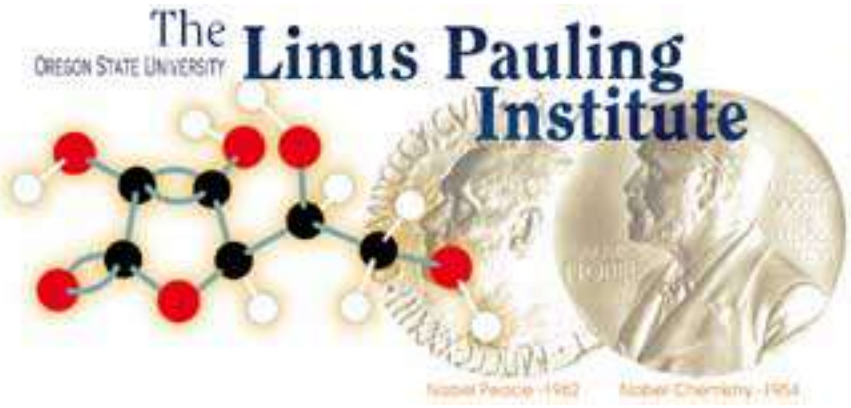

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VITAMIN C

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. Unlike most mammals, humans do not have the ability to make their own vitamin C. Therefore, we must obtain vitamin C through our diet.

FUNCTION

Vitamin C is required for the synthesis of collagen, an important structural component of blood vessels, tendons, ligaments, and bone. Vitamin C also plays an important role in the synthesis of the neurotransmitter, norepinephrine. Neurotransmitters are critical to brain function and are known to affect mood. In addition, vitamin C is required for the synthesis of carnitine, a small molecule that is essential for the transport of fat to cellular organelles called mitochondria, for conversion to energy (1). Recent research also suggests that vitamin C is involved in the metabolism of cholesterol to bile acids, which may have implications for blood cholesterol levels and the incidence of gallstones (2).

Vitamin C is also a highly effective antioxidant. Even in small amounts vitamin C can protect indispensable molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA) from damage by free radicals and reactive oxygen species that can be generated during normal metabolism as well as through exposure to toxins and pollutants (e.g. smoking). Vitamin C may also be able to regenerate other antioxidants such as vitamin E (1).

DEFICIENCY

Scurvy

Severe vitamin C deficiency has been known for many centuries as the potentially fatal disease, scurvy. By the late 1700's the British navy was aware that scurvy could be cured by eating oranges or lemons, even though vitamin C would not be isolated until the early 1930's. Symptoms of scurvy include bleeding

and bruising easily, hair and tooth loss, joint pain and swelling. Such symptoms appear to be related to the weakening of blood vessels, connective tissue, and bone, which contain collagen. Early symptoms of scurvy such as fatigue may result from diminished levels of carnitine, needed to derive energy from fat, or decreased synthesis of the neurotransmitter norepinephrine (see Function). Scurvy is rare in developed countries because it can be prevented by as little as 10 mg of vitamin C daily (2). However, recent cases have occurred in children and the elderly on very restricted diets (4,5).

The Recommended Dietary Allowance (RDA)

In the U.S., the recommended dietary allowance (RDA) for vitamin C was recently revised upward from 60 mg daily for men and women. The RDA continues to be based primarily on the prevention of deficiency disease, rather than the prevention of chronic disease and the promotion of optimum health. The recommended intake for smokers is 35 mg/day higher than for nonsmokers, because smokers are under increased oxidative stress from the toxins in cigarette smoke and generally have lower blood levels of vitamin C (6).

Recommended Dietary Allowance (RDA) for Vitamin C

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	40 (AI)	40 (AI)
Infants	7-12 months	50 (AI)	50 (AI)
Children	1-3 years	15	15
Children	4-8 years	25	25
Children	9-13 years	45	45
Adolescents	14-18 years	75	65
Adults	19 years and older	90	75
Smokers	19 years and older	125	110
Pregnancy	18 years and younger	-	80
Pregnancy	19-years and older	-	85
Breastfeeding	18 years and younger	-	115
Breastfeeding	19 years and older	-	120

DISEASE PREVENTION

The amount of vitamin C required to prevent chronic disease appears to be more than that required for prevention of scurvy. Much of the information regarding vitamin C and the prevention of chronic disease is based on prospective studies, in which vitamin C intake is assessed in large numbers of people who are followed over time to determine whether they develop specific chronic diseases.

Cardiovascular diseases (heart disease and stroke)

Until recently, the results of most prospective studies indicated that low or deficient intakes of vitamin C were associated with an increased risk of cardiovascular diseases and that modest dietary intakes of about 100 mg/day were sufficient for maximum reduction of cardiovascular disease risk among nonsmoking men and women (1). In addition, several studies had failed to find significant reductions in the risk of coronary heart disease (CHD) among vitamin C supplement users in well-nourished populations (7,8). One notable exception was the First National Health and Nutrition Examination Study (NHANES I) Epidemiologic Follow-up Study (9). This study found that the risk of death from cardiovascular diseases was 42% lower in men and 25% lower in women who consumed more than 50 mg/day of dietary vitamin C and who regularly took vitamin C supplements, corresponding to a total vitamin C intake of about 300 mg/day (10). Recent results from the Nurses' Health Study, based on the follow-up of more than 85,000 women over 16 years, also suggest that higher vitamin C intakes may be cardioprotective (11). In this study, vitamin C intakes of more than 359 mg/day from diet plus supplements or supplement use itself were associated with a 27-28% reduction in CHD risk. However, in those women who did not take vitamin C supplements, dietary vitamin C intake was not significantly associated with CHD risk. This finding is inconsistent with data from numerous other prospective cohort studies that found inverse associations between dietary vitamin C intake or vitamin C plasma levels and CHD risk (1,12). Data from the National Institutes of Health (NIH) indicated that plasma and circulating cells in healthy, young subjects became fully saturated with vitamin C at a dose of 400 mg/day (13). The results of the NHANES I Epidemiologic Follow-up Study and the Nurses' Health Study suggest that maximum reduction of cardiovascular disease risk may require vitamin C intakes high enough to saturate plasma and circulating cells, and thus the vitamin C body pool (14).

With respect to vitamin C and cerebrovascular disease, a prospective study that followed more than 2,000 residents of a rural Japanese community for 20 years found that the risk of stroke in those with the highest serum levels of vitamin C was 29% lower than in those with the lowest serum levels of vitamin C (15). Additionally, the risk of stroke in those who consumed vegetables 6-7 days of the week was 54% lower than in those who consumed vegetables 0-2 days of the week. In this population, serum levels of vitamin C were highly correlated with fruit and vegetable intakes. Therefore, as in many studies of vitamin C intake and cardiovascular disease risk, it is difficult to separate the effects of vitamin C on stroke risk from the effects of other components of fruits and vegetables, emphasizing the benefits of a diet rich in fruits and vegetables.

Cancer

A large number of studies have shown that increased consumption of fresh fruits and vegetables is associated with a reduced risk for most types of cancer (16). Such studies are the basis for dietary guidelines endorsed by the U.S. Department of Agriculture and the National Cancer Institute, which recommend at least 5 servings of fruits and vegetables per day. A number of case-control studies have investigated the role of vitamin C in cancer prevention. Most have shown that higher intakes of vitamin C are associated with decreased incidence of cancers of the mouth, throat and vocal chords, esophagus, stomach, colon-rectum, and lung. Because the possibility of bias is greater in case-control studies, prospective studies are generally given more weight in the evaluation of the effect of nutrient intake on disease. In general, prospective studies in which the lowest intake group consumed more than 86 mg of vitamin C daily have not found differences in cancer risk, while studies finding significant cancer risk reductions found them in people consuming at least 80 to 110 mg of vitamin C daily (1).

A prospective study of 870 men over a period of 25 years found that those who consumed more than 83 mg of vitamin C daily had a striking 64% reduction in lung cancer compared with those who consumed less than 63 mg per day (17). Although most large prospective studies found no association between breast cancer and vitamin C intake, two recent studies found dietary vitamin C intake to be inversely associated with breast cancer risk in certain subgroups. In the Nurses' Health Study, premenopausal women with a family history of breast cancer who consumed an average of 205 mg/day of vitamin C from foods had a 63% lower risk of breast cancer than those who consumed an average of 70 mg/day (18). In the Swedish Mammography Cohort, women who were overweight and consumed an average of 110 mg/day of vitamin C had a 39% lower risk of breast cancer compared to overweight women who consumed an average of 31 mg/day (19). A number of observational studies have found increased dietary vitamin C intake to be associated with decreased risk of stomach cancer, and laboratory experiments indicate that vitamin C inhibits the formation of carcinogenic compounds in the stomach. Infection with the bacteria, *helicobacter pylori* (*H. pylori*) is known to increase the risk of stomach cancer and also appears to lower the vitamin C content of stomach secretions. Although two intervention studies did not find a decrease in the occurrence of stomach cancer with vitamin C supplementation (6), more recent research suggests that vitamin C supplementation may be a useful addition to standard *H. pylori* eradication therapy in reducing the risk of gastric cancer (20).

Cataracts

Cataracts are a leading cause of visual impairment throughout the world. In the U.S., cataract-related expenditure is estimated to exceed 3 billion dollars annually (21). Cataracts occur more frequently and become more severe as people age. Decreased vitamin C levels in the lens of the eye have been associated with increased severity of cataracts in humans. Some, but not all, studies have observed increased dietary vitamin C intake (22) and increased blood levels of vitamin C (23) to be associated with decreased risk of cataracts. Those studies that have found a relationship suggest that vitamin C intake may have to be higher than 300 mg/day for a number of years before a protective effect can be detected (1). Recently, a 7-year controlled intervention trial of a daily antioxidant supplement containing 500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta-carotene in 4,629 men and women found

no difference between the antioxidant combination and a placebo on the development and progression of age-related cataracts (24). Therefore, the relationship between vitamin C intake and the development of cataracts requires further clarification before specific recommendations can be made.

Lead toxicity

Although the use of lead paint and leaded gasoline has been discontinued in the U.S., lead toxicity continues to be a significant health problem, especially in children living in urban areas. Abnormal growth and development has been observed in infants of women exposed to lead during pregnancy, while children who are chronically exposed to lead are more likely to develop learning disabilities, behavioral problems, and to have low IQs. In adults, lead toxicity may result in kidney damage and high blood pressure. In a study of 747 older men, blood lead levels were significantly higher in those who reported total dietary vitamin C intakes averaging less than 109 mg/day compared to men who reported higher vitamin C intakes (25). A much larger study of 19,578 people, including 4,214 children from 6 to 16 years of age, found higher serum vitamin C levels to be associated with significantly lower blood lead level (26). An intervention trial that examined the effects of vitamin C supplementation on blood lead levels in 75 adult male smokers found that 1,000 mg/day of vitamin C resulted in significantly lower blood lead levels over a 4-week treatment period compared to placebo (27). A lower dose of 200 mg/day did not significantly affect blood lead levels, despite the finding that serum vitamin C levels were not different than those of the group that took 1,000 mg/day. The mechanism for the relationship between vitamin C intake and blood lead levels is not known, although it has been postulated that vitamin C may inhibit intestinal absorption or enhance urinary excretion of lead.

DISEASE TREATMENT

Cardiovascular diseases

Vasodilation: The ability of blood vessels to relax or dilate is compromised in individuals with atherosclerosis. The damage to the heart muscle caused by a heart attack and damage to the brain caused by a stroke is related, in part, to the inability of blood vessels to dilate enough to allow blood flow to the affected areas. The pain of angina pectoris is also related to insufficient dilation of the coronary arteries. Treatment with vitamin C has consistently resulted in improved dilation of blood vessels in individuals with atherosclerosis as well as those with angina pectoris, congestive heart failure, high cholesterol, and high blood pressure. Improved blood vessel dilation has been demonstrated at a dose of 500 mg of vitamin C daily (28).

Hypertension (high blood pressure): Individuals with high blood pressure are at increased risk of developing cardiovascular diseases. Several studies have demonstrated a blood pressure lowering effect of vitamin C supplementation. One recent study of individuals with high blood pressure found that a daily supplement of 500 mg of vitamin C resulted in an average drop in systolic blood pressure of 9% after 4 weeks (29). It should be noted that those participants who were taking antihypertensive

medication continued taking it throughout the 4-week study. Because the findings regarding vitamin C and high blood pressure have not yet been replicated in larger studies it is important for individuals with significantly high blood pressure to continue current therapy (medication, lifestyle changes, etc.) in consultation with their health care provider.

Cancer

Studies in the 1970's and 1980's conducted by Linus Pauling and colleagues suggested that very large doses of vitamin C (10 grams/day intravenously for 10 days followed by at least 10 grams/day orally indefinitely) were helpful in increasing the survival time and improving the quality of life of terminal cancer patients (30). However, two randomized placebo-controlled studies conducted at the Mayo clinic found no differences in outcome between terminal cancer patients receiving 10 grams of vitamin C/day orally or placebo (31,32) There were significant methodological differences between the Mayo Clinic and Pauling's studies, and recently, two researchers from the NIH suggested that the route of administration (intravenous versus oral) may have been the key to the discrepant results. Intravenous (IV) administration can result in much higher blood levels of vitamin C than oral administration, and levels that are toxic to certain types of cancer cells in culture can be achieved with intravenous but not oral administration of vitamin C (33). Thus, it appears reasonable to reevaluate the use of high-dose vitamin C as cancer therapy.

Currently, there are no results from controlled clinical trials indicating that vitamin C would adversely affect the survival of cancer patients. However, vitamin C should not be used in place of therapy that has been demonstrated effective in the treatment of a particular type of cancer, for example, chemotherapy or radiation therapy. If an individual with cancer chooses to take vitamin supplements, it is important that the clinician coordinating his or her treatment is aware of the type and dose of each supplement. While research is underway to determine whether combinations of antioxidant vitamins might be beneficial as an adjunct to conventional cancer therapy, definitive conclusions are not yet possible (34).

In a presentation at a meeting of the American Cancer Society, a scientist suggested that supplemental vitamin C might enhance the growth of cancer cells or protect them from cell-killing free radicals produced by radiation and some forms of chemotherapy. An article published in the Spring/Summer 2000 issue of the Linus Pauling Institute newsletter, Is vitamin C harmful for cancer patients?, provides additional insight on this topic.

Diabetes

Cardiovascular diseases (heart disease and stroke) are the leading cause of death in individuals with diabetes. Evidence that diabetes is a condition of increased oxidative stress led to the hypothesis that higher intakes of antioxidant nutrients could help decrease cardiovascular disease risk in diabetic individuals. In support of this hypothesis, a 16-year study of 85,000 women, 2% of whom were diabetic, found that vitamin C supplement use (400 mg/day or more) was associated with significant reductions in

the risk of fatal and nonfatal coronary heart disease in the entire cohort as well as those with diabetes (11). In contrast, a 15-year study of postmenopausal women found that diabetic women who reported taking at least 300 mg/day of vitamin C from supplements when the study began were at significantly higher risk of death from coronary heart disease and stroke than those who did not take vitamin C supplements (35). Vitamin C supplement use was not associated with a significant increase in cardiovascular disease mortality in the cohort as a whole. Although a number of observational studies have found that higher dietary intakes of vitamin C are associated with lower cardiovascular disease risk, randomized controlled trials have not found antioxidant supplementation that included vitamin C to reduce the risk of cardiovascular disease in diabetic or other high-risk individuals (36, 37).

It is possible that genetic differences may influence the effect of vitamin C supplementation on cardiovascular disease. When the results of one randomized controlled trial were reanalyzed based on haptoglobin genotype, antioxidant therapy (1000 mg/d vitamin C + 800 IU/d vitamin E) was associated with improvement of coronary atherosclerosis in diabetic women with two copies of the haptoglobin 1 gene but worsening of coronary atherosclerosis in those with two copies of the haptoglobin 2 gene (38). The significance of these findings is not entirely clear, but they suggest that there may be a subpopulation of people with diabetes who will benefit from antioxidant therapy while others may not benefit or could actually be harmed. Since randomized controlled trials have not found that supplementation with vitamin C is beneficial in preventing or treating heart disease in individuals with diabetes, individuals with diabetes should avoid consuming more than 250 mg/day from vitamin C supplements until more research is available. Since vitamin C intake from foods was not associated with increased mortality from cardiovascular disease, there is no reason to limit the intake of vitamin C-rich fruits and vegetables.

Common cold

The work of Linus Pauling stimulated public interest in the use of large doses (greater than 1 gram/day) of vitamin C to prevent infection with the viruses responsible for the common cold. Reviews of the research conducted on this issue over the past 20 years conclude that, in general, large doses of vitamin C do not have a significant effect on the incidence of the common cold (39). However, a few studies have indicated that certain susceptible groups (e.g., individuals with low dietary intake and marathoners) may be less susceptible to the common cold when taking supplemental vitamin C. Additionally, large doses of vitamin C have been found to decrease the duration and severity of colds, an effect that may be related to the antihistamine effects found to occur with large doses (2 grams) of vitamin C (40).

SOURCES

Food sources

As shown in the table below different fruits and vegetables vary in their vitamin C content, but five servings should average out to at least 200 mg of vitamin C. (What is a serving?) If you wish to check foods you eat frequently for their nutrient content, search the USDA food composition database.

Food	Serving	Vitamin C (mg)
Orange juice	3/4 cup (6 ounces)	75
Grapefruit juice	3/4 cup (6 ounces)	60
Orange	1 medium	70
Grapefruit	1/2 medium	44
Strawberries	1 cup, whole	82
Tomato	1 medium	23
Sweet red pepper	1/2 cup, raw chopped	141
Broccoli	1/2 cup, cooked	58
Potato	1 medium, baked	26

Supplements

Vitamin C (L-ascorbic acid) is available in many forms, but there is little scientific evidence that any one form is better absorbed or more effective than another.

Natural vs. synthetic vitamin C: Natural and synthetic L-ascorbic acid are chemically identical and there are no known differences in their biological activities or bioavailability (41).

Mineral ascorbates: Mineral salts of ascorbic acid are buffered and therefore, less acidic than ascorbic acid. Some people find them less irritating to the gastrointestinal tract than ascorbic acid. Sodium ascorbate and calcium ascorbate are the most common forms, although a number of other mineral ascorbates are available. Sodium ascorbate generally provides 131 mg of sodium per 1,000 mg of ascorbic acid, and pure calcium ascorbate provides 114 mg of calcium per 1,000 mg of ascorbic acid.

Vitamin C with bioflavonoids: Bioflavonoids are a class of water-soluble plant pigments that are often found in vitamin C-rich fruits and vegetables, especially citrus fruits. Although many bioflavonoids are thought to function as antioxidants, there is little evidence that the bioflavonoids in most commercial preparations increase the bioavailability or efficacy of vitamin C (42).

Ascorbate and vitamin C metabolites: One such supplement (Ester-C®) contains mainly calcium ascorbate, but also contains small amounts of the vitamin C metabolites dehydroascorbate (oxidized ascorbic acid), calcium threonate, and trace levels of xylonate and lyxonate. Although the metabolites are supposed to increase the bioavailability of vitamin C, the only published study in humans found no difference between Ester-C® and commercially available ascorbic acid

tablets with respect to the absorption and urinary excretion of vitamin C (42). Ester-C® should not be confused with ascorbyl palmitate, which is also marketed as "vitamin C ester" (see below).

Ascorbyl palmitate: Ascorbyl palmitate is actually a vitamin C ester (vitamin C that has been esterified to a fatty acid). In this case, vitamin C is esterified to the saturated fatty acid, palmitic acid, resulting in a fat-soluble form of vitamin C. Ascorbyl palmitate has been added to a number of skin creams due to interest in its antioxidant properties as well as the important role of vitamin C in collagen synthesis (43). Although ascorbyl palmitate is also available as an oral supplement, it is likely that most of it is hydrolyzed (broken apart) to ascorbic acid and palmitic acid in the digestive tract before it is absorbed (44). Ascorbyl palmitate is also marketed as, "vitamin C ester," which should not be confused with Ester-C® (see above).

For a more detailed review of scientific research on the bioavailability of different forms of vitamin C, see **The Bioavailability of Different Forms of Vitamin C**.

SAFETY

Toxicity

A number of possible problems with very large doses of vitamin C have been suggested, mainly based on in vitro experiments or isolated case reports, including: genetic mutations, birth defects, cancer, atherosclerosis, kidney stones, "rebound scurvy", increased oxidative stress, excess iron absorption, vitamin B-12 deficiency, and erosion of dental enamel. However, none of these adverse health effects have been confirmed, and there is no reliable scientific evidence that large amounts of vitamin C (up to 10 grams/day in adults) are toxic or detrimental to health. With the latest RDA published in 2000, a tolerable upper intake level (UL) for vitamin C was set for the first time. A UL of 2 grams (2,000 milligrams) daily was recommended in order to prevent most adults from experiencing diarrhea and gastrointestinal disturbances (6). Such symptoms are not generally serious, especially if they resolve with temporary discontinuation or reduction of high-dose vitamin C supplementation. For a more thorough discussion of the Linus Pauling Institute's response to the UL for vitamin C, see the article, **The New Recommendations for Dietary Antioxidants: A Response and Position Statement by the Linus Pauling Institute**, in the Spring/Summer 2000 newsletter. A more detailed discussion of vitamin C and the risk of kidney stones can be found in the article, **What About Vitamin C and Kidney Stones?**, in the Fall/Winter 1999 newsletter.

Tolerable Upper Intake Level (UL) for Vitamin C	
Age Group	**UL (mg/day)**
Infants 0-12 months	Not possible to establish*

Children 1-3 years	400
Children 4-8 years	650
Children 9-13 years	1,200
Adolescents 14-18 years	1,800
Adults 19 years and older	2,000

*Source of intake should be from foods or formula only.

Does vitamin C promote oxidative damage under physiological conditions? Vitamin C is known to function as a highly effective antioxidant in living organisms. However, in test tube experiments, vitamin C can interact with some free metal ions to produce potentially damaging free radicals. Although free metal ions are not generally found under physiological conditions, the idea that high doses of vitamin C might be able to promote oxidative damage in vivo has received a great deal of attention. Widespread publicity has been given to a few studies suggesting a pro-oxidant effect of vitamin C (45,46), but these studies turned out to be either flawed or of no physiological relevance. A recent comprehensive review of the literature found no credible scientific evidence that supplemental vitamin C promotes oxidative damage under physiological conditions or in humans (47). Studies that report a pro-oxidant effect for vitamin C should be evaluated carefully to determine whether the study system was physiologically relevant, and to rule out the possibility of methodological and design flaws.

For example, a study in the June 15, 2001, issue of the journal *Science* shows that lipid hydroperoxides (rancid fat molecules) can react with vitamin C to form products that could potentially harm DNA, although the reaction of these products with DNA was not demonstrated in the study (45). To find out why the Linus Pauling Institute considers the study's conclusions unwarranted, see **Vitamin C doesn't cause cancer!** in the Linus Pauling Institute Newsletter.

Drug interactions

A number of drugs are known to lower vitamin C levels, requiring an increase in its intake. Estrogen-containing contraceptives (birth control pills) are known to lower vitamin C levels in plasma and white blood cells. Aspirin can lower vitamin C levels if taken frequently. For example, two aspirin tablets taken every six hours for a week has been reported to lower white blood cell vitamin C by 50%, primarily by increasing urinary excretion of vitamin C (48).

There is some evidence, though controversial, that vitamin C interacts with anticoagulant medications (blood thinners) such as warfarin (Coumadin). Large doses of vitamin C may block the action of warfarin, requiring an increase in dose to maintain its effectiveness. Individuals on anticoagulants should limit their vitamin C intake to 1 gram/day and have their prothrombin time monitored by the clinician following their anticoagulant therapy. Because high doses of vitamin C have also been found to interfere

with the interpretation of certain laboratory tests (e.g., serum bilirubin, serum creatinine, and the guaiac assay for occult blood) it is important to inform one's health care provider of any recent supplement use (49).

Antioxidant Supplements and HMG-CoA Reductase Inhibitors (Statins)

A 3-year randomized controlled trial in 160 patients with documented coronary heart disease (CHD) and low HDL levels found that a combination of simvastatin (Zocor) and niacin increased HDL_2 levels, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, such as myocardial infarction (heart attack) and stroke (50). Surprisingly, when an antioxidant combination (1,000 mg vitamin C, 800 IU alpha-tocopherol, 100 mcg selenium, and 25 mg beta-carotene daily) was taken with the simvastatin-niacin combination, the protective effects were diminished. Since the antioxidants were taken together in this trial, the individual contribution of vitamin C cannot be determined. In contrast, a much larger randomized controlled trial of simvastatin and an antioxidant combination (600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) in more than 20,000 men and women with coronary artery disease or diabetes found that the antioxidant combination did not diminish the cardioprotective effects of simvastatin therapy over a 5-year period (51). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplements and cholesterol-lowering agents, such as HMG-CoA reductase inhibitors (statins).

THE LINUS PAULING INSTITUTE RECOMMENDATION

The Linus Pauling Institute recommends a vitamin C intake of at least 400 mg daily—the amount that has been found to fully saturate plasma and circulating cells with vitamin C in young, healthy nonsmokers (13). Consuming at least five servings (What is a serving?) of fruits and vegetables daily may provide about 200 mg of vitamin C. Most multivitamin supplements provide 60 mg of vitamin C.

Older adults (65 years and older)

Although it is not yet known with certainty whether older adults have higher requirements for vitamin C than younger people, some older populations have been found to have vitamin C intakes considerably below the RDA of 75 and 90 mg/day for women and men, respectively. A vitamin C intake of at least 400 mg daily may be particularly important for older adults who are at higher risk for chronic diseases.

For more information on the difference between **Dr Linus Pauling's recommendation and the Linus Pauling Institute's recommendation for vitamin C intake**, click on the highlighted text.

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Is Vitamin C Harmful to Cancer Patients?

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In a recent presentation at the American Cancer Society meeting, Dr. David Golde of Memorial Sloan-Kettering Cancer Center speculated that supplemental vitamin C may be harmful to cancer patients. Dr. Golde had previously shown how vitamin C gets into and accumulates in cancer cells. Golde and others are concerned that the extra vitamin C in cancer cells may enhance their growth or protect them from the cell-killing free radicals produced by radiation and some chemotherapeutic drugs.

While different cancer cells may respond differently to vitamin C, it is important to view these concerns in the context of the experimental cell culture, small animal, and human clinical studies. In some cell culture and small animal studies, vitamin C has enhanced cancer cell growth. Dr. Chan Park has found that the growth of leukemic cells from some leukemia patients put into culture was enhanced by vitamin C. The growth of cells taken from other leukemia patients was either inhibited or unaffected by vitamin C. It is unknown whether similar effects would have been observed in the same patients taking supplemental vitamin C. Dr. Joel Schwartz of the National Institutes of Health has published studies in which supplemental vitamin C enhanced the growth of tumors induced in hamsters by a chemical carcinogen. Interestingly, the growth of tumors was significantly inhibited by supplemental vitamin E and by a mixture of antioxidants, including beta-carotene, vitamin E, and vitamin C.

Studies published by LPI scientists since the 1970s have demonstrated that supplemental vitamin C delayed the onset of tumors in mice that developed spontaneous mammary tumors, in mice exposed to ultraviolet radiation, and in guinea pigs implanted with liver cancer cells. In these experiments, vitamin C did not appreciably affect the growth rate of tumors once they formed. Other studies published by Dr. Constance Tsao and her colleagues at LPI showed that supplemental vitamin C (sometimes combined with oxidation products of vitamin C) inhibited the growth of human colon, lung, and mammary tumors implanted into mice. LPI investigations also demonstrated that vitamin C and its derivatives have anticancer effects against a number of cancer cell lines in culture.

What about clinical studies on vitamin C in cancer patients? Dr. Pauling and his medical collaborator, Dr. Ewan Cameron, former Chief of Surgery at Vale of Leven Hospital in Scotland, published numerous papers on the response of cancer patients given large doses of supplemental vitamin C as an adjunct to the appropriate conventional treatment for cancer. In their book *Cancer and Vitamin C*, they concluded that supplemental vitamin C is of benefit to most cancer patients. The benefit ranged from an increased sense of well-being to a prolongation of survival time in terminal patients to rare complete regressions. However, two clinical studies carried out by Drs. Edward Creagan and Charles Moertel of the Mayo Clinic and

published in 1979 and 1985 showed no benefit from supplemental vitamin C on survival time. As Drs. Cameron and Pauling pointed out, however, the patients in the first Mayo Clinic study had undergone extensive chemotherapy that damaged their immune systems prior to the use of vitamin C. In the second study supplemental vitamin C was abruptly stopped after only about two months. There was also evidence that some of the patients in the placebo group were taking extra vitamin C, thus muddying the differences between groups.

When *Cancer and Vitamin C* was first published in 1979, Drs. Cameron and Pauling noted that little information was available on the interaction between vitamin C and chemotherapeutic drugs. They cautioned that patients undergoing aggressive chemotherapy expected to be curative should refrain from taking large doses of vitamin C at the same time in case the vitamin interfered with the drug action. There is some evidence that vitamin C increases the activity of liver enzymes that detoxify xenobiotics, including drugs. When the chemotherapy was merely palliative, they did not believe that the use of concurrent vitamin C was contraindicated. They believed that vitamin C potentiates radiation, and even many clinicians who disagree on this point nevertheless agree that supplemental vitamin C given after radiation ameliorates radiation sickness.

In the early 1990s, Dr. Pauling published two papers with Dr. Abram Hoffer, who developed a regimen for use in cancer patients that includes B vitamins, vitamin E, large doses of vitamin C, beta-carotene, selenium, zinc, and other substances. The statistical analysis of their data revealed that about 40% of the cancer patients survived five years or more after the initiation of the regimen. (A new book by Dr. Hoffer, *Vitamin C & Cancer*, features major contributions by Linus Pauling and further discussion of these results.) Only about 10% of the patients treated by Dr. Cameron in Scotland with vitamin C alone survived as long, although all of the Scottish study patients had terminal cancer. These studies, as well as Dr. Cameron's studies in Scotland, were not designed as placebo- controlled, randomized, double-blind trials because of ethical concerns and practical problems concerning appropriate placebos.

Interestingly, Dr. Hoffer's regimen is remarkably similar to that recommended by Dr. Kedar Prasad of the University of Colorado and his colleagues, who advocate the use of a combination of B vitamins, large doses of calcium ascorbate (vitamin C), vitamin E, and beta-carotene for cancer patients undergoing either chemotherapy or radiation. Dr. Prasad acknowledges the accumulation of antioxidant vitamins in cancer cells, but argues that this has favorable biochemical effects, including the inhibition of oncogenes and the induction of factors that inhibit cell growth, favor differentation, or induce apoptosis (programmed cell death). In an extensive and well-referenced recent review published in the *Journal of the American College of Nutrition*, Dr. Prasad presented results from cell culture experiments demonstrating that the killing effect of many cancer drugs or radiation on mouse and human cancer cells is enhanced in the presence of vitamins C or E. Of course, cell culture studies (or animal studies) cannot always predict what will happen in humans. In another extensive review published in *Alternative Medicine Review* in 1999, Drs. Lamson and Brignall reached conclusions similar to those of Dr. Prasad. These authors noted that "considerable data exists showing increased effectiveness of many cancer therapeutic agents, as well as a decrease in adverse effects, when given concurrently with antioxidants."

A Finnish non-randomized clinical study published in *Anticancer Research* in 1992 by Dr. Jaakkola and colleagues showed that the provision of B vitamins, large doses of vitamins C and E, beta-carotene, fatty acids, and minerals in combination with chemotherapy and radiation to patients with small-cell lung cancer resulted in significantly prolonged survival, especially when started early. These patients were compared to patients in other studies who were treated only with chemotherapy and radiation. Another clinical study by Dr. Emmanuel Cheraskin published in 1968 showed that the response to radiation among women with cervical carcinoma was enhanced by daily supplements of 750 mg of vitamin C given during radiation.

What can we conclude about vitamin C and cancer? While the theoretical speculation by Dr. Golde seems plausible, there is no clinical evidence that supplemental antioxidant vitamins, including vitamin C, harm cancer patients. Indeed, much of the recent cell culture and clinical research suggests that a *combination* of antioxidant vitamins and minerals as an adjunct to conventional therapy may have benefit. This is a complex issue, however, and there is clearly more to learn from controlled clinical trials about the use of