Ascorbic Acid in the Prevention and Treatment of Cancer

by Kathleen A. Head, N.D.

Abstract

Proposed mechanisms of action for ascorbic acid (ascorbate, vitamin C) in the prevention and treatment of cancer include enhancement of the immune system, stimulation of collagen formation necessary for "walling off" tumors, inhibition of hyaluronidase which keeps the ground substance around the tumor intact and prevents metastasis, prevention of oncogenic viruses, correction of an ascorbate deficiency often seen in cancer patients, expedition of wound healing after cancer surgery, enhancement of the effect of certain chemotherapy drugs, reduction of the toxicity of other chemotherapeutic agents such as Adriamycin, prevention of free radical damage, and neutralization of carcinogenic substances. Scottish as well as Japanese studies have pointed to the potential benefit of high dose vitamin C for the treatment of "terminal" cancer. Mayo Clinic studies, however, have contradicted the Scottish and Japanese findings, resulting in accusations of methodological flaws from both sides. Numerous epidemiological studies have pointed to the importance of dietary and supplemental ascorbate in the prevention of various types of cancer including bladder, breast, cervical, colorectal, esophageal, lung, pancreatic, prostate, salivary gland, stomach, leukemia, and non-Hodgkin's lymphoma.

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Introduction

In the mid-18th century, James Lind first demonstrated that the juice of fresh citrus cures scurvy. The active agent, the enolic form of 3-keto-L-gulofurnlactone, or ascorbic acid, was isolated in the late 1920s by Albert Szent-Gyorgyi (see figure 1). By the mid-1930s, methods had been devised to synthesize ascorbic acid, making it widely available at low cost. In the 1990s, it is the most commonly used single supplement in the U.S.[1]

In 1954, W.J. McCormick, a Canadian physician, formulated the hypothesis that cancer is a collagen disease, secondary to a vitamin C deficiency.[2] While alternative cancer treatments, such as The Gerson therapy, have been incorporating diets high in vitamin C for many years, the use of vitamin C supplementation in large doses for the prevention and treatment of cancer was further advanced in 1971 by Linus Pauling, PhD, and Ewan Cameron, MD. A discussion of their use of high-dose vitamin C for treatment of patients with advanced cancer can be found below. Since 1971, considerable attention has been paid to vitamin C and cancer, particularly in

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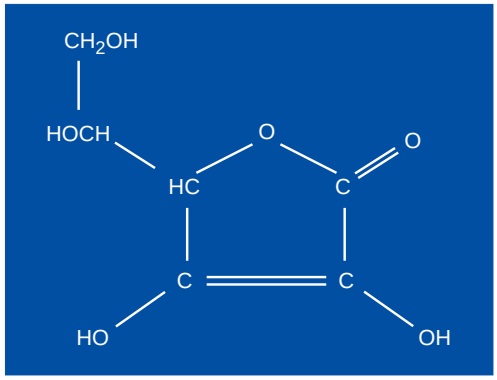
the area of prevention. However, there has been a paucity of human studies using vitamin C to treat already existing cancer.

Biochemistry of Ascorbic Acid

Ascorbic acid is widely distributed in plants, its concentration varying from 0.01 percent in apples to about 1 percent in rose hips and citrus. It is one of the most important reducing agents occurring in living tissue. While most animals synthesize their own vitamin C, humans and a few other animals, such as non-human primates, guinea pigs, and fruit bats do not. Ascorbate accelerates hydroxylation reactions, in part by donating electrons to metal ion cofactors of hydroxylase enzymes. Hydroxylation reactions are important in collagen synthesis, conversion of lysine to carnitine, conversion of dopamine to norepinephrine, and in tyrosine metabolism. Ascorbate is also utilized to catalyze other enzymatic reactions, such as amidation necessary for maximum activity of the hormones oxytocin, vasopressin, cholecystokinin, and alpha-melanotropin.[3]

Figure 1. Structure of Ascorbic Acid.



Ascorbic acid is a water-soluble, chain-breaking antioxidant which reacts directly with singlet oxygen, hydroxyl, and superoxide radicals. It also may react with tocopheroxy radicals to regenerate vitamin E.[1] Conversely, ascorbyl radicals are quenched by vitamin E.

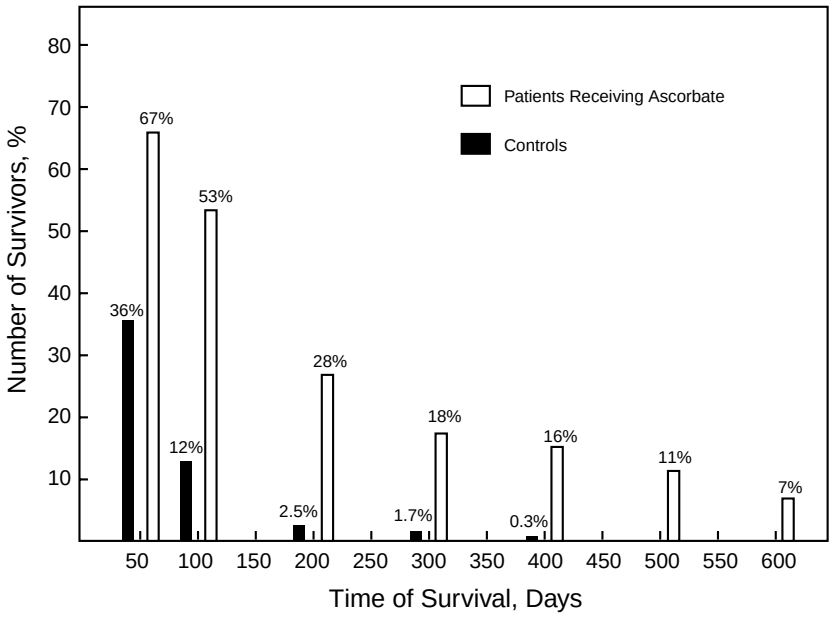
Mechanisms of Action

Proposed mechanisms of vitamin C activity in the prevention and treatment of cancer include: (1) enhancement of the immune system by increased lymphocyte production; (2) stimulation of collagen formation, necessary for "walling off" tumors; (3) inhibition of hyaluronidase, keeping the ground substance around the tumor intact and preventing metastasis;[4] (4) inhibition of oncogenic viruses; (5) correction of an ascorbate deficiency, often seen in cancer patients; (6) expedition of wound healing after cancer surgery;[5] (7) enhancement of the effect of certain chemotherapy drugs, such as tamoxifen, cisplatin, DTIC and others;[6-8] (8) reduction of the toxicity of other chemotherapeutic agents, such as Adriamycin;[9] (9) prevention of cellular free radical damage;[10] and (10) neutralization of carcinogenic substances.[11]

Taking a closer look at the phenomenon of hyaluronidase inhibition Cameron, Pauling and Leibovitz wrote in "Ascorbic Acid and Cancer: A Review": ..."the dangerous features of neoplastic cell behavior (invasiveness, selective nutrition, and perhaps growth) are caused by microenvironmental depolymerization. In turn, this matrix destabilization is brought about by constant exposure to lysosomal glycosidases continually released by the neoplastic cells. Finally, ascorbate is involved in the natural restraint of this degradative enzyme activity."[12]

Proper collagen formation is an important factor in the encapsulation of tumors or the slowing of metastasis via the development of an almost impermeable barrier (known as the schirrus response). Ascorbic acid plays an important role in collagen synthesis and stability. A lack of ascorbate significantly reduces hydroxylation of proline and lysine to hydroxyproline and hydroxylysine, respectively, jeopardizing proper collagen cross-linking. This leads to instability of the triple helix of collagen which,

Figure 2. A comparison of survival times in ascorbate-treated patients and matched controls. Adapted from Cameron and Pauling.[16]



in turn, results in increased collagen catabolism. *In vitro*, vitamin C also has been found to increase collagen synthesis by fibroblasts.[12]

Cancer patients tend to be immunocompromised, demonstrating low lymphocyte ascorbate levels. The immune surveillance system is important, both in inhibiting the initiation phase of cancerous growth, and also in the prevention of spread. Ascorbate supplementation increases the number and effectiveness of lymphocytes and enhances phagocytosis.[12]

Vitamin C in the Treatment of Cancer

The Vale of Leven Studies: Most of the studies on vitamin C and cancer relate to its protective effect, rather than use of the vitamin for the treatment of active cancer. The Vale of Leven studies conducted by Ewan Cameron, MD and his associates, (later including Linus Pauling, PhD), at his hospital in Loch Lomondside, Scotland, are among the few exceptions. In preliminary studies which began in November 1971, a small group of patients with advanced cancer were given 10 grams of sodium ascorbate daily. The initial testing was an uncontrolled study, conducted on 50 patients. Seventeen of these patients exhibited seemingly no response, 10 a minimal response, 11 retardation of the tumor growth, 3 ceasing of the tumor growth, 5 regression of tumor growth with long-term survival, and 6 experienced hemorrhage and necrosis of the tumors, which destroyed the tumors but killed the patients in the process.[13] An evaluation of the life expectancy of these first 50 "terminally ill" patients treated with ascorbate yielded promising results. Based on data from previous similar groups of patients, it was expected that 90 percent of the group would be dead within three months of being labeled "terminal." When 10 g ascorbate was prescribed daily (beginning at the time the patient was labeled "terminal"), by the 100th day of treatment the mortality rate was only 50 percent. Of the remaining 25 patients, 20 died between days 110 and 659, with an average survival time of 261 days; and five had an average survival time of greater than 610 days.[14]

Subsequently, a controlled retrospective study was conducted, comparing survival times of 100 terminally ill cancer patients at Vale of Leven Hospital with 1,000 matched controls from the same hospital. The patients were randomly selected from the database of those terminal cancer patients who had received ascorbate. Each ascorbate-treated patient was matched with 10 controls from the same hospital of the same age, sex, and type and stage of cancer who had not been prescribed vitamin C. In 90 percent of the cases,

the ascorbate-treated group lived three times longer than the control group. For the other 10 percent, long-term survival made it impossible to assess survival time with certainty, but at the time of publication of the study, the ascorbate group exhibited greater than 20 times the survival rate of the control group.[15](see Figure 2)[16]

Having been criticized by some investigators for not assuring the subjects were randomly chosen from the same representative subpopulations in the treated and control groups, a second retrospective evaluation at the Vale of Leven hospital was undertaken in 1978 – again with 100 patients receiving ascorbic acid compared to 1,000 matched controls without vitamin C.[17] Most of the ascorbate-treated group and about half the controls were the same subjects as in the initial study. This time, since there are different mean survival times for different types of cancer, the groups were further divided according to types of cancer, and controls carefully matched (see Table 1). In addition, the groups passed several "randomness" tests. In each of the nine types of cancer the ascorbate group had a considerably longer survival time than their matched controls. At the time of evaluation, eight patients in the vitamin C group were still living, while no one was alive in the control group; this resulted in 321+ days longer lifespan for the vitamin C treated group. Factoring out those in the ascorbate group who were still living at the time of evaluation, the vitamin C group lived an average of 251 days longer than the control group.

Cameron and Pauling later evaluated the first 500 "terminal" cancer patients to receive ascorbate. In most cases, subjective improvement – increased feeling of well-being, more energy, more alertness, decrease or elimination of pain, better appetite – were noted by the ascorbate patients. Cameron reported a quite dramatic relief of bone pain from metastases in four out of five patients. Objective improvements included a decrease in malignant ascites and pleural effusion, relief from hematuria, some reversal of hepatomegaly and jaundice, and decreases in erythrocyte SED rate and serum seromucoid levels, all accepted indicators of a decrease in malignant activity.[14] Furthermore, patients who had been on large doses of narcotics, such as morphine, for pain relief, showed none of the typical withdrawal symptoms.

Based on the above cited studies the researchers concluded: "It is our conclusion that this simple and safe treatment, the ingestion of large amounts of vitamin C, is of definite value in the treatment of patients with advanced cancer. Although the evidence is as yet not so strong, we believe that vitamin C has even greater value for the treatment of cancer patients with the disease in earlier stages and also for the prevention of cancer."[18]

The Vale of Leven protocol called for a ten-day course via intravenous (IV), continuous slow-drip infusion of sodium ascorbate in half-strength Ringer's Lactate Solution. After the IV treatment, assuming the patient was able to take medication by mouth, an oral dose of vitamin C was begun at a dose of 2.5 grams every 6 hours for a total of 10 grams in 24 hours. The dosage varied somewhat, ranging from 10-30 grams daily, and was continued indefinitely. The goal was to maintain plasma ascorbate levels of at least 3 mg/dl. The researchers reported generally a subjective improvement in well-being, vigor, pain relief, and appetite was apparent within 5-7 days. Increased energy was believed to be a result of improved carnitine synthesis with a resulting increase in triglyceride transport into cell mitochondria.[19]

Japanese Studies: Uncontrolled trials conducted at two different hospitals in Japan during the 1970s also confirmed the increase in survival time of terminal cancer patients supplemented with ascorbate. At the Fukuoka Torikai Hospital, the average survival time

Table 1. Survival times: Ascorbate-treated patients vs. matched controls for various tumor sites. Adapted from Cameron and Pauling.[17]

Primary tumor type	Patients, No.		Mean survival times, days				Increased survival times of ascorbate -treated patients, days*		
			From first hospital attendance		From date of untreatability				
			A	B	C	D	E	F	
	Test	Controls	Test	Control	Test	Control	A - B	C - D	G
Colon	17	170	458+	316	352+	33	142+	319+	324
Bronchus	17	170	219+	118	186+	31	101+	155+	184+
Stomach	13	130	286+	159	182+	32	127+	150+	134+
Breast	11	110	1396+	1020	487+	52	376+	435+	378+
Kidney	8	80	774+	492	381+	39	282+	342+	348+
Bladder	7	70	1669+	420	355+	21	1249+	334+	226+
Rectum	7	70	634	336	270	43	298	227	247
Ovary	6	60	884	366	183	69	518	114	157
Others	14	140	706+	279	278+	37	427+	241+	189+
All	100	1000	681+	360	293+	38	321+	255+	234+

* E, calculated as A - B; F, calculated as C - D; G, additional survival time of first set of ascorbate-treated patients with first set of controls. The + following a number indicates that one patient in the group (two in the bladder group) continued to survive after 15 May 1978.

after being labeled "terminal" was 43 days for 44 patients supplemented with low levels of ascorbate (less than 4 grams daily), and 246 days for 55 patients supplemented with higher dosages of ascorbate (greater than 5 grams daily — averaging 29 grams daily) and starting at the time of "terminal" diagnosis.[20] The researchers found no differences in survival times between the groups receiving 5-9 grams daily and those receiving 10-29 grams daily. A decline in effect was noted in those receiving 30-60 grams daily. They found the best results with uterine cancer, and the smallest increases in survival time with lung and stomach cancer.

Effectiveness of ascorbate was also observed at the Kamioka Kozan Hospital where 19 terminally-ill control patients survived an average of 48 days compared to six patients on high levels of vitamin C who lived an average of 115 days, or 2.4 times longer than the control group.[21] These researchers also reported the improved quality of life observed in the Scottish studies.

Mayo Clinic Studies: In an attempt to either duplicate or refute the Cameron and Pauling results, the Mayo Clinic initiated a test on 150 patients.[22] Subjects were randomly divided into two groups, one group of 60 received 10 grams of ascorbic acid daily in four divided doses while the control group of 63 received an equal number of placebo capsules. After randomization, 27 patients elected not to participate and comprised a third "no treatment" group. Treatment was continued until death or until the patient was no longer able to take medication orally. The two groups were evenly balanced with regard to age, sex, tumor site, initial performance status, and previous treatment. Fifty-eight percent of those receiving placebo and 63 percent of those receiving ascorbate reported subjective improvement in symptoms during the treatment period. The researchers reported no significant difference between the vitamin C and placebo groups in regard to survival time; however, the 27 patients who received no treatment experienced a significantly lower survival time, living an average of 25 days

compared to an average of 51 days for the vitamin C or placebo groups. All but nine of the 123 subjects had received prior chemotherapy, radiation, or both.

Based on other researchers' complaints that the Mayo study had not addressed the effect of vitamin C on cancer patients who had not received prior chemotherapy or radiation, a second trial was initiated by the same researchers.[23] In this study, only patients with advanced colorectal cancer were included. At the time of administration of vitamin C, the researchers deemed them all inappropriate candidates for chemotherapy. One hundred patients were randomly assigned to receive either 10 grams ascorbic acid or placebo daily. Patients continued on the treatment for as long as they were able to take oral medications or until there was evidence of tumor progression. At this point, over half of the subjects received subsequent chemotherapy. The researchers did not report survival times as they did not continue the patients on vitamin C until they died. Instead, they reported that after one year 49 percent of the vitamin C group and 47 percent of the placebo group were still living. They reported that for both groups survival time was comparable to the Cameron and Pauling untreated group. When they selected patients with a bias toward those with a more favorable prognosis, they found results in both groups similar to the Cameron and Pauling vitamin C treated groups, implying bias selection on the part of Cameron and Pauling. Because of the differences in study design, it is impossible to compare the results of these trials.

The Controversy: It is impossible to have a discussion about vitamin C and cancer without discussing the controversy stirred by the Vale of Leven and Mayo studies. Both sides accused the other of serious study flaws. The Mayo researchers claimed that, because the Vale of Leven studies were retrospective instead of prospective, and since the subjects were not randomly assigned to groups ahead of time but chosen after the fact, that selection bias occurred, with the researchers consciously or subconsciously selecting the ascorbate-treated patients who had the best prognosis and outcomes to be part of the study group. The Mayo researchers made this statement:

"Uncontrolled or historically controlled studies have a necessary purpose in the evaluation of any therapeutic method, since they serve to develop a hypothesis of therapeutic effectiveness. Such studies, however, rarely prove such effectiveness, which in most circumstances should be established by prospective randomized study. Whether one is dealing with the treatment of the common cold or of cancer, and whether one is dealing with a benign vitamin or a highly toxic chemotherapy program, it would seem to serve the interest of the patient best for public advocacy of a proposed treatment to be withheld until that treatment had been proved effective by definitive studies of sound scientific design."[23]

The initial Mayo study was criticized by Pauling and Cameron as they felt the two groups were not comparable. In the initial Cameron study, only 4 of the 100 patients had received prior chemotherapy or radiation, while in the first Mayo study the majority of patients had received prior chemotherapy. As previously mentioned, the Mayo Clinic conducted a second study with patients who had not received prior chemotherapy or radiation.

Regarding the second study, in a personal interview with Dr. Pauling, he told this author:[24]

"I have formulated three criteria for validity of a clinical trial. The Mayo Clinic paper fails on all three." When asked what the three criteria were, this is what he said: "Well, first if you want to test something with a cohort of patients, every patient should be treated the same way as the other patients and the same way over the period of the trial. In the Mayo

Clinic study, there were perhaps four separate periods. There was a period when the vitamin C patients received vitamin C every day. So that would be like Cameron's patients. They received vitamin C every day. Then there was a period when they didn't receive vitamin C and that would be a trial of patients during a period after they receive vitamin C for awhile and then stop it. Then there was a period when they were being given chemotherapy. This was a rather short period, maybe a month or two. Then there was a period when they didn't receive anything after they'd been given chemotherapy. So, there were four periods. The first period lasted a median time of 2.5 months and nobody died. None of the vitamin C or control patients died. Since none of the vitamin C patients died you don't have any mortality data similar to Cameron's, of patients who received vitamin C every day until their death. So, it just doesn't have any relation to Cameron's work. Then there is the period after the vitamin C or placebo was stopped. None of the placebo patients died for some strange reason. During this period, after stopping the vitamin C, the vitamin C and placebo patients died off at about the same rate. That's perhaps what you would expect, not expect the vitamin C given the year before to be [effective]. Then there's no information about what happened when they started giving chemotherapy to the patients, but about 58 out of 100 got chemotherapy and they began dying faster than when they weren't getting chemotherapy. So, that may be significant. Well, that's the first criteria.

"The second criteria is if you plot the logarithm of the fraction surviving against time, you either get a straight line or it can be bending up, it can't bend down unless you do something that causes them to die. Well, theirs bent down because they started giving them chemotherapy.

"Thirdly, for a well-conducted study, the death line, surviving line extrapolates back to the origin. They had a period of 90 days when only one patient died out of 100. They should have had about 30 dying in that first 90 days according to the rate at which they died afterward. So, there's something fishy about that."

In a personal interview with Dr. Ewan Cameron, he said of the Mayo study:[25]

"They give a drug in tolerable doses for a particular period of time and then suddenly stop it. If they don't see significant results they go to the next drug and so on. That's not how to test vitamin C. We're talking about a totally different therapy. We're talking about something that supports the patient for the rest of his life, not for ten weeks, which was what the Mayo clinic did. Then they stopped it abruptly and gave them 5FU."

Vitamin C in the Prevention of Cancer: Epidemiological Evidence

There is considerable epidemiological evidence pointing to the benefits of vitamin C in the prevention of a number of types of cancer. Unfortunately, epidemiological evidence is often difficult to assess since general dietary factors are difficult to pinpoint. For instance, is high fruit consumption indicative of a high vitamin C intake – or is it the fiber that is the key? In addition, frequently the studies report the effects of a number of antioxidants without separating the results for each. The following examines epidemiological evidence according to site of primary tumor.

Bladder: Interest in vitamin C and cancer of the lower urinary tract, including the bladder, stems in part from the discovery that dye-workers exposed to certain carcinogens in the workplace (which oxidize to endogenous orthohydroxy and hydroxylamine derivatives) were more likely to develop bladder cancer. It was hypothesized by at least one group of researchers that higher levels of ascorbate in the urine might prevent the oxidation of these

carcinogens. They found that a dosage of 300 mg vitamin C in the form of 3 glasses of orange juice daily raised urinary ascorbate to a level capable of preventing, at least to some degree, the oxidation (or activation) of these carcinogens.[26] The most important known risk factor for the development of bladder cancer is cigarette smoking.[27] It is interesting to note that cigarette smokers tend to be lower in serum ascorbate than non-smokers.

An epidemiological study in Hawaii comparing 195 males and 66 females with cancer of the lower urinary tract with two matched controls each found a decreasing risk of cancer with increasing levels of vitamin C consumption for women but not for men.[28] Another group of researchers noted low serum ascorbate levels in the majority of 35 patients with bladder cancer.[29]

Breast Cancer: Plasma levels of ascorbate were significantly lower while platelet levels were higher in a group of recently diagnosed breast cancer patients when compared to a matched group of controls.[30] Epidemiological studies appear to point to ascorbate as a possible chemopreventive for breast cancer. In the Iowa Women's Health Study, women who reported consuming at least 500 mg vitamin C daily had a relative risk of developing breast cancer of 0.79 (not statistically significant), compared with women who did not supplement with vitamin C.[31] Rohan et al reported a small, statistically insignificant decrease in risks with vitamin C consumption (as assessed by dietary reporting).[32] In a Spanish study comparing vitamin C intake among breast cancer patients and matched controls, the patients reported significantly lower intakes of dietary vitamin C than controls.[33]

A meta-analysis of 12 studies and a number of different nutrients and their relationship to breast cancer found "vitamin C intake had the most consistent and statistically significant inverse association with breast cancer risk."[34] Verhoeven et al found no significant association between vitamin C supplementation and decreased breast cancer risk. To make the claim as they did, however, that supplementation with vitamin C does not confer protection from breast cancer, is erroneous since their "higher doses" were an average of 165.3 mg daily. (The group was divided according to supplemental intake as reported on a questionnaire into quintiles with the average reported intake of vitamin C daily ranged from 58.6 mg in the lowest quintile to 165.3 mg in the highest).[35]

A study to compare the 5-year survival rates of women diagnosed in the early stages of breast cancer who were supplemented with 3 grams daily ascorbate, with a similar group who was not supplemented, found similar 5-year survival rates in both groups.[36] Since the prognosis for women with breast cancer which is detected early is quite good in general, this is not surprising, as you would expect a good prognosis, with or without ascorbate supplementation.

In an animal study, the effect of selenium in the form of sodium selinite on protection from mammary tumorigenesis was interfered with by high doses of vitamin C, while the effect of seleno-DL-methionine was not affected by vitamin C.[37]

Cervical Cancer: A Latin American study compared nutrient intake and dietary patterns of 748 cervical cancer patients with 1,411 controls.[38] The results supported a protective affect of vitamin C against invasive cervical cancer. Other researchers have found a similar inverse relationship between cervical neoplasia and dietary vitamin C.[39,40] A review article examining a number of studies concluded that in many, but not all studies, an inverse relationship between vitamin C status and risk for cervical dysplasia was observed.[41]

Colorectal Cancer: Colonic polyps are recognized as a frequent precursor to colorectal cancer. In a group of 36 patients with polyps, 19 received 3 grams ascorbate daily and 17

received placebo. The researchers noted a decrease in polyp area after nine months of treatment with ascorbate but not placebo. In addition, a trend toward decrease in polyp number was noted.[42] Other researchers have used antioxidants to prevent recurrence of polyps in patients who had undergone surgical removal of their polyps. Patients were divided into three groups receiving either lactulose, a combination of vitamins A, C, and E, or nothing. Among 209 patients, polyps recurred in 5.7 percent of those given the vitamins, in 14.7 percent of those receiving lactulose, and in 35.9 percent of the untreated controls.[43]

An Australian study examining dietary habits and incidence of colorectal cancer found vitamin C but not A to be protective.[44] A similar study on patients of a major health plan in Los Angeles found a weak inverse relationship between supplemental and dietary vitamin C and incidence of colorectal cancer.[45]

Esophageal Cancer: Esophageal cancer is among the more common types found in Lin-Xian County in northern China. Higher levels of nitrosamines have been detected in the gastric juices and urine of people in this area compared to those from a low-risk area of China. A positive correlation was found between esophageal lesions and nitrosamine levels. Intake of moderate doses of ascorbic acid by Lin-Xian subjects was found to decrease urinary nitrosamines to the level detected in the low-risk area.[46]

The relationships of dietary and supplemental factors with esophageal cancer were examined in 147 males with esophageal cancer and 264 males with other diagnoses at Roswell Park Memorial Institute. Vitamins C, A, and intakes of fruits and vegetables were associated with decreased risks of esophageal cancer.[47]

Leukemia: An *in vitro* examination of bone marrow cells taken from patients with acute nonlymphocytic leukemia was conducted. The cells were allowed to colonize on agar culture. In seven of 28 patients, the numbers of leukemic cell colonies were reduced to 21 percent of that of controls by the addition of ascorbate to the culture medium. Neither glutathione (similar oxidation-reduction potential as ascorbate) or HCl (added to cause a comparable pH reduction to ascorbic acid) resulted in a decrease in colonization. It was the researchers opinion that ..."suppression was a specific effect of L-ascorbic acid and was not due to its oxidation-reduction potential or pH change. Leukemic cells were selectively affected at an L-ascorbic acid concentration attainable *in vivo* while normal hemopoietic cells were not suppressed."[48]

Lung Cancer: Blood samples from 139 lung cancer patients were examined for both plasma and buffy coat ascorbate levels. Most samples showed hypovitaminosis C below the levels for clinical scurvy.[49] Other researchers found hypovitaminosis C in the majority of 24 lung cancer patients.[29] The First National Health and Nutrition Examination Survey related dietary habits with lung cancer risk. An estimate of dietary vitamin C intake by 24-hour recall was used. The amount of vitamin C in vitamins was estimated (i.e., guessed to be 60 mg in a multiple and 500 mg if taken as a sole supplement). The researchers found a protective effect of vitamin C (as well as vitamin E and carotenes) from dietary sources of these vitamins but reported no added benefit from vitamin supplementation.[50]

Non-Hodgkin's Lymphoma: An epidemiological study of factors contributing to non-Hodgkin's lymphoma (NHL) in men and women in Nebraska found a statistically significant inverse relationship between intakes of vitamin C, carotenes, green leafy vegetables and citrus fruits, and incidence of NHL.[51]

Pancreatic Cancer: A review of the epidemiological evidence of a dietary link to pancreatic cancer reported consistent inverse relationships between vitamin C and fiber, and the incidence of pancreatic cancer.[52]

Reticulum Cell Sarcoma: Cameron et al reported on a case of disseminated reticulum cell sarcoma successfully treated with high dose ascorbate. Within 10 days of beginning treatment the patient felt subjectively much better and subsequent chest x-rays indicated he had gone into remission. When ascorbic acid was discontinued, reactivation of the disease coincided. A second but slower complete remission occurred when vitamin C was reinstated.[53]

Salivary Cancer: A case-control study conducted in the San Francisco area examined dietary effects on incidence of salivary gland cancer. When 141 patients with salivary gland cancer were compared to 271 controls, it was determined that vitamin C intake of greater than 200 mg daily compared to 100 mg daily or less resulted in a 60 percent decrease in incidence of salivary gland cancer.[54]

Stomach/Gastrointestinal Cancer: There are normally high levels of ascorbic acid in the gastric mucosa and gastric juices, suggesting that vitamin C might play an important metabolic role in the stomach.[55] *Helicobacter pylori* has been implicated as a risk factor for gastric cancer. In a group of 88 dyspeptic patients, 58 tested positive for *H. pylori.* Gastric juice vitamin C levels were examined in these patients as well as in the *H. pylori*-negative patients. Gastric ascorbate levels were significantly lower in the *H. pylori*-positive group when compared both with the negative group and to themselves after eradication of the bacteria.[56]

Cohen and associates examined epidemiological studies and found 9 of 10 case-control studies and 10 of 11 non-controlled studies yielded a significant inverse relationship between ascorbic acid intake and stomach cancer risk.[57] Administration of vitamin C to patients with asymptomatic peptic ulcer disease resulted in a decrease in DNA damage in 28 of 43 subjects.[58]

Safety of Vitamin C

Due to the popularity of vitamin C as a nutritional supplement, a rash of potentially harmful side-effects have been reported, including: calcium oxalate kidney stones, B-12 destruction, iron overload, and elevated urinary uric acid. Although reports have been contradictory, an extensive literature search yielded a lack of support for these effects in healthy individuals.[59] Ingestion of large amounts of vitamin C results in only small increases in urinary oxalates[60] or urates.[61] Until more information is available it is probably prudent to avoid high doses of ascorbate in calcium oxalate stone formers, with patients on dialysis or with serious kidney disease,[1] and possibly in patients with hemochromatosis and other iron overload diseases.[3]

Cameron and Campbell reported on the catastrophic effect of vitamin C in a certain sub-population of terminal cancer patients. These patients suffered from widely disseminated metastasis and the administration of high doses of ascorbate provoked tumor hemorrhage and necrosis, resulting in the destruction of the tumor but the concomitant death of the patient.[13]

Recently, a team of researchers in England reported in a one-page scientific correspondence to the journal, *Nature*, that higher dosages of vitamin C (500 mg daily) could actually have a pro-oxidant, rather than an antioxidant effect by reacting with metal ions in DNA. They found that while the blood samples from patients supplemented with vitamin C showed antioxidant effects on guanine, the oxidation of another purine, adenine, seemed to be increased.[62] They concluded that vitamin C can be dangerous. Certainly vitamin C has the potential to produce free radicals in the form of ascorbyl radicals in the same way that vitamin E forms tocopheryl radicals. A symbiotic relationship occurs with each quenching the other's radicals. Thus, administration of high doses

of vitamin C may best be accompanied by vitamin E. In addition, the fact that adenine was oxidized may have nothing to do with the ascorbic acid and everything to do with the test procedures. Jenner et al, reported frequent artifactual oxidation of DNA bases unless specific precautions are taken.[63]

Conclusions

Vitamin C in high dosages appears to be safe for the majority of individuals. Extensive epidemiological evidence points to the capacity of ascorbic acid to prevent cancer at a number of sites. In addition, some of the limited studies which have been conducted on the use of high dose ascorbate in the treatment of cancer have yielded promising results. While vitamin C alone may not be enough of an intervention in the treatment of most active cancers, since it appears to improve quality of life and extend survival time, it should be considered as part of a treatment protocol for all patients with cancer, whether they have chosen a primarily orthodox, alternative medical, or complementary approach.

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