Vitamin C and cancer prevention: the epidemiologic evidence\textsuperscript{1,2}

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ABSTRACT  Epidemiologic evidence of a protective effect of vitamin C for non-hormone-dependent cancers is strong. Of the 46 such studies in which a dietary vitamin C index was calculated, 33 found statistically significant protection, with high intake conferring approximately a twofold protective effect compared with low intake. Of 29 additional studies that assessed fruit intake, 21 found significant protection. For cancers of the esophagus, larynx, oral cavity, and pancreas, evidence for a protective effect of vitamin C or some component in fruit is strong and consistent. For cancers of the stomach, rectum, breast, and cervix there is also strong evidence. Several recent lung cancer studies found significant protective effects of vitamin C or of foods that are better sources of vitamin C than of \( \beta \)-carotene. It is likely that ascorbic acid, carotenoids, and other factors in fruits and vegetables act jointly. Increased consumption of fruits and vegetables in general should be encouraged.

KEY WORDS  Ascorbic acid, vitamin C, epidemiologic studies, epithelial cancers, cancer, review

Introduction

Ascorbic acid is increasingly recognized as an agent with broad biologic function and importance. Well-established functions include synthesis of hormones and neurotransmitters, cytochrome P-450 activity and detoxification of exogenous compounds, carnitine synthesis and cholesterol metabolism (1,2), as well as its well-known antioxidant functions with protective results that may extend to cancer, coronary artery disease, arthritis, and aging. Several possible mechanisms of action of ascorbic acid in cancer prevention have been described extensively elsewhere (3–5). It plays a major and perhaps even predominant role in free-radical scavenging and protection against lipid peroxidation (6, 7). It appears to have a role in sparing or reconstituting the active forms of vitamin E (8–14), and spares other important antioxidants (7). Several functions of vitamin C in the immune system have been described (15, 16), including enhancement of leukocyte chemotaxis (17), stimulation of interferon production (18), and complement C1q activity (19). Its role in collagen synthesis and basement membrane integrity and in hyaluronidase inhibition (20–22) may be important in inhibiting tumor spread and micrometastases.

Before an examination of the epidemiologic evidence that exists regarding ascorbic acid and cancer prevention, it is important to consider several sources of potential misinterpretation. These have been discussed in some detail elsewhere (4, 23). Briefly, studies of the role of nutrients in disease are hampered by at least three sources of error: 1) error in the classification of individuals with respect to their nutrient intake, 2) errors of interpretation arising from the fact that nutrients are correlated both negatively and positively with other nutrients, and 3) studies within populations that are quite homogeneous with respect to intake of a nutrient may be unable to detect an effect of high or low intake.

Misclassification errors cause a bias of observed risk estimates toward the null, making the observed risk estimate appear weaker than it really is and making it more difficult to achieve statistical significance. Studies that nevertheless show an effect in the face of the misclassification inherent in dietary or biochemical assessment probably indicate an even stronger effect if the true long-term dietary or biochemical status could be known.

Correlated variables mislead investigators into identifying the wrong nutrient as the effective one because, although an index for a certain nutrient may be calculated, other nutrients inevitably accompany it in the food and are correlated with it in the plasma. The nutrient that is calculated reflects the interests and presuppositions of the investigator and does not necessarily reflect the true causal agent. Furthermore, in biological systems it is likely that nutrients do not act singly but jointly and very rarely have investigators studied the joint effects of having a low intake of two or more nutrients simultaneously.

Finally, studies in homogeneous populations may produce negative results that are difficult to interpret. For example, in studies in very high risk populations everyone in the population may have a very low intake of a protective nutrient, control subjects as well as cases. Some of these are highlighted under esophageal cancer, below, but the problem may be more widespread. The same situation may exist in the opposite direction; if all in a study group are very well nourished with respect to a nutrient, the effect of low levels cannot be assessed well.

Epidemiologic studies by cancer site

The studies reported below are limited to analytic epidemiologic studies in humans—that is, case-control and prospective

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studies. No international correlation studies are included nor any studies that simply attempt to relate nutrient intake in a region with population mortality or morbidity rates in a region. The studies reported below are all at the individual level: individuals with and without cancer are identified and dietary intake in those same individuals is assessed. Such studies generally result in estimates of relative risk (occasionally termed risk ratio or odds ratio and abbreviated RR or OR). The risk in the group exposed to a risk factor (here, low intake of vitamin C or foods rich in it) is expressed as a ratio of those not exposed (here, those with high intake). For simplicity, all risks have been expressed in this direction so that a relative risk > 1.0 means an elevated risk of the cancer among those with low intake. For example, a relative risk (RR) = 2.0 indicates that those with low intake of vitamin C are estimated to have twice the risk of that cancer compared with those with high intake.

Studies are described below if they reported either an actual vitamin C score or estimate or if they reported on a food that is rich in vitamin C, usually fruit but occasionally tomatoes or raw vegetables. Studies that simply reported on green vegetables are not included because, although those foods may contain vitamin C, their carotenoid content is usually such that it is impossible to attribute a protective effect to vitamin C with any confidence.

Non-hormone-dependent cancers

Cancers of the oral cavity, larynx, or esophagus

Oral cancer has been the subject of seven case-control studies, most of them large and well controlled, investigating the role of dietary factors (24-30). All but one have found significant protective effects for increasing vitamin C intake or fruit intake. Most of these studies included control for smoking and alcohol. McLaughlin et al (25) found that those in the lowest quartile of vitamin C intake had a risk ratio of 1.7 (men) or 2.0 (women). Winn et al (28) found that those who reported consuming fruit once per week or less often had 1.7 times the risk of those who consumed it seven times a week or more. Two of the studies also found protection from carotene-containing vegetables, whereas in the others these foods were weaker or nonsignificant.

Two studies of cancer of the larynx have examined the role of vitamin C (31) or fruit (32). Graham et al (31) studied 374 patients with cancer of the larynx and hospital control subjects using the Roswell Park questionnaire. After control for possible confounding by alcohol intake and smoking, a low intake of vitamin C was associated with a risk ratio of 2.4 (P < 0.005). Notani and Jayant (32) observed a statistically significant increased risk of 2.0 associated with consumption of fruit less than once a week compared with at least once a week. Vegetable consumption was also a significant factor.

Cancer of the esophagus has been studied by several investigators (33-44) and again, most have found strong and statistically significant relationships with vitamin C or fruit intake. All four that examined a vitamin C index (33, 34, 36, 37) found statistically significant relative risks of >2.0 after adjustment for smoking and alcohol consumption. Brown et al (33) found that compared with those in the upper third of the distribution for vitamin C intake, those in the lower third had a statistically significant twofold risk ratio. Fiber was also significantly protective but carotenoids were not. Fruits, especially citrus fruits and juices, were the only significantly protective foods or food groups. Tuyns et al (34, 35) studied esophageal cancer in a large case-control study conducted in a high-risk region of France. A statistically significant protective effect was observed for citrus fruit (34) and for vitamin C (35). Compared with heavy consumers of vitamin C, light consumers had a risk ratio of 2.6 after adjustment for age, smoking, and alcohol consumption. Carotene also had a significant but somewhat weaker effect. Ziegler et al (36) used a 31-item next-of-kin questionnaire to investigate the role of diet among 120 black males who died of esophageal cancer and 250 others who died of other causes. Vitamin C was the only nutrient with a statistically significant elevation in risk associated with being in the low one third of the distribution, RR = 1.8 after adjustment for ethanol intake. Finally, Mettlin et al (37) found a risk ratio of 2.4 (P = 0.004) for low vs high quartile of vitamin C intake even after adjustment for smoking and alcohol.

Four studies have found fruit or citrus fruit to be lower in cases with esophageal cancer (38-41, 44). Decarli et al (44) investigated the role of diet among 105 cases of esophageal cancer and hospital controls. Fruit and vegetable questions consisted of only three items, carrots, green vegetables, and fresh fruit. All were in the protective direction, but after adjustment for alcohol, smoking, and other factors only fruit intake remained strong (RR = 3.3) and statistically significant (trend P < 0.001). Cook-Mozaffari et al (38) studied 354 patients with esophageal cancer and population controls in Iran, an area of high esophageal cancer incidence. Low intake of fresh fruit and vegetables was strongly associated with risk of esophageal cancer, with frequent consumption of oranges the most significantly protective food. In Japan, Hiyayama (39) found a risk ratio of ~2.7 for less than daily consumption of fruit in a case-control study of esophageal cancer. Bjelke (40, 41), in a study of 32 patients with esophageal cancer and hospital control subjects in Minnesota, observed nonsignificantly lower intake of apples and green salad in case subjects, but did not report on a vitamin C index.

Some studies represent classic examples of population homogeneity of intake that may make the existence of a protective effect impossible to detect. In a region of China with very high esophageal cancer rates, Li et al (42) conducted a large case-control study of esophageal or gastric carcinoma. No protective effect was seen for fruit consumption. However, the authors note that fruit is very infrequently eaten in this high-risk area, and the highest intake category consisted of those who ate fresh fruit > 35 times per year. Martinez (43) studied risk factors for esophageal and oral cancer in Puerto Rico, an area in which the incidence of these cancers is among the highest in the world. Risk ratios were not specifically reported, but the author reported that both patients and control subjects were chronically deficient; 75% of both patients and control subjects never had fresh fruit in their diets and 87% of both patients and control subjects had only two portions or less of vegetables per week. Similarly, Notani and Jayant (32) studied esophageal and oral cancer in regions of India where incidence of these diseases is among the highest in the world. Fruit consumption showed a nonsignificant effect, but was so infrequent that the distribution was dichotomized into those who ate it once a week and those who ate it less often. Vegetable consumption, dichotomized on daily rather than weekly consumption, was significant.

In summary, of eight studies that have reported on a vitamin C index in cancer of the oral cavity, larynx, or esophagus, every one has found a statistically significant elevation in risk associated
with low intake. Three of these studies found carotene to be weak and nonsignificant, whereas in two vitamin A was also found to be significant but weaker than vitamin C. Of the 12 studies of foods rather than nutrients, 6 found statistically significant risk for low fruit intake, 2 found suggestive results or did not report statistical significance, 3 found extremely low intakes in both patients and control subjects in extremely high-risk populations, and 1 found no effect.

Lung cancer

Of the ~30 epidemiologic studies that have examined the relationship between dietary factors and lung cancer, most have focused on vitamin A or carotenoids. Because of this focus, in many cases the diet questionnaire food list was not designed to assess vitamin C well and the investigators did not attempt to draw any conclusions about the role of vitamin C. A few investigators have examined the role of vitamin C, however, and these are reported below, as well as investigations in which the role of vitamin C-rich foods could be separately assessed.

Fontham et al (45) examined 1253 lung cancer cases and 1274 age-, sex-, and race-matched controls in the New Orleans area. Approximately 31% of the study group was black and 26% were nonsmokers or former smokers who had quit for ≥ 3 y. Results were adjusted for smoking, income, and other confounders. Compared with those who consumed 140 mg or more of vitamin C per day (as estimated by the questionnaire), those who consumed < 90 mg had a risk estimate of 1.5 (P < 0.001). The vitamin C effect became stronger (RR = 1.9) after adjustment for carotene intake, whereas the apparent protection due to carotene disappeared after adjustment for vitamin C intake.

Koo (46) studied 88 Hong Kong women with lung cancer and 137 control subjects to examine risk factors among individuals who have never smoked. Risk estimates were adjusted for age, parity, and education. Only fresh fruit and fresh fish consumption were found to be significantly related to a reduction in lung cancer risk. Leafy green vegetables and carrots were in the protective direction but nonsignificant. By contrast, those who consumed fresh fruit less than once a week had a risk ratio < 0.90 mg had a risk estimate of 1.5 (P < 0.001). The vitamin C effect became stronger (RR = 1.9) after adjustment for carotene intake, whereas the apparent protection due to carotene disappeared after adjustment for vitamin C intake.

In a study conducted in the Netherlands, Holst et al (47) studied 49 lung cancer patients in a case-control study. After adjustment for smoking and other risk factors, persons with a vitamin C index < 50 mg/d (as estimated by questionnaire) had a risk 4.3 times greater than those with a higher intake. This result was highly statistically significant. No effect of a \( \beta \)-carotene score was seen.

Le Marchand et al (48) studied 230 male and 102 female lung cancer cases and population-based controls in Hawaii. Among males, both total vitamin C and vitamin C from foods alone was significantly protective, RR = 2.0 for the contrast between lowest and highest quartile, a stronger effect for vitamin C controlled for \( \beta \)-carotene than was seen for \( \beta \)-carotene controlled for vitamin C. However, among females a nonsignificant effect in the protective direction was seen only for intake from foods, not supplements, whereas a \( \beta \)-carotene effect was stronger and significant. Vegetables were strongly protective, whereas fruit was not.

Kromhout (49) analyzed the results of a prospective study in which a dietary history interview was completed in 1960 on 870 men aged 40–59 y; 63 subsequently died of lung cancer over the 25-y follow-up. Compared with men consuming ≥ 100 mg vitamin C/d in 1960 (as estimated by the diet history interview), those consuming < 60 mg had a 2.8-fold increased risk (age but not smoking adjusted, P < 0.01). Dietary vitamin C intake remained a statistically significant protective factor after appropriate multivariate adjustment for age, cigarette smoking, and vitamin supplement use. A 55-y-old, male, one-pack-a-day smoker with low dietary and supplement vitamin C had a 25% chance of dying from lung cancer in the 25-y follow-up, whereas the same smoker with high dietary and supplement vitamin C had only a 7% chance of lung cancer mortality. Fruit intake was also significantly and inversely related to subsequent lung cancer mortality, after age and smoking adjustment. \( \beta \)-carotene intake was not related to lung cancer mortality.

The above five recent studies of diet in lung cancer have all found a statistically significant protective effect of vitamin C. Four of them have found a weak and nonsignificant effect of \( \beta \)-carotene; the fifth (48) found an equal effect of \( \beta \)-carotene and vitamin C from foods in men, and a stronger effect of \( \beta \)-carotene in women. The comparison with vitamin C from foods is the appropriate one since the \( \beta \)-carotene is all from foods and since supplement use is a behavior commonly increased in prodromal states, particularly among women.

Four additional studies have reported on a vitamin C index from the diet (50–52) or in plasma (53) and have found suggestive but nonsignificant results. Investigators in Hawaii (50, 54) conducted a retrospective study in Hawaii of 261 male and 103 female patients, including all five ethnic groups of Hawaii, and population control subjects. The effect of vitamin C was in the protective direction, RR = 1.6 for males, but was not statistically significant. The effect of vitamin C from foods alone was not reported; instead, vitamin C intake included supplements used in the 3 mo preceding recognition of lung cancer symptoms. Supplement use is generally much greater for vitamin C than vitamin A, greater for women than men, and greater for Caucasians than other ethnic groups (55). Consequently, inclusion of supplement use introduces difficulties of interpretation since individuals may start taking supplements when they experience malaise or other prodromal symptoms. This may explain why in LeMarchand’s study in Hawaii vitamin C from supplements was in the harmful direction, but only among Caucasian women. In all ethnic and sex groups, vitamin C from foods alone appeared to reduce the risk of lung cancer.

Kvale et al (51) and Bjelke (56) conducted a prospective study of respondents to a mailed diet questionnaire that included ~10 ascorbic acid-rich foods. They observed 153 subsequent lung cancer deaths and found no effect for a vitamin C score. Tomatoes, however, rich in vitamin C but not \( \beta \)-carotene, were one of only two foods that approached significance as individual items (trend \( P = 0.07 \) for squamous and small-cell carcinomas). Shekelle et al (52) also conducted a prospective study and observed a total of 33 lung cancer cases. Unlike the \( \beta \)-carotene score, the vitamin C score was based on a 24-h recall. Considering the limitations of that method for vitamin C and the small number of cases, the \( P \) value of 0.20 for the difference between the mean of 91.8 mg of vitamin C per day among those who later developed lung cancer and the mean of 101.0 mg among those who did not is suggestive.

Stähelin et al (53, 57) collected plasma from respondents in
1971–1973 and followed them for mortality through 1980. In that time there were 35 lung cancer deaths for which baseline plasma vitamins could be analyzed. Persons who subsequently died of lung cancer had lower plasma ascorbate (0.79 mg/dL) than control subjects (0.90 mg/dL), \( P = 0.2 \). Plasma \( \beta \)-carotene was significantly different. Subsequent analyses by StäHELIN (58) of more recent cancer deaths did not reveal any differences in mean plasma ascorbate between lung cancer patients and control subjects.

Finally, two studies have reported no effect of a dietary vitamin C index. Two reports using the 1957 Roswell Park questionnaire (59, 60) found no effect of vitamin C after control for other factors. The instrument was not well designed to assess vitamin C as noted by the authors (61). Byers et al (62) found no effect for vitamin C in a 1987 study in upstate New York; however, three fourths of the eligible cases could not be interviewed because of illness or death. Thus, it is possible that a nutrient effect could be missed if low intake had the effect of increasing the severity or progression of disease.

Although numerous investigators have studied the role of caroten-containing vegetables, in relatively few could the role of fruits, especially vitamin C-rich fruits or raw vegetables, be examined separately. These are reported below. Long-de and Hammond (63) examined data from a prospective study in which 136,000 white males in the United States provided information on their frequency of consumption of fruit and green salad; 671 lung cancer deaths were seen over the subsequent 11-y follow-up. Men who consumed fruit less than three times per week had 1.7 times the lung cancer risk of those who ate it 5–7 times per week, a statistically significant increase. Green salad showed a lower effect in the same direction. Bond et al (64) reported on a carotenoid and not a vitamin C index. However, of the six food items found to be individually significant, five (tomatoes, melon, pasta with sauce, broccoli, and fortified cereals) are rich in vitamin C as well as (or in some cases instead of) carotenoids. Others have reported protective effects of green (65) or green and yellow (66) vegetables. Whereas the protective factor is generally assumed to be a carotenoid, it is worth noting that many green vegetables are rich in vitamin C.

Of the 11 lung cancer studies that have specifically mentioned a vitamin C score, 5 have found a statistically significant protective effect, 4 have found effects in the protective direction but not significant, and 2 have reported no effect. In two of the studies that found suggestive but nonsignificant results (52, 57), the lack of statistical significance was based on tests involving small numbers of lung cancer cases, \( n = 33 \) and 35, respectively. Of two additional studies that assessed fruit intake, both have found significant protective effects. Four studies have found stronger effects for vitamin C than for carotenoids. Whereas a large body of evidence suggests an important effect for carotenoids in lung cancer protection, the recent data reported above suggest that there may also be an independent protective effect of vitamin C intake. The role of vitamin C not only as an antioxidant and free-radical scavenger in its own right (6, 7) but also in enhancing the action of vitamin E (8–14) is well established.

**Pancreatic cancer**

Five studies have examined the risk of pancreatic cancer in relation to either a vitamin C index (67) or fruit (68–71). Falk et al (67) investigated 363 cases and matched hospital control subjects in Louisiana. The questionnaire was designed to assess a wide range of nutrients and asked about usual adult diet. Those who consumed less than \( \sim 70 \) mg vitamin C/d (as estimated by the questionnaire) had a relative risk of 2.6 for males, or 1.8 for females compared with those who consumed \( \geq 159 \) mg/d (in both cases, trend \( P < 0.05 \)). Fruit consumption (based on frequency of consumption of six fruits, three of which are rich in vitamin C) conferred a 1.6-fold protective effect after adjustment for multiple confounding factors.

Norell et al (68), in a case-control study in Sweden of 99 patients and matched hospital and population control subjects, found a highly significant protective effect both for carrots and for citrus fruits. For citrus fruits there was a two- to threefold protective effect for those who ate them daily compared with those who ate them less than weekly. Mack et al (69) studied 490 pancreas cancer patients and matched neighborhood controls. For those who consumed fresh fruit or vegetables less than five times a week there was a statistically significant elevated risk, \( RR = 1.4 \) compared with those who ate them more often. The diet instrument included only very broad food categories, the only relevant one here being "fresh fruit or raw vegetables." Considering the obvious crudity of the instrument, the observation of a significant effect is striking. Finally, Gold et al (70) studied 201 persons with pancreatic cancer and both hospital and neighborhood control subjects. Adjusted for several confounding factors, frequent consumption of raw fruits and vegetables was highly protective, \( RR = 1.8 \) for those who ate them less than five times a week compared with those who ate them five or more times (\( P < 0.02 \)).

A prospective study among Seventh Day Adventists (71) observed 40 deaths from pancreatic cancer (17 men and 23 women). The intake distributions of dietary variables were divided into thirds and risk within each third was adjusted for age and sex, a process which, although appropriate, results in small numbers and reduced statistical power. Frequent consumption of dried fruit was significantly protective; use of tomatoes, fresh citrus fruit, and fresh winter fruit showed a "suggestive, though nonsignificant, protective relationship."

Pancreatic cancer is the fifth most common cause of cancer mortality in the United States (72) and is a disease with extremely poor prognosis. In the current state of our ability to treat this disease, prevention is of primary importance. All five pancreas cancer studies have found statistically significant protective effects for fruit, and in some instances for vegetables as well. The one study that calculated a vitamin C index found a significant twofold reduction in risk associated with high intake.

**Stomach cancer**

Several studies of an ecological nature have been conducted (73–75) that suggested a protective role for fruit or for vitamin C intake in stomach cancer. Ascorbic acid has recently been demonstrated to be concentrated at three times the plasma level in the gastric juice of persons with normal gastric histology, but not in those with chronic gastritis (76). Moreover, in normal persons it is predominantly in the reduced form, ascorbic acid, the form required for the antinitrosation reaction; in gastritis patients, by contrast, it is predominantly in the oxidized form, dehydroascorbic acid. A similar pattern is seen for gastric tissue ascorbic acid, which often falls to "immeasurable levels" (77) in patients with chronic gastritis. The focus below is on studies at the individual level, but it should be noted that indices of vitamin C intake have heretofore not differentiated between...
ascorbic and dehydroascorbic acid or considered the conversion of ascorbic to dehydroascorbic acid during cooking, and that furthermore the correlation between vitamin C intake and gastric ascorbic acid was low, only \( r = 0.22 \) (77).

Several studies have found a statistically significant protective effect of vitamin C or fruit in gastric cancer. Bjelke (40, 41, 78) found vitamin C to be the ‘dietary variable which discriminated most strongly between the total group of stomach cancer cases . . . and the controls’ (40). The effect was particularly strong for gastric carcinomas of the diffuse and intestinal types. For the combined group of diffuse and intestinal carcinomas, the relative odds for low vitamin C intake were 1.8 (40). In Norway, a statistically significant difference was seen in both males and females (41) and a strong effect was also observed in Minnesota (40). No effect of vitamin A was seen for stomach cancer. The author notes (40) that ‘the data for stomach cancer are consistent with an increased risk being associated with a classical deficiency affecting a minority of the population.’

In a study of dietary factors and gastric cancer in Louisiana, Correa et al (79) found fruits as a group and dietary vitamin C to be statistically significantly protective in both blacks and whites after multivariate control for smoking and other factors. Those in the lower quarter of the intake distribution had twice the risk (whites) or three times the risk (blacks) compared with those in the upper quarter. A nonsignificant protective effect for carotenoids disappeared after control for vitamin C, whereas the vitamin C effect remained after control for carotenoids and other risk factors.

In a high-risk region of China, You et al (80) observed a statistically significant twofold relative risk of stomach cancer for the lowest quartile of vitamin C intake after control for sex, age, and income. A similar effect was also seen for carotenoids. Fruit intake was also significantly protective among those who ate > 5 kg/y. A stronger effect was seen for fresh vegetables where the lowest intake quartile was < 73 kg/y.

La Vecchia et al (81) conducted a case-control study in Italy of 206 gastric cancer patients and hospital control subjects. Those in the bottom one third of the distribution of vitamin C intake had a 2.5-fold elevated risk, \( P < 0.001 \). The effect of \( \beta \)-carotene was similar in multiple regression analysis. In Canada, Risch et al (82) studied 246 gastric cancer patients and population control subjects. Although the questionnaire included ~15 good vegetable sources of vitamin C and three fruit sources, two important sources, citrus juices and tomatoes, were either omitted or combined with poor vitamin C sources, a characteristic that may have generated imprecision in the vitamin C estimate. Citrus fruit, excluding juice, was highly significant, whereas the overall vitamin C estimate was significant only at \( P < 0.10 \). However, when ascorbate was examined just from the 21 nitrate-containing vegetables, a strongly protective and statistically significant effect was seen for increasing ascorbate intake. This analysis tends to confirm the hypothesis of an antinitrosation mechanism for protection by ascorbic acid in stomach cancer. Similarly, Meinsma (83) found strong increased risk with high bacon intake and a strong protective effect (\( P < 0.01 \)) of high consumption of citrus fruit and vitamin C.

In a prospective investigation of the relationship between plasma levels of nutrients and subsequent cancer, Stähelin et al (53, 57, 58) observed lower levels of vitamin C in the plasma of 20 persons who later developed stomach cancer (42.6 \( \mu \)mol/L) than those who did not (52.8 \( \mu \)mol/L). An examination of their dietary intake (83) revealed approximately a threefold risk of subsequent stomach cancer among those who reported infrequent citrus fruit consumption in 1971–1973 (\( P = 0.07 \)).

Several investigators did not report a vitamin C index but did report specifically on fruit intake. In a study of gastric cancer in Japan, Kono et al (85) found a significant twofold elevation in risk for those who consumed fruit less often than daily, after adjustment for smoking and other dietary factors. Jedrychowski et al (86), in Poland, found a statistically significant relative risk of 3.2 for those who ate fruit less often than twice a week compared with those who ate it daily. In Greece, Trichopoulos et al (87) observed a statistically significant protective effect of frequent consumption of citrus fruits and of raw salad-type vegetables in 110 patients with adenocarcinoma of the stomach. Graham et al (88), in a matched-pair reanalysis of a previously-reported negative study (89), observed a reduced risk of gastric cancer associated with consuming various vegetables in the uncooked state. Coggon et al (90) in a study of 95 patients and population control subjects in England found statistically significant reductions in risk, twofold or greater, for fruit and for salad vegetables. For fruit intake, the high-consumption category consisted of those consuming it six or more times per week. In 1972 Haenszel et al (91) reported effects for several vegetables, but only tomatoes (a source of vitamin C but not of \( \beta \)-carotene) showed protective effects in both Issei and Nisei. No effect of fruit was seen in this Japanese American population. A study in Japan (92) found no effect of orange consumption. Finally, in 1966 Higinson (93) found less frequent consumption of fresh fruit and raw vegetables among stomach cancer patients than matched hospital controls. Fontham et al (94) found a statistically significant 2.5-fold elevation in risk of gastric cancer precursor lesions for those below the median intake of vitamin C in a high-risk black population in Louisiana. In a negative study of precursor lesions, however, Haenszel et al (95) found no difference between the mean plasma levels of total ascorbate in persons with atrophic gastritis and control subjects in Colombia.

In summary, seven investigators have reported on vitamin C dietary intake and stomach cancer risk. All seven have found statistically significant protective effects of approximately twofold, usually in the overall vitamin C score although in one instance statistical significance was limited to the vitamin C contained in nitrate-containing vegetables. One prospective study found lower plasma vitamin C levels in those who subsequently developed stomach cancer, nearly significant at \( P = 0.06 \) despite having only 19 cases. In two studies that also examined \( \beta \)-carotene, that factor was also significantly protective; in two other studies that simultaneously examined \( \beta \)-carotene and vitamin C in multivariate models both remained significant in one study, whereas the effect of \( \beta \)-carotene disappeared in the other (79). Eight studies have reported on the role of fruit intake; seven have found lower fruit consumption in those who developed stomach cancer, in most instances a statistically significant twofold effect. Consumption of raw salad vegetables is often found to be protective as well.

**Cervical cancer**

The role of ascorbic acid in the precancerous condition, cervical dysplasia, was examined by Wassertheil-Smoller et al (96) and by Romney et al (97). Plasma ascorbic acid levels were 0.36 mg/dL in women with the precursor lesion and 0.75 mg/dL in...
control subjects, \( P < 0.0001 \) even after control for factors such as multiple partners, multiple pregnancies, early onset of sexual activity, and socioeconomic status (97). Dietary factors were also examined in a different case-control series of 87 women with cervical dysplasia and matched control subjects (96). Compared with those above the median intake of 88 mg/d, those below that median had a significant excess risk \( (RR = 4.35) \) for severe dysplasia or carcinoma in situ. Vitamin C intake remained a significant factor even after control for age and sexual activity.

Brock et al (98) studied 117 in situ cervical cancer patients and matched community controls in Australia. Those in the lowest quarter of the distribution of intake of vitamin C had a significantly elevated risk \( (RR \sim 2.5) \). After control for eight sexual activity and dietary variables, including caroten, the risk estimate was still \( \sim 2.0 \), although this was no longer statistically significant. In contrast, carotene no longer appeared to be protective after control for vitamin C and the other variables. Fruit intake more than once per day remained significantly protective \( (RR = 2.5) \). Plasma \( \beta \)-carotene was significantly protective; plasma ascorbic acid was not measured.

Verreault et al (99) examined 189 women with invasive cervical cancer and population controls. Low intake of vitamin C was associated with a statistically significant twofold increased risk. The effect of fruit juices was even stronger \( (OR = 3, P < 0.01) \). The effect of carotene and dark green vegetables was in the same direction, although weaker.

Marshall et al (61) failed to observe a protective effect of vitamin C in a study of 513 cervical cancer patients and hospital control subjects. An effect was seen for the carotene index. The authors point out that the Roswell Park instrument was "extremely imprecise in the measurement of a key source of vitamin C, fresh fruits."

**Colorectal cancer**

The role of vitamin C in the occurrence of rectal polyps is unclear. Sporadic or nonsignificant polyp regression (100), reductions in polyp area (101), or nonsignificant reductions in recurrence rate (102, 103) have been reported. In the latter study, 35% of patients who had been receiving vitamins for 2½ y were polyp free compared with 23% of those on placebo, an effect that the study had insufficient power to detect as significant. A recent report found minimal effect of vitamin C alone on occurrence of polyps in familial polyposis patients (104), whereas cereal fiber was effective; the most striking effects were seen in those who had a high compliance to both fiber and vitamin supplements. Such studies have been quite small and effects of such manipulations on actual progression to cancer have not been observed.

A possible role of vitamin C in prevention or reduction of fecal mutagens in stool has been observed in two studies (105, 106). In a study of diet and fecapentaene levels conducted by the National Cancer Institute (106), a strong protective effect was observed for both dietary and supplemental vitamin C intake. Consumption of citrus fruit and of supplemental vitamin E was also significantly negatively associated with fecapentaene levels. Thus, if fecal mutagens are associated with colon carcinogenesis, vitamin C may play an independent role or may act synergistically with vitamin E in blocking their effect.

Several studies have examined rectal and colon cancer separately. An examination of these data suggest that vitamin C may act differently at these two sites. Rectal cancer will be discussed first below followed by colon cancer and studies addressing only the combined group, colorectal cancer.

Seven studies have reported on the association of a vitamin C index, fruit or raw vegetable intake with rectal cancer, often with statistically significant results. Kune et al (107, 108) examined rectal and colon cancer separately in a large case-control study in Australia. A statistically significant protective effect \( (OR = 1.7) \) was seen for high intake of dietary vitamin C as well as for vitamin supplements in rectal cancer. Tuyns et al (109–111) conducted a study in Belgium of 365 persons with rectal cancer and population controls. Vitamin C was significantly protective \( (RR = 1.5, P < 0.03) \) after adjustment for age, sex, province, and total calorie intake (109, 111). Total fiber was also protective but \( \beta \)-carotene was not. Vegetables, both cooked and raw, were also found to be highly protective (110) with lesser effects for fruit. Potter and McMichael (112) found a protective effect of vitamin C in a study of 124 male and 75 female cases of rectal cancer and appropriate control subjects. The relative risk associated with being in the lowest quintile of intake compared with the highest was 1.7 among men, 3.3 among women, the latter being statistically significant. The role of \( \beta \)-carotene and fiber was weak and inconsistent.

Heilbrun et al (113) compared the baseline 24-h recalls of 60 Japanese men in Hawaii who subsequently developed rectal cancer and control subjects who did not. Vitamin C intake was generally quite high, and although lower in patients (105 mg/d) than in control subjects (116 mg/d), it was not statistically significant. No effect was seen in a quintile analysis among the 60 patients and their control subjects, nor was an effect of dietary fiber or \( \beta \)-carotene observed. La Vecchia et al (114) studied 236 rectal cancer patients and hospital control subjects and observed an effect in the protective direction but that effect was nonsignificant. Several vitamin C-rich foods were significantly protective. Brolke (40) reported data for rectal cancer cases separately in studies conducted both in Norway and in Minnesota using a nutrient index based on 100-g portions. For rectal but not for colon cancer, patients had "a lower consumption of fruits and berries and, in particular, of vitamin C" in Norway (40). The same was true in Minnesota where the vitamin C difference between rectal cancer patients and control subjects achieved statistical significance.

Finally, Graham et al (115) found a significantly increased risk \( (RR = 1.6) \) among men eating raw vegetables infrequently and an even stronger effect among women. The role of fruit was not examined.

Thus, there have been four statistically significant and two suggestive results for vitamin C in rectal cancer and an additional significant result for raw vegetables. \( \beta \)-Carotene effects were weaker and nonsignificant in all but one study.

Numerous studies have examined colon cancer or a combined category, colorectal, that generally would contain predominantly colon cancer cases. A few have found a statistically significant protective effect of vitamin C. Heilbrun et al (113) examined 102 colon cancer patients in Hawaii. Vitamin C intake was significantly lower among those who developed colon cancer over the subsequent 16-y period (92 mg/d by 24-h recall) compared with those who did not (116 mg/d). Those in the lowest quintile of intake had 1.9 times the risk of those in the upper quintile \( (P = 0.01) \). In Australia, Kune et al (107, 108) conducted a large study of 715 colorectal cancer patients and matched community
control subjects. Both dietary and supplemental vitamin C were significantly protective with a threefold risk associated with the low quintile of dietary vitamin C after adjustment for other dietary factors. Consumption of a high-fiber diet was also protective provided that vegetable intake was also high. Macquart-Moulin et al (116) examined 399 cases of colorectal cancer in Marseilles and matched injury controls. After adjustment for age, sex, caloric intake, and body weight, a highly significant protective effect was seen for vitamin C intake (RR = 1.8 for low vs high quartile of intake). A similar protective effect was seen for several micronutrients and minerals and for fiber from vegetables, but not for vitamin A or fiber from flour.

Some investigators have found suggestive results in colon cancer. La Vecchia et al (114) observed a protective but non-significant effect of dietary ascorbic acid in colon cancer adjusted for age and sex. However, tomatoes, green peppers, and melon were highly significantly protective. The cutpoint for low intake suggests a very high intake even in the lower tertile and little dispersion between the low and high tertile. Bjelke (40, 41, 78) found no effect for a vitamin C index in Norway. In Minnesota he found vitamin C to be significantly lower not only in patients with rectal cancer but also in patients with cancer of the left colon (40). Although preliminary results by Tuyns (109) indicated a significant protective effect, a later analysis revealed no consistent effects of a vitamin C index (111). Several foods rich in vitamin C were, however, significantly protective (110).

Of the eight groups of investigators who have reported on a dietary vitamin C index, two have found no evidence of protection for colon cancer. Potter and McMichael (112) found no relationship with colon cancer in a study of 220 patients and community control subjects in Australia. Canadian investigators (117, 118) found no evidence of a protective effect of either a vitamin C index or of citrus fruit in a case-control study of 348 colon cancer patients and control subjects in Canada. Average vitamin C intake among male cases in that study was 170 mg/d as estimated by questionnaire. Fiber intake was also not protective.

Several investigations have reported protective effects of fruit or vegetables but have not specifically reported on risks associated with low vitamin C intake. Many have found protective effects of vegetables, but evidence for an effect of fruit in colon cancer is inconsistent. Modan et al (119) found that several vitamin C-rich foods, including oranges, tomatoes, and green peppers, were highly significantly protective. Slattery et al (120) also found protection conferred by fruit as well as vegetables. Higginson (92), in 1966, found a lower consumption of fresh fruit in colorectal cancer patients than in control subjects (not statistically significant). Dales et al (121) found nonsignificant effects in the protective direction for persons above the median on a fiber index consisting of 6 fruits, 14 vegetables, 3 grain products, and 5 legumes. Some fruits were protective in a study of colorectal cancer in Hawaiian Japanese (122). In a large case-control study in Wisconsin, Young and Wolf (123) found a significant protective effect for vegetables and for vitamin supplements, but not for fruit. Similarly, Manousos et al (124) found significant protection conferred by high intake of vegetables, but found no effect of fruit. Graham et al (115) found a significant protective effect for raw and cooked vegetables.

Finally, in a very small study which examined baseline plasma ascorbate levels, Stähelin et al (53, 57, 84) found no difference between 14 colorectal cancer patients and their 32 control subjects in the ascorbic acid level in plasma collected in 1965–1966 or 1971–1973. A later analysis of colorectal cancer patients found lower plasma ascorbate in patients than in control subjects (P = 0.06).

For colon cancer, as distinct from rectal cancer, the existing evidence is less consistent. Four groups found a statistically significant protective effect of vitamin C, two found suggestive but nonsignificant effects, two found no effect of the nutrient index, but one of these observed a significant effect of vitamin C-rich foods. Overall, for both colon and rectal cancer, of the nine groups that have reported on a vitamin C index, six have found statistically significant results in one or the other site, two were nonsignificant but in the protective direction, and one reported no effect.

**Bladder cancer**

Several investigators demonstrated that ascorbic acid inhibits nitrosation in humans and animals and inhibits carcinogen-induced bladder tumors in animals (125–127). Following up on this lead, Kolonel et al (54) examined 123 male and 41 female patients with bladder cancer and population control subjects in two ethnic groups in Hawaii. Vitamin C intake from supplements was lower in patients than in control subjects in all four ethnic-sex groups. The same was true for food sources among females but not males. For the combined total intake from both sources, patients averaged 389 mg/d and control subjects 513 mg/d. None of the differences within the four individual ethnic-sex groups was statistically significant; significance of the overall case-control comparison was not reported. No effects were found for a vitamin A index. La Vecchia et al (128) examined 163 bladder cancer patients and hospital control subjects in northern Italy. The questionnaire included three fruit/vegetable items: carrots, green vegetables, and fruit. Although there was a significant association with the former, there appeared to be no association between case-control status and intake of this fruit item in this population. It is notable that this population reported a high intake of fruit, averaging more than once a day in both patients and control subjects, and thus the possible effects of low intake cannot be examined. Mettlin and Graham (129) and Paganini-Hill et al (130) found an effect for vitamin A, but did not report on the role of vitamin C. Table 1 summarizes the epidemiologic studies of vitamin C and cancer prevention for non-hormone-dependent cancer sites.

**Hormone-dependent and other nonepithelial cancers**

**Childhood brain tumors**

Only one study has been conducted on dietary factors in this cancer. Thomas Sinks and John R Wilkins III (personal communication, 1989) interviewed parents of 100 children with brain tumors and 200 matched control subjects, regarding the mothers' diets during pregnancy. A statistically significant threelfold increased risk of delivering a child who later developed brain tumors was associated with low maternal intake of vitamin C during pregnancy, an effect that remained after adjustment for other factors.

**Breast, ovary, endometrium and prostate cancer**

For ovarian, endometrial and prostate cancer, the little evidence that exists does not support an important role for vitamin
C, whereas recent analyses suggest an important role in breast cancer. Slattery et al (131) studied 85 women with ovarian cancer and population control subjects. An effect in the protective direction was observed for those in the lower one-third of the distribution (OR = 1.4). However, this did not achieve statistical significance. La Vecchia et al (132, 133) have reported two studies of ovarian cancer in Italy. Both found a statistically significant protective effect for more frequent consumption of two vegetable items, but no effect of reported consumption of a single item, fruit. In a study in China, Shu et al (134) found no relationship between vitamin C intake and ovarian cancer, although it is notable that the lowest quartile consisted of those who consumed ≤ 68 mg. Finally, Byers et al (135) found no effect of vitamin C as calculated from the 1957 Roswell Park questionnaire, but did find a protection from vitamin A calculated from fruits and vegetables. Thus, the existing studies do not provide evidence of a role for vitamin C in ovarian cancer. It is notable, however, that two of these studies appeared to be in populations with a very high intake of this nutrient: in Slattery et al (131), the low intake category was defined as vitamin C < 98 mg/d, and in La Vecchia et al (132) the study group consumed an average of 12 servings of fruit per week.

In a single study of endometrial cancer, La Vecchia et al (136) investigated 206 patients and age-matched hospital control subjects in Italy. Patients reported significantly lower intake of green vegetables than control subjects, and lower intake of fruit, although not significantly so. Consumption of fruit in this population appears to be high with both patients and control subjects averaging >1½ servings/d.

Several investigations have suggested an increased risk for prostate cancer associated with increased vitamin A and in some instances vitamin C intake. Reports using the Roswell Park 1957 questionnaire and the same study population (137, 138) found an increased risk for increasing vitamin A and vitamin C intake, trend significant for men aged > 70 y. Investigators in Hawaii (54, 139, 140) have also reported in the same case series a significantly increased risk associated with vitamin A, and the same direction of effect for vitamin C, but not statistically significant. Two similar studies in Washington, DC (141, 142) assessed diet from the distant past (when the patients and control subjects were aged 30–49 y, and ≥ 50 y). The results suggested an elevated risk for increasing vitamin A intake, but not for vitamin C. A prospective study of Japanese men in Hawaii (143) found similar results. Two analyses of a case-control study in Japan (144, 145) have found a protective effect of β-carotene in contrast to the above studies, but no evidence of an effect of vitamin C.

Other studies have found protective effects for increasing consumption of fruits or vegetables or of carotenoid indices calculated from them, but either did not report on vitamin C or did not use food lists designed to assess it (146–148). Thus, with

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**TABLE 1**

Summary of epidemiologic studies of vitamin C and cancer prevention*

<table>
<thead>
<tr>
<th>Non-hormone-dependent cancer sites</th>
<th>References</th>
<th>No of studies</th>
<th>No of statistically significantly protective</th>
<th>Median relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites in this category</td>
<td>See below</td>
<td>Vitamin C index: 46</td>
<td>33</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fruit: 29</td>
<td>21</td>
<td>1.7</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>(24-26)</td>
<td>Vitamin C index: 3</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(27, 29, 32)</td>
<td>Fruit: 4</td>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>Larynx</td>
<td>(31)</td>
<td>Vitamin C index: 1</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(32)</td>
<td>Fruit: 1</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>(33, 35–37)</td>
<td>Vitamin C index: 4</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(38–40, 42–44)</td>
<td>Fruit: 7</td>
<td>3†</td>
<td>ID‡</td>
</tr>
<tr>
<td>Lung</td>
<td>(45–52, 60, 62)</td>
<td>Vitamin C index: 10</td>
<td>5†</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>(63, 64)</td>
<td>Fruit: 2</td>
<td>2</td>
<td>1.7§</td>
</tr>
<tr>
<td>Pancreas</td>
<td>(67)</td>
<td>Vitamin C index: 1</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(68–71)</td>
<td>Fruit: 4</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Stomach or precursors</td>
<td>(40, 41, 78–83, 94)</td>
<td>Vitamin C index: 7</td>
<td>7</td>
<td>2.0$</td>
</tr>
<tr>
<td></td>
<td>(84–97, 90)</td>
<td>Fruit: 5</td>
<td>5$</td>
<td>2.5</td>
</tr>
<tr>
<td>Cervix or precursors</td>
<td>(61, 96, 98, 99)</td>
<td>Vitamin C index: 4</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>(40, 107, 108)</td>
<td>Vitamin C index: 6</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Colon or colorectal</td>
<td>(40, 107, 111–114, 116, 117)</td>
<td>Vitamin C index: 8</td>
<td>4</td>
<td>1.1</td>
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<tr>
<td></td>
<td>(119, 120, 122–124)</td>
<td>Fruit: 5</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Bladder</td>
<td>(128)</td>
<td>Vitamin C index: 1</td>
<td>0</td>
<td>ID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fruit: 1</td>
<td>0</td>
<td>ID</td>
</tr>
<tr>
<td>Brain</td>
<td>(Sinks, personal communication, 1989)</td>
<td>Vitamin C index: 1</td>
<td>1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* Studies that assessed the role of a dietary vitamin C index or of fruit intake. Studies that reported on the role of both are included only under "Vitamin C Index," even if the fruit effect was stronger or more statistically significant. Because sample sizes in subgroups were sometimes small, in some cases results are classified as statistically significant if a major subgroup (eg, males) produced significance. Significance is defined as P < 0.05; in many studies levels of P < 0.01 or stronger were observed, and some of these are noted in the text. Median relative risk refers to the median over all studies in the group, not simply the statistically significant ones.

† See text.
‡ ID, Insufficient data.
§ Estimate based on only those for which relative risk was reported.
|| In one study, P = 0.07, n = 19.
regard to prostate cancer and vitamin C or foods rich in vitamin C, the evidence is meager and conflicting with little evidence of an effect.

For breast cancer, Howe et al (149–154) recently examined a series of studies in a major meta-analysis of the role of dietary factors. Saturated fat was positively associated with breast cancer, but in addition "vitamin C intake had the most consistent and statistically significant inverse association with breast cancer risk." When β-carotene, fiber, and vitamin C were examined simultaneously, only the latter remained significant, and the authors consequently used vitamin C as the marker for the effective agent(s) in fruit and vegetables. The results for vitamin C remained after control for fat intake. In terms of attributable risk, the authors conclude that "if all postmenopausal women in the population modify their saturated fat intake to (that of the lower one-fifth of the population), the current rate of breast cancer would be reduced by 10% in postmenopausal women in North America. . . If all postmenopausal women . . . were to increase fruit and vegetable intakes to reach an average daily consumption of vitamin C (equivalent to that of the highest one-fifth of the population), risk of breast cancer . . . would be reduced by 16%." The effects were approximately additive, and simultaneously making both changes would reduce the risk by 24%. The authors also point out that misclassification of dietary intake would lead to underestimation of the relative risk and therefore of the attributable risk. Thus, for breast cancer the protective effect of vitamin C appears to be very consistent in the studies examined by Howe et al (149–154), and of a magnitude at least equal to that of saturated fat. Table 2 summarizes the epidemiologic studies of vitamin C and cancer prevention for hormone-dependent cancer sites.

Summary

In the 11 non-hormone-dependent cancer sites described above, 46 studies have specifically reported on a vitamin C index or plasma ascorbate values; 33 of these found statistically significant protective effects, and several more were in the protective direction but did not achieve significance. None has found elevated risk with increasing intake. In addition to those, 29 studies reported on the effect of fruit consumption, 21 of which found significant protection associated with frequent consumption or high risk associated with low consumption. For oral, esophageal, gastric, and pancreatic cancer, the evidence is extremely strong, with virtually all studies showing a significant protective effect. The cervical and rectal cancer data are also very strong, with only a few studies failing to find significant protection. In lung cancer, five recent studies observed statistically significant protection, although several earlier studies found nonsignificant results. In breast cancer, there appears to be a very consistent protective effect, in the meta-analysis by Howe et al (149). However, none of the studies of ovarian or prostate cancer have found a statistically significant protective effect of vitamin C.

Dietary estimates involve uncertainties in nutrient content of foods, in degree of nutrient destruction in cooking and storage, in portion size quantification, and in the individual's ability to estimate his or her frequency of consumption, as well as subsequent altering of blood and tissue levels by host factors. All of these result in substantial misclassification of the individual's true nutrient status. Misclassification results in a severe bias of risk estimates toward the null. A great deal has been made of this problem in discussions of the effects of fat intake, in which risk estimates have frequently been found to be low and nonsignificant. In studies reported here for several cancer sites, however, particularly the epithelial cancers, the risk estimates have frequently been substantial and statistically significant. The fact that misclassification undoubtedly exists can only mean that the observed effects reported here are underestimates of the true risk.

These results appear suggestive enough to warrant more intensive investigations in the future. Few studies have examined plasma vitamin C values and none has examined leukocyte vitamin C values and their relationships with cancer. Leukocyte values would be preferable because they represent a target tissue for ascorbate concentration and they are not affected by very recent dietary intake. Such analyses are needed in prospective studies or case-control studies nested in a prospective cohort. These values represent what is actually available to the body for

<table>
<thead>
<tr>
<th>Hormone-dependent cancer sites</th>
<th>References</th>
<th>No studies</th>
<th>No statistically significantly protective</th>
<th>Median relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites in this category</td>
<td>See below</td>
<td>Vitamin C index: 9</td>
<td>0†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fruit: 3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>(131, 134, 135)</td>
<td>Vitamin C index: 3</td>
<td>0‡</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(132)</td>
<td>Fruit: 1</td>
<td>0</td>
<td>I.D.</td>
</tr>
<tr>
<td>Endometrium</td>
<td>(136)</td>
<td>Fruit: 1</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Prostate</td>
<td>(137, 139, 141–144)</td>
<td>Vitamin C index: 6</td>
<td>0§</td>
<td>0.8</td>
</tr>
<tr>
<td>Breast</td>
<td>(149–154)</td>
<td>Vitamin C index: 9</td>
<td>See text †</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Studies that assessed the role of a dietary vitamin C index or of fruit intake. Studies that reported on the role of both are included only under "Vitamin C Index," even if the fruit effect was stronger or more statistically significant. Because sample sizes in subgroups were sometimes small, in some cases results are classified as statistically significant if a major subgroup (eg, males) produced significance. Significance is defined as P < 0.05; in many studies levels of P < 0.01 or stronger were observed, and of these are noted in the text. Median relative risk refers to the median over all studies in the group, not simply the statistically significant ones.

† Howe et al (149), in a meta-analysis, found vitamin C to be consistently inversely associated with breast cancer risk, in nine studies examined. See text.

‡ None were significant in either the protective or harmful direction.

§ Two studies found significantly elevated risk with high intake, in some age subgroups or control comparisons.
antioxidant or other functions. Dietary data, on the other hand, are severely hampered by inaccuracies in food table values, loss of ascorbate in foods as a result of storage and cooking, and other factors comprising the chasm of assumptions between the estimates of dietary intake and the level of ascorbate actually reaching the tissues. Very important among these is the role of other characteristics of the individual that alter blood and tissue levels after the food is consumed. Smoking dramatically lowers blood ascorbate levels, as does aspirin consumption, oral contraceptives, acute and chronic diseases, and a variety of other stresses. The fact that smoking is usually included in multivariate models adds another complication to the interpretation, since they may be in the same causal pathway—smoking may exert part of its effect by virtue of its reduction of plasma ascorbate levels. Because of factors such as these, it would appear that clarification of the role of vitamin C in cancer prevention would be greatly enhanced by studies that examine blood levels, carefully prepared and stored, in relation to cancer outcome.

In addition to assessing blood levels, some additional methodologic features might be considered in future investigations. First, sample size has been inadequate in several studies described here; even when apparently adequate, investigators often divide their sample into quartiles or quintiles and then impose control for numerous confounders [eg, eight in Brock et al (98), each with several levels] on each of the quantiles. The result is extremely unstable estimates and poor statistical power. Prestudy sample size and power calculations should be based on the real analyses that will be performed. Second, estimates of the mean nutrient intake and standard deviation based on several 24-h recalls or records should be collected in a subset of the study population. This would permit correction of the mean and distribution obtained in the food frequency questionnaire so that the nutrient intake corresponding to the quantile cutpoints could be more accurately estimated. If this were done, it might ultimately be possible to compare studies in different populations and with different instruments and to estimate risks for levels of actual nutrient intake. Third, analyses should take into account effect modification rather than simply confounding by other factors. For example, the effect of vitamin C (or \( \beta \)-carotene) may only exist when fat (or meat) intake is high or low. Ross et al (147) found a suggestion that \( \beta \)-carotene was only protective for prostate cancer when fat intake was low, and Heilbrun et al (113) found similar results with regard to the protective effect of dietary fiber in colon cancer at different fat levels. Joint effects of two variables and effect modifications such as these have rarely been examined, but may explain some of the differences in results seen in different population groups. Future investigators may wish to design their studies with sample sizes adequate to examine their data in this way.

Because other nutrients, especially carotenoids and folate, are often obtained in the same foods, with dietary data we cannot be completely certain that the effect is due to vitamin C and not to other factors. Nevertheless, the strength and consistency of the results reported here for several sites suggests that there may be a real and important effect of ascorbic acid in cancer prevention. It may be more productive to stop thinking in terms of "or"—"Is it vitamin C or carotenoids?" It is very likely that both are needed, that all the nutrients packaged together in fruits and vegetables are synergistic and provide optimal benefit when all are present in optimal quantities. Vitamin C is apparently the first line of antioxidant defense (7), spares vitamin E (8–14), may be an effective radical scavenger under different partial pressures of oxygen than those that are optimal for \( \beta \)-carotene, and may act synergistically with other biologic antioxidants and radical scavengers in quenching different elements of a radical cascade (155). Future research should focus on analyses of risks in individuals in which two or more nutrients are low or high. Public health action should be directed towards increasing the consumption of fruit, as well as vegetables, in which nature has packaged a variety of protective nutrients.

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