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The Role of Ascorbic Acid in the Prevention of Cancer

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Dietary antioxidants such as ascorbic acid (vitamin C), beta carotene and carotenoids, and the tocopherols and tocotrienols (vitamin E) are suggested as having protective roles against carcinogenesis. In additions, these agents are believed to provide antimicrobial defense, protection against radiation damage and photobiological effects, protection against age-related degeneration, and reduced risk of cardiovascular disease. However, there have been several conflicting reports of the efficacy of these antioxidants for cancer prevention. The American public seems confused about these scientific reports, amidst the claims of the media and the mass marketing of antioxidant nutrients. It has been established that oxidative and free radical damage to DNA and cell membranes are important factors in cancer initiation. Ascorbic acid is probably the most effective and least toxic antioxidant identified in mammalian systems (4). Direct experimental evidence clearly show the effectiveness of ascorbic acid as an antioxidant and scavenger of free radicals (3). Many epidemiological studies have demonstrated an inverse relationship between dietary ascorbic acid and cancers of the stomach, uterine cervix, and upper aerodigestive tract (6, 10, 9, 11, 3). The strongest evidence supports the role of ascorbic acid in prevention of stomach cancer, which has been demonstrated by intervention trials as well as epidemiological studies (7).

Oxidative damage can act at all levels of carcinogenesis: initiation, promotion, progression and metastasis. A side-effect of aerobic metabolism in cells is the production of reactive oxygen species which can damage DNA, proteins, carbohydrates, and lipids. The normal aerobic steady-state is characterized by a prooxidant-antioxidant balance. Oxidative stress occurs in cells in which there is a shift towards the prooxidant state. Reactive oxygen species result from the partial reduction of oxygen in oxidative phosphorylation. These species include the hydroxyl radical, hydrogen peroxide, superoxide and singlet oxygen. Other important oxidants are hypochlorite, nitric oxygen radical and peroxyxynitrite. The carcinogenic effects of these species are believed to involve altered gene expression, oxidation-reduction sensitive transcriptional factors, and direct DNA damage, all due to the free-radical attack of lipids, enzymes, proteins and DNA. Damage to DNA includes adducts, oxidative products and strand breaks (8). One important alteration is the formation of OH8 Gua which has been shown in E. Coli to induce GC to TA transversions (2).

It is therefore very important for aerobic organisms to have defense mechanisms against this oxidative damage. These defenses can be classified into prevention, interception, and repair (1). In general, repair of oxidative damage is achieved by enzymes, and is particularly important for repair of DNA damage before it becomes a fixed mutation. Several studies have demonstrated that antioxidative enzyme activity (e.g. catalase) is decreased in human gastric, colon and liver cancers (1). Interception of prooxidants is accomplished by chain-breaking antioxidants and by physical quenching of free radicals. These effects are carried out by non-enzymatic antioxidant systems such as vitamins and micronutrients.

Ascorbic acid is an effective water soluble, chain-breaking antioxidant. It efficiently scavenges superoxide, hydrogen peroxide, hypochlorite, the hydroxyl radical, peroxy radicals, and singlet oxygen. Ascorbic acid protects membranes against peroxidative damage by trapping peroxy radicals in the aqueous phase before they can initiate lipid peroxidation. It also has an indirect antioxidant action in that it can interact with the tocopherol radical to regenerate tocopherol (another powerful antioxidant) (4). Ascorbic acid can also spare the important antioxidant glutathione, as well as protect glutathione-deficient tissues against oxidation (2). In addition to antioxidant activity, ascorbic acid may also protect against carcinogenesis by enhancing and stimulating the immune response, involvement in collagen synthesis, and prevention of formation of carcinogenic N-nitroso compounds (6).

Given that the antioxidative properties of ascorbic acid are well established, an important question is then how the dietary intake is related to the prevention of certain cancers. There have been a large number of epidemiological studies on the association of dietary levels of ascorbic acid and the incidence of cancer. These studies strongly suggest that high intakes of foods rich in vitamin C (as well as vitamin E and beta carotene) reduce the risk of several, but not all, types of cancer (6, 10, 9, 11). Most of the studies assessed the intake by means of dietary questionnaires, from which the nutritional status of foods was then estimated. Some studies measured blood levels of ascorbate (9, 11). The accuracy of both these methods are limited: dietary records are often inaccurate, and the ascorbate content of many foods is difficult to estimate. Also, blood levels are not always an indication of ascorbate activity for a variety of reasons, including the fact that serum levels may differ from that of the organ of interest where cancer may occur (6). Perhaps the greatest difficulty of these studies is separating the effect of ascorbic acid from the effect of

other antioxidants (e.g. beta carotene and vitamin E) that are also present in the same foods, especially leafy green vegetables and fruits. Nevertheless, many of these studies have addressed these factors, and the findings have been relatively consistent. This, in addition to evidence of dose-responsive relationships and a sound biological explanation of the action of the antioxidant not only demonstrate an association, but also suggest a causal relationship. A recent review of epidemiological evidence shows that for upper aerodigestive tract cancers (oral cavity, pharynx and larynx), 4 of 5 studies demonstrate evidence of a protective effect of ascorbic acid. 4 of 5 studies demonstrated similar evidence for cancer of the uterine cervix (6). The strongest evidence is for its role in gastric cancer, in which 7 of 7 studies show evidence for a significant protective effect (9). One large study of over 12,000 men from 7 countries found a strong inverse relationship between the average intake of vitamin C and the 25-year stomach cancer mortality rate, after adjustments for smoking and intake of salt or nitrate (10). According to one review, there is little evidence of a protective effect of ascorbic acid for cancers of the colon, breast and prostate, and only weak evidence for lung cancer (6).

Relatively few intervention trials have been conducted that have studied the effect of antioxidants on the carcinogenic process. In general, these trials have demonstrated mixed results. Some of the problems of the earlier trials are that populations studied were high risk groups with a likelihood of cancer occurrence or recurrence. Yet it is now believed that antioxidants are most effective in the initiation or promotion stage rather than the progressive stage of carcinogenesis. Also, pathologic biomarkers and biomarkers of oxidative action were not understood, the studies have been too short, and the doses may have been inappropriate (8). One recent 4-year clinical trial involving 751 patients with previously diagnosed adenomas demonstrated no evidence that vitamins C, E or beta carotene reduced the incidence of adenomas (12). Yet this study also involved high risk patients in which the likelihood of the presence of small adenomas may have been higher, as well as the potential for developing the growth during the trial. Another experiment showed that even moderate dietary ascorbate (250 mg/day) can reduce endogenous oxidative DNA damage in human sperm. The group suggested that this could decrease the risk of genetic defects, especially in populations with low ascorbate such as smokers (1). The most compelling evidence from intervention trials, similar to the findings of epidemiological studies, is for the protection of ascorbic acid against gastric cancer. One such study measured the effect of gastric mucosal DNA damage using a ³²P postlabelling assay to detect DNA adducts. With vitamin C supplementation (1g/day) they found an overall reduction in adduct levels. They concluded that vitamin C administration may decrease the levels of gastric mucosal DNA damage. However, the role of DNA adducts in human carcinogenesis is poorly understood. This group also concluded that the effect of ascorbic acid on DNA adduction is least pronounced in those most at risk, i.e. with severe atrophic gastritis (7).

A hypothesis of the development of stomach cancer suggested by one group involves ascorbic acid as playing a pivotal role (3). This model describes a multistep and multifactorial process involving a number of precancerous lesions. One of these first steps is infection with the bacteria *Helicobacter pylori* (causing chronic gastritis) and excessive salt intake. This infection interferes with the normal secretion of ascorbic acid by the stomach, most likely compromising a major defense mechanism against oxidative stress. Because of the altered environment, carcinogenic N-nitroso compounds are synthesized, presumably due to the hyposecretion of acid and the abundance of nitrate reductases from the overgrowth of bacteria. The next steps are mutations of metaplastic epithelia, dysplastic epithelia, and then carcinoma (3). Ascorbic acid is normally able to block the formation and action of these N-nitroso compounds.

The majority of the data collected thus far from both epidemiological and intervention trials seem to implicate the action of ascorbic acid in preventing gastric carcinogenesis. In addition, there is a strong association between high levels of dietary intake of ascorbic acid and lower levels of other forms of cancer, particularly of the upper aerodigestive tract, and the uterine cervix. Although there have been no intervention trials that have demonstrated the role of ascorbic acid in these latter cancers, the epidemiological evidence has shown a strong association, consistency of results across studies, and evidence of dose-responsive relationships. The biological mechanism is also well understood of the antioxidant properties of ascorbic acid and how this prevents carcinogenesis. This evidence would suggest a causal relationship. Yet there needs to be more intervention trials to study the role of ascorbic acid in these other cancers. One reason why animal studies have not been widely conducted, presumably, is because most animals synthesize their own ascorbate (13). When conducting the intervention trials, the

appropriate population should be studied, since the majority of evidence points to the effect being at initiation and prevention, rather than progression, stages of the cancer. The intervention trials in the future should also address more dose-responsive effects.. The effective supplemental dose in most of these trials so far has been 1g/day, far greater than estimated 140mg/day of ascorbic acid that is necessary to saturate the total vitamin C pool in the body (4). In addition, the Recommended Dietary Allowance is only 60 mg/day. The effective antioxidant properties of ascorbic acid are at levels well above that needed to prevent deficiency, yet the exact levels need to be further studied. Nevertheless, there is evidence of many beneficial effects of ascorbic acid, not only in some cancers but in other health and age-related areas. Also, given its low toxicity, maintaining a high level of dietary intake and/or taking supplements seems to be a good recommendation.

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