few epidemiologic studies have been performed using prediagnostic blood levels of vitamin C as an indicator of dietary intake. Only findings from a cohort study by Gey et al[43] in which vitamin C was analyzed in fresh plasma are included in this review.

The association of dietary vitamin C with risk of cancer has been investigated in numerous epidemiologic studies. Dietary and plasma vitamin C were not associated with total cancer mortality after adjustment for age and cigarette smoking in two cohort studies.[43, 85] Studies of cancers at specific sites, however, provide fairly strong support for an inverse associ-

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ation of vitamin C with oral cancers and cancers of the esophagus and stomach. Studies of vitamin C in relation to cancers of the lung, colon, pancreas, cervix, and breast have been inconsistent. Currently available data provide little support for a protective effect of vitamin C on cancers of the bladder, ovary, and prostate. Because vitamin C's protective effect has been observed only for specific sites, studies of vitamin C in relation to cancer in humans are also discussed by site.

Lung. Results of epidemiologic studies on the association of vitamin C and lung cancer risk are inconsistent. Long-de et al[96] reported a significant protective effect of fruit consumption on lung cancer in a large cohort of Chinese men and women. Kromhout[85] also reported significant protective effects of citrus fruit and vitamin C intake in a cohort of men. Three other cohort studies, however, failed to detect an association of citrus fruit[172] or vitamin C[87, 165] intake with lung cancer risk. Four case-control studies showed no association of vitamin C with lung cancer.[16, 17, 58, 69] Fontham et al,[38] however, found a significant inverse association of vitamin C intake and lung cancer risk in a case-control study. Le Marchand et al[94] also observed a significant protective effect in men. Lower levels of vitamin C in prediagnostic plasma of men who subsequently died of lung cancer were reported by Gey et al,[43] but differences were not statistically significant.

Esophagus. Populations with a high incidence of esophageal cancer tend to consume fewer fruits and vegetables and have poorer vitamin C nutrition than populations with a low incidence of this cancer.[52, 61, 202] Low vitamin C intake has also been associated with a significantly increased risk of cancer of the esophagus in four case-control studies.[11, 113, 183, 209] Smoking and alcohol adjusted relative odds for the lowest compared to highest vitamin C consumers were 1.8 to 2.6. In eight case-control studies, consumption of fruits or vegetables was associated with a decreased risk of cancer of the esophagus.[11, 29, 30, 113, 121, 183, 205, 209] Fruits,[29, 30, 209] particularly citrus fruits,[11, 183] had a stronger protective effect than did vegetables. In a study by Graham et al,[48] there was no association between vitamin C from vegetables and cancer of the esophagus.

Oral Cavity, Pharynx. Significant protective effects of dietary vitamin C on oral or pharyngeal cancers have been reported in three case-control studies.[101, 107, 148] Smoking and alcohol adjusted relative odds for low versus high consumers ranged from 1.7 to 2.5. Fruit, including citrus fruit, and vegetable consumption were also associated with a decreased risk of cancers at these sites.[107, 200] The association with fruits was more consistent than with vegetables. In the study of McLaughlin et al,[107] vitamin C from fruits, but not vegetables, had a significant protective effect.

Stomach. Because vitamin C blocks the formation of nitrosamines in the stomach,[118] a protective role for vitamin C on stomach cancer risk is especially plausible. Ecologic studies within countries indicate lower intakes of vitamin C and fruits and vegetables in areas with higher rates of stomach cancer.[14, 26] Bright-See,[9] however, did not find a significant international correlation of per capita vitamin C availability with stomach cancer mortality. In a cohort study, Stahelin et al[172] observed a marginally significant increased relative odds of stomach cancer of 3.2 for men who ate citrus fruit less than three times per week compared to those who ate it more

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frequently. Four case-control studies reported an inverse association between dietary vitamin C and stomach cancer, with relative odds for low versus high intake ranging from 2.0 to 3.0.[27, 93, 144, 203] Consumption of vegetables,[12, 27, 50, 93, 144, 180, 203] fruit,[12, 27, 71, 84, 93, 203] and citrus fruit[12, 93, 144, 180] have also been associated with a decreased risk in case-control studies. In the one study that investigated vitamin C in prediagnostic plasma, men who subsequently died of stomach cancer had significantly lower levels.[43]

Pancreas. In a prospective study of Seventh Day Adventists, Mills et al[116] found that citrus fruit consumption was associated with a nonsignificant decreased risk of cancer of the pancreas. Consumption of fresh fruits and vegetables,[36, 44, 98] including citrus fruits,[125] was associated with a decreased risk of pancreatic cancer in four case-control studies. After adjusting for smoking, Falk et al[36] found a significant inverse association of vitamin C with pancreatic cancer risk. For men and women in the lowest compared to the highest tercile of vitamin C intake, relative odds were 2.8 and 1.8, respectively. In contrast to other studies, Olsen et al[128] found no evidence of a protective effect of fruits and vegetables, other than cruciferous vegetables, on pancreatic cancer risk.

Colon and Rectum. Dion et al[31] reported that vitamin C reduced the level of fecal mutagens, and it has since been hypothesized that vitamin C may protect against cancers of the colon and rectum. In an intervention study, McKeown-Eyssen et al[106] showed a small, nonsignificant protective effect of vitamin C and E supplementation on adenomatous polyp recurrence. In a cohort study, Heilbrun et al[55] reported a protective effect of vitamin C on colon but not rectal cancer risk. The relative odds of colon cancer was 1.9 (95% confidence interval: 1.0 to 3.4) for men in the lowest compared to highest quintile of vitamin C intake. Results of case-control studies on the association between vitamin C and colorectal cancer are inconsistent. Of eight studies that investigated dietary vitamin C, five reported an inverse association with risk of cancer of the colon or rectum.[39, 47, 70, 86, 92, 100, 137, 194] In two studies a protective effect of vitamin C was observed for cancers of both the colon and rectum.[86, 92] In two other studies the effect was limited to rectal cancer and was significant for women only.[39, 137] The fifth study that reported an association with vitamin C did not differentiate cancers of the colon and rectum.[100] Consumption of fruits or vegetables has been associated with a decreased risk of cancer of the colon or rectum in numerous studies.[45, 86, 92, 100, 133, 170, 194, 204] However, when analyzed separately, citrus fruit consumption was not significantly associated with colorectal cancer risk.[92, 115]

Bladder. In a case-control study, Kolonel et al[82] observed a nonsignificant inverse association between dietary vitamin C and bladder cancer. Claude et al[20] found that male, but not female, bladder cancer patients were less likely to eat fresh fruits and vegetables regularly as compared to controls. Three other case-control studies found no association between vitamin C,[143] fruit,[91] or citrus fruit[33] consumption and bladder cancer risk.

Cervix. Per capita vitamin C availability from food was highly negatively correlated with age-adjusted mortality from cervical cancer in 38 countries.[9] Cervical dysplasia has been reported to be strongly associated with low plasma[146] and dietary[192] vitamin C levels. Case-control studies of diet and

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Breast. Vitamin C consumption was not associated with breast cancer risk in three case-control studies.[49, 75, 178] Iscovich et al,[68] however, reported a marginally significant protective effect of vitamin C and a significant protective effect of citrus fruit consumption on breast cancer risk. In a reanalysis of combined data from nine studies, including several that did not originally report results on vitamin C, Howe et al[63] also found a significant protective effect of vitamin C on breast cancer. The relative odds of breast cancer for women in the lowest compared to highest quintile of intake was 1.4. When analyzed by menopausal status, the effect was significant for postmenopausal women only.

Ovary. Three case-control studies failed to detect an association of dietary vitamin C with ovarian cancer.[15, 168, 169]

Prostate. Mills et al[117] reported a significant inverse association of citrus fruit consumption with prostate cancer risk in a cohort of Seventh Day Adventist men. However, no association of fruit consumption with prostate cancer was reported in two other cohort studies.[163, 171] The majority of case-control studies do not support an association between vitamin C and prostate cancer.[57, 76, 83, 127] In a study by Graham et al,[46] there also was no association between vitamin C and prostate cancer in younger men, but in men 70 or more years old, there was a significant trend of increasing risk of prostate cancer with increasing vitamin C intake.

In summary, diet and plasma studies support a protective effect of vitamin C on stomach cancer risk. Case-control diet studies also provide considerable support for a protective effect of vitamin C on oral and esophageal cancers. It is unclear, however, whether these apparent protective effects are due to vitamin C or some other constituent of fruits and vegetables. Studies of the association of vitamin C with cancers of the lung, colon and rectum, pancreas, cervix, and breast have been inconsistent. Data generally fail to support an association of vitamin C with cancers of the bladder, ovary, or prostate.

VITAMIN E

Vitamin E is the major lipid-soluble antioxidant found in cell membranes, where it protects against lipid peroxidation.[97] Like vitamin C, vitamin E reduces nitrite, inhibiting the production of nitrosamines and nitrosamides.[118] Vitamin E may also play a role in the immune system, potentiating the immune response.[111]

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Animal Studies

Vitamin E has been reported to inhibit chemical carcinogenesis in some, but not all, animal studies. Dietary vitamin E delayed the appearance[167] and decreased the incidence and multiplicity[181] of oral tumors in hamsters treated with chemical carcinogens. In rats fed diets high in polyunsaturated fats, vitamin E decreased the incidence of chemically induced mammary tumors, but in rats fed diets low in polyunsaturated fats it had no effect.[65] Both inhibition[25] and enhancement[179] of chemically induced colon tumors were reported in mice supplemented with vitamin E. In rats, vitamin E delayed the appearance but did not affect the incidence or multiplicity of colon tumors.[174] Although topical vitamin E decreased the incidence of chemically induced skin tumors in mice,[132] dietary vitamin E had no effect.[35] Dietary vitamin E also had no effect on the incidence of tumors of the forestomach in mice.[193]

Human Studies

Major dietary sources of vitamin E are vegetable oils, margarine, and shortening, with nuts, seeds, whole grains, and wheat germ providing additional sources. Because the vitamin E content of many specific foods has not been determined, few epidemiologic studies have investigated the association of dietary vitamin E with cancer. A number of studies have, however, investigated the association of serum α-tocopherol with cancer risk. Serum α-tocopherol levels are moderately responsive to changes in dietary vitamin E, and single measurements are a good indicator of long-term dietary intake. Because α-tocopherol is carried by the lipoproteins in the blood, conditions that alter blood lipoprotein concentrations also affect α-tocopherol levels.[195]

The few studies that have attempted to investigate the association of dietary vitamin E with cancer risk have generally been negative. Dolecek[32] failed to detect an association of dietary vitamin E with the development of cancer at all sites in a cohort of men. Case-control studies of cancers of the lung,[17] oral cavity and pharynx,[107] stomach,[144] rectum,[39] and breast[178] have also been negative. However, significant protective effects of dietary vitamin E on risks of esophageal[183] and cervical[186] cancers have been reported.

Results of studies on the association of prediagnostic serum vitamin E and cancer risk have been mixed. Low levels of serum α-tocopherol were associated with an increased risk of cancer at all sites in three cohort studies.[77, 79, 81] In the cohort of men studied by Knekt et al,[79] the protective effect of α-tocopherol was limited to those less than 70 years old. Salonen et al[151] reported a protective effect of α-tocopherol in male nonsmokers but not male smokers or females. There was no association of serum or plasma α-tocopherol and the development of cancer at all sites in four additional cohort studies.[24, 43, 190, 197]

Cohort studies of blood levels of vitamin E and the development of cancers at specific sites are also inconsistent. Some studies suggest a possible protective effect for stomach, bladder, and cervical cancers, but these findings are not supported by results of other studies. Gey et al[43] observed a significantly increased risk of stomach cancer among men with low levels

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Currently available data do not support an association of vitamin E with cancers of the lung, colon and rectum, pancreas, breast, ovary, or prostate. Although Menkes et al[110] reported a significantly increased risk of lung cancer in individuals with low α-tocopherol levels in prediagnostic serum, six other cohort studies failed to detect an association.[24, 43, 79, 81, 124, 197] There also was no association of serum vitamin E with the development of colon or rectal cancer in four cohort studies.[23, 79, 124, 156] Although Knekt et al[79] reported a significantly increased risk of cancer of the pancreas among men with low serum α-tocopherol levels, controls in this study had exceptionally high levels of α-tocopherol. Burney et al[13] reported a nonsignificant decreased risk of pancreatic cancer among individuals with low α-tocopherol levels. There was no association of α-tocopherol with risk of developing breast cancer in four cohort studies.[23, 77, 149, 197] Although Wald et al[188] reported a significant protective effect of plasma α-tocopherol on breast cancer risk, further analyses revealed that this may have been due to differential degradation of α-tocopherol in plasma from cancer patients and controls.[189] Three cohort studies failed to detect an association between α-tocopherol and prostate cancer risk.[23, 79, 197] Additionally, Knekt[77] found no association of serum α-tocopherol with ovarian or endometrial cancer.

SELENIUM

Selenium is an essential constituent of the enzyme glutathione peroxidase, which reduces peroxides before they can attack intracellular membranes. However, glutathione peroxidase activity is probably not the primary mechanism by which selenium protects against cancer. Other proposed mechanisms include inhibition of DNA synthesis and cell proliferation and stimulation of the immune system.[109]

Animal Studies

Animal studies have demonstrated a protective effect of selenium on risk of some cancers. Dietary selenium supplementation in mice decreased the incidence of skin tumors induced by ultraviolet light[129] and chemical carcinogens.[164] Selenium supplementation of rats has been reported to decrease the incidence and multiplicity of chemically induced colon tumors,[7, 139] but selenium deficiency has also been reported to be protective.[140] In rats, selenium decreased the incidence of chemically induced liver

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tumors[28, 51] and delayed the appearance of aflatoxin-induced tumors.[54] Selenium also decreased the incidence of chemically induced lung tumors in rats,[7] but not in hamsters.[3] Selenium supplementation had no effect on the induction of tumors of the trachea in hamsters.[177] Depending on experimental conditions, selenium had no effect on or enhanced the development of pancreatic tumors in hamsters.[6]

The effect of selenium on mammary tumorigenesis has been studied extensively in animals. Selenium inhibited the development of spontaneous[159] and virally induced[157] mammary tumors in mice. It also delayed the appearance and decreased the incidence of mammary tumors in mice[108] and rats[66, 67] exposed to chemical carcinogens. The effect of selenium deficiency in rats on susceptibility to chemically induced mammary tumors, however, depends on the fat content of the diet.[67] In rats fed low-fat diets and diets high in saturated fats, selenium deficiency had no effect on induction of tumors. But in rats fed diets high in polyunsaturated fats, selenium deprivation resulted in a marked increase in the incidence and multiplicity of chemically induced mammary tumors. The protective effect of selenium supplementation was greatest during the induction or early promotion phases, although later supplementation was also weakly protective.[66] Maximal inhibition of tumors was achieved by continuous supplementation.

Although the underlying mechanism is unclear, animal studies indicate an interaction of vitamin E and selenium in the prevention of mammary tumors. In rats fed a high polyunsaturated fat diet, vitamin E enhanced the ability of selenium to inhibit the development of chemically induced tumors, although vitamin E alone had no effect.[62] Similarly, the anticarcinogenic effect of selenium was attenuated when rats were fed diets deficient in vitamin E.[64]

Human Studies

Good dietary sources of selenium are seafood and organ meats, followed by other meats and grains. However, the selenium content of grain depends on the level of selenium in the soil in which it is grown, and the selenium content of meat depends on the selenium content of grain used in animal feed. Because there is much diversity in soil selenium levels, the selenium content of food items varies considerably. Therefore, it is not usually possible to estimate the selenium content of individual diets in epidemiologic studies. Plasma selenium responds to dietary changes and is a useful indicator of short-term intake, whereas selenium in nails reflects long-term intake.[195]

Much of the evidence for a protective effect of selenium in humans comes from ecologic studies that have correlated dietary and blood levels of selenium with cancer incidence in populations. Based on per capita food consumption, dietary selenium in 27 countries was inversely correlated with age-adjusted mortality from cancers at all sites.[158] Significant inverse correlations were observed for cancers of the colon, rectum, prostate, breast, and ovary, and for leukemia. Additionally, there was a significant inverse correlation with lung cancer in men and a marginally significant inverse association with pancreatic cancer. Within the United States, local plant selenium levels are inversely correlated with age-adjusted mortality

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from cancers at all sites and cancers of the lung, colon, rectum, bladder, esophagus, pancreas, breast, ovary, and cervix.[19] Blood selenium concentrations are inversely correlated with age-adjusted mortality from cancer of the colon, rectum, breast, lung, and all sites combined both within the United States and internationally.[158] Mortality from cancers of the skin and prostate, and from leukemia, are also significantly correlated with blood selenium levels internationally.

The association of dietary selenium with cancer risk was investigated in one cohort study. Kromhout[85] found no association of selenium intake with risk of dying from cancer at all sites during 15 years of follow-up. Dietary selenium also was not associated with risk of dying of lung cancer when this site was considered separately.

Low blood selenium levels were associated with an increased risk of cancer at all sites in six cohort studies.[37, 78, 80, 150, 151, 196] However, in four of these studies results were significant only for men.[78, 80, 151, 196] Additionally, in studies by Salonen et al[151] and Willett et al,[196] differences were significant only for smokers. Ringstad et al[142] reported a significant association of low serum selenium with risk of fatal cancer but not nonfatal cancer. In three other cohort studies there was no association of serum selenium with risk of cancer at all sites.[21, 131, 187] The risk of cancer associated with low serum selenium levels was enhanced by low serum α-tocopherol levels in four cohort studies.[78, 80, 151, 196] In the study by Salonen et al,[151] there was a significant interaction of selenium and α-tocopherol in relation to cancer risk.

Cohort studies using prediagnostic serum do not provide strong support for an association of serum selenium with cancer at any specific site. Although there is some support for a protective effect of selenium on cancers of the bladder, pancreas, stomach, and colon, results are inconsistent. Helzlsouer et al[56] reported a significant inverse association between serum selenium and bladder cancer. An increased risk of bladder cancer among men with the lowest levels of serum selenium was also reported by Nomura et al.[123] However, Knekt et al[78] failed to detect an association of serum selenium with cancers of the urinary tract. Burney et al[13] and Knekt et al[78] observed a significantly increased risk of pancreatic cancer in men with low levels of serum selenium. There was no association of selenium with pancreatic cancer in women in either study. The association of selenium with cancer of the pancreas in men remained significant after adjusting for smoking in the study by Burney et al[13] but not in the study by Knekt et al.[78] Knekt et al[78] also reported a protective effect of serum selenium on stomach cancer risk in men that remained significant after adjusting for several other risk factors. However, there was no association of serum selenium with stomach cancer risk in two other cohort studies.[123, 187] A marginally significant increased risk of colon cancer in men with low serum selenium levels was reported by Nomura et al.[123] Schober et al[156] also found lower mean selenium levels in serum of individuals who developed colon cancer, but no difference in relative odds of colon cancer for individuals in the highest and lowest quintiles of selenium intake. Knekt et al[78] found no association of serum selenium with risk of colorectal cancer. Additionally, there was no association of serum selenium with rectal cancer in the study by Nomura et al.[123]

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Cohort studies generally do not support a protective effect of selenium on cancers of the lung, breast, prostate, or cervix. Knekt et al[78] reported a significant inverse association of serum selenium and lung cancer risk in men but not in women. Conversely, Menkes et al[110] reported a marginally significant direct association of serum selenium with lung cancer risk. Six additional cohort studies failed to detect an association between selenium and lung cancer.[21, 81, 123, 131, 187, 196] Coates et al[21] reported a marginally significant direct association of serum selenium with breast cancer risk. Additionally, Ringstad et al[142] reported marginally significant higher levels of selenium in serum of women who developed breast cancer. There was, however, no association between serum selenium and breast cancer in three other cohort studies.[78, 131, 196] Additionally, Van Noord et al[184] failed to detect an association between selenium in nails and breast cancer risk. The results of Willett et al[196] and Coates et al[21] suggest a possible protective effect of selenium on prostate cancer risk. However, there was no evidence of an association in three other cohort studies.[78, 131, 187] There was no association between selenium in prediagnostic serum and cervical cancer risk in the one study that reported on this site.[21]

DISCUSSION

The function of carotenoids, vitamin C, vitamin E, and selenium as antioxidants makes them potential chemopreventive agents. That these micronutrients protect against cancer in a number of animal models provides further support for a possible protective effect in humans. There is considerable evidence from human studies for protective effects of β-carotene on lung cancer and for vitamin C on oral, esophageal, and stomach cancers. Although there are inverse correlations of selenium with cancers at numerous sites in ecologic studies, observational studies do not provide strong support for a protective role of selenium at any site. There also is not good evidence for a protective effect of vitamin E on cancer in humans.

Results of studies on the association of antioxidant micronutrients with cancer at most sites are inconsistent. Because one of the criteria for causal inference in epidemiologic research is consistency of findings, this could indicate that there is no true underlying relationship between antioxidant micronutrients and cancer. However, inconsistencies in findings could also be related to methodologic problems in assessing dietary intake in epidemiologic studies.

Most epidemiologic studies on the association of diet and cancer rely on food frequency questionnaires to assess dietary intake. Even when quantified, these questionnaires provide only an approximate measure of habitual dietary intake. Pietinen et al,[134] for example, compared estimates of dietary intake from a quantified food frequency questionnaire with estimates from food records and reported correlations of 0.51 for vitamin A and 0.59 for vitamin C. Moreover, food frequency questionnaires used in various studies differ in the types and number of foods assessed and in the detail of information collected on portion sizes, food preparation methods, and seasonal use of foods. In the study by Pietinen et al,[135] correlations

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with diet records were 25 and 32% lower for vitamins A and C, respectively, when a short, simple, nonquantified food frequency questionnaire was used to estimate dietary intake, as compared to one that was longer and more detailed and that included questions on portion sizes.

The ability of subjects to recall eating patterns can vary among studies and also contribute to inconsistencies in findings. Although past diet is of greater interest than current diet in cancer prevention, recall of past diet is not as good as knowledge of current diet. Willett et al[198] correlated nutrient intakes estimated from food frequency questionnaires that ascertained information on current diet and diet 4 years earlier with diet records from the respective time periods. Correlations for vitamin A and vitamin C were 19 and 25% lower, respectively, when subjects were asked to complete food frequency questionnaires about their diets 4 years earlier. Adjustment for calories substantially improved the correspondence of results, especially for vitamin A. Because cancer is frequently fatal, next-of-kin are frequently used as surrogate respondents. Agreement between spouses on frequencies of intake of several fruits and vegetables ranged from 40 to 84% in a study by Marshall et al.[102]

Blood levels of micronutrients are influenced not only by dietary intake but also by absorption, transport, and metabolism. Correlations between plasma and dietary carotenoids have been reported to be in the range of 0.28 to 0.38.[173] For plasma α-tocopherol and dietary vitamin E, somewhat better correlations of 0.46 to 0.50 were observed after adjusting for plasma lipid levels. Differences in storage, handling, and analytic techniques could also contribute to inconsistencies in epidemiologic studies.

Because the magnitude of the association of antioxidant micronutrients with cancer may be small and the variances in estimates of dietary intake tend to be large, sizable samples are needed to test hypotheses regarding a protective effect of antioxidant micronutrients on cancer risk. Many cohort studies have not had sufficient numbers to test hypotheses regarding the association of antioxidant micronutrients to cancers at specific sites. Although site-specific analyses can be performed in case-control studies, reliance on recall limits the conclusions that can be drawn from these studies. Because cancer influences current diet, and current diet influences recall of past diet,[18, 185] case-control studies on the association of diet and cancer are vulnerable to recall bias.

Inconsistencies in results of epidemiologic studies on the relation of antioxidant micronutrients and cancer could indicate that there is no true underlying association. However, even with the limitations of available methods for dietary assessment, data suggest a possible protective effect of antioxidant micronutrients at some sites. The carotenoids, vitamin C, vitamin E, and selenium represent only a fraction of the antioxidant potential of the diet. Little is known about the combined effects of antioxidant micronutrients on cancer risk. Salonen et al[151] reported a significant interaction of selenium and α-tocopherol in prediagnostic serum on cancer prevention. Gey et al[43] also found that a cumulative index of plasma β-carotene, vitamin C, and α-tocopherol was a more sensitive predictor of cancer than any single antioxidant but did not report a significant interaction. Cohort studies that are large enough to investigate

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the combined effects of antioxidant micronutrients on cancer at specific sites are needed. Finally, clinical trials will be required to determine if observed associations reflect cause and effect relations.

SUMMARY

Antioxidant micronutrients are one of the body's primary defenses against free radicals and reactive oxygen molecules. Carotenoids, vitamin C, and vitamin E trap these molecules, and selenium is an essential component of an antioxidant enzyme. There is considerable support from animal studies for a protective effect of antioxidant micronutrients on cancer. However, the role of these micronutrients in cancer prevention in humans is less clear. Diet studies suggest protective effects of fruits and vegetables on risk of cancer at several sites. Inverse associations between dietary carotenoids and serum β-carotene and lung cancer have been observed repeatedly. Vitamin C has also been consistently inversely associated with risk of oral and esophageal cancer in diet studies and with stomach cancer in both diet and plasma studies. It remains unknown, however, whether carotenoids and vitamin C or some other component of fruits and vegetables, the primary sources of these micronutrients, prevent cancer in humans. Selenium has been inversely correlated with cancers at numerous sites in ecologic studies, but observational studies do not provide strong support for a protective effect of selenium on cancer at any site. There also is not strong support for a protective effect of vitamin E on cancer in humans. Results of studies on the association of antioxidant micronutrients with cancer at many sites are inconsistent. This could be due to lack of a true protective effect or could be related to methodologic problems in assessing dietary intake in epidemiologic studies.

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