
Benefits of Antioxidants: May Help Protect Against Cancer

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Epidemiological evidence shows that people who consume large amounts of fruits and vegetables have reduced risk of many types of cancer. Many researchers believe that antioxidant nutrients may be responsible for some of the protective effects of fruits and vegetables. Some studies have examined the specific role of supplements of antioxidant nutrients, with mixed results.

Over a decade ago, Dr. Gladys Block (then at the National Cancer Institute, now at the University of California at Berkeley) reported that 33 of 46 studies relating to nonhormone-dependent cancers found a significant protective effect of vitamin C. People with low vitamin C intakes had about twice the cancer risk, compared to people with higher intakes. The protective effects of vitamin C were seen against cancers at several sites, including the oral cavity, larynx, esophagus, lung, stomach, colon, rectum, and cervix. (Block 1991)

One group of researchers has pointed out that the potential effects of vitamin and mineral supplements on cancer risk are of special interest for several very practical reasons. (White 1997)

- “First, supplement use can lead to a higher intake of some nutrients than can be obtained from food,” which could produce a more detectable effect.
- Second, supplement use over time may be easier to assess than long-term food intake patterns, and it is the long-term pattern that is more likely to be a predictor of cancer risk.
- “Finally, if supplements prove to reduce cancer risk, increasing intake of micronutrients by use of vitamin supplements rather than food may be an attractive public health strategy. Community and worksite interventions to increase fruit and vegetable consumption have had only modest success. In contrast, large numbers of Americans are taking supplements, although supplement use has not been explicitly recommended by scientific or government agencies.”

Dr. Bruce Ames of the University of California at Berkeley has suggested that DNA damage resulting from micronutrient deficiencies is a major cause of cancer. “Micronutrient deficiency can mimic radiation (or chemicals) in damaging DNA by causing single- and double-strand breaks, or oxidative lesions, or both.” The key nutrients involved include folic acid, vitamins B-12 and B-6, vitamins C and E, iron, and zinc. “Optimizing micronutrient intake (through better diets, fortification of foods, or multivitamin-mineral pills) can have a major impact on public health at low cost.” (Ames 2001)

Key Scientific Studies

A recent review of research on nutritional supplements and cancer risk evaluated the results of seven clinical trials, 16 cohort studies, and 36 case-control studies. The cohort studies have not been positive. The randomized clinical trials have not shown any significant protective effect of beta-carotene, “but have found protective effects of: alpha-tocopherol [vitamin E] against prostate cancer; mixtures of retinol/zinc and beta-carotene/alpha-tocopherol/selenium against stomach cancer; and selenium against total, lung, and prostate cancers.” The case-control studies have reported apparently protective effects of vitamin C against bladder cancer, several supplemental vitamins against oral/pharyngeal cancer, and vitamin E against several cancers. “Overall, there is modest evidence for protective effects of nutrients from supplements against several cancers.” (Patterson 1997)

The World Cancer Research Fund and the American Institute for Cancer Research published a massive review of the evidence on nutrition and cancer prevention in 1997. In reviewing specific nutrient effects, they concluded that the evidence was “probable” that carotenoids play a role in reducing the risk of lung cancer and that vitamin C reduces the risk of stomach cancer. They also concluded that the evidence suggests a “possible” protective effect of carotenoids, vitamin C, vitamin E, and selenium on various cancers. (World Cancer Research Fund 1997)

In an epidemiologic follow-up study to the First National Health and Nutrition Examination Survey (NHANES I), involving 3968 men and 6100 women, researchers at the National Cancer Institute studied the relationship between lung cancer risk and the intake of vitamins C, E, and A. Those with the highest dietary intakes of vitamin C, vitamin A (as beta-carotene), and vitamin E had a reduced risk of lung cancer. People who had high intakes of all three antioxidant nutrients obtained the strongest protective effect, with a 68 percent reduction in risk. (Yong 1997)

In a review on prevention of gastrointestinal cancers, Dr. Elizabeth Fontham of the Louisiana State University Medical Center indicates that it is “abundantly clear” that generous intakes of fruits and vegetables have a protective effect. Studies based on blood levels of specific nutrients suggest that the protective effects may be related to dietary antioxidants such as vitamin C, beta-carotene, vitamin E and selenium. “The efficacy of vitamin/mineral supplements has not yet been established in clinical trials; however, in case-control and cohort studies the individuals in the highest level of intake of specific

micronutrients often combine high dietary intake with supplements. With the obvious caution to avoid excessive intake, a multivitamin/mineral supplement or specific antioxidant supplement may complement dietary intake, particularly among persons with excessive oxidative stress, such as smokers.” (Fontham 1997)

In the Health Professionals Followup Study, men who had higher dietary vitamin E intake or who used vitamin E supplements had a lower risk of bladder cancer over a 12-year period, and “taking vitamin E supplements for 10 or more years decreased risk by more than 30 percent.” (Michaud 2000)

In a retrospective case-control study in Washington state involving almost 450 colon cancer patients and a similar number of controls, the use of multivitamins and vitamin E supplements was associated with a reduced risk of colon cancer. “Men and women who used multivitamin supplements daily for the entire 10-year reference period had one-half the risk of colon cancer compared with those who never used multivitamins during this time period Those who averaged 200 IU or more of vitamin E per day over the 10 years had a 57% reduction in risk compared with non-users of vitamin E.” (White 1997)

Selenium is part of the antioxidant enzymes glutathione peroxidase and thioredoxin. A recent randomized controlled multicenter study showed a lower cancer incidence and lower cancer mortality in people who were given 200 µg of selenium for an average of 4.5 years. The participants were then followed up for an additional 6.4 years. The selenium group had a lower incidence of lung, colorectal, and prostate cancers. The reductions in cancer incidence and mortality in the selenium-treated group were significant enough that the trial was stopped early. (Clark 1996)

“Prostate cancer is a major public health problem in the developed world. It is the most common human cancer and the second leading cause of cancer deaths among North American men.” In 1999, it was estimated that about 180,000 new cases of prostate cancer were diagnosed and that almost 40,000 men died from it, in North America alone. There is evidence that oxidative damage may play a role in prostate cancer. In a Finnish study of vitamin E and beta-carotene, “there was a 32% reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality among the men who received supplementary vitamin E.” In the Health Professionals Followup Study, men with high selenium levels had only 35 percent as great a risk of prostate cancer as men with low selenium levels. And in a multiyear study of selenium and skin cancer, men who received a supplement of 200 µg of selenium showed “a 3- to 4-fold reduction in prostate cancer incidence.” Other studies suggest that men who eat a lot of tomatoes (rich in lycopene) may also have a lower risk of prostate cancer. The National Institutes of Health are currently funding a study on selenium, vitamin E and prostate cancer, called the SELECT study (Selenium Vitamin E Chemoprevention Trial), which will involve more than 30,000 men. (Fleshner 2001)

In a study involving over 10,000 men in Maryland, researchers examined the relationship between vitamin E, selenium, and prostate cancer risk. “The major form of vitamin E in supplements is alpha-tocopherol, whereas gamma-tocopherol is the main form in the diet

and is becoming increasingly important” as soy consumption increases. Soy oil has an 8:1 ratio of gamma-tocopherol to alpha-tocopherol. Men with the highest serum levels of gamma-tocopherol had a fivefold reduction in their risk of developing prostate cancer, compared to men with the lowest levels. Alpha-tocopherol and selenium had a protective effect only in men who had high levels of gamma-tocopherol. It is suggested that “consideration should be given to supplementation with combined alpha- and gamma-tocopherols in future prostate cancer prevention trials.” (Helzlsouer 2000)

For many years, it was believed that the nutrient most likely to protect against lung cancer was beta-carotene. This assumption was based on population studies showing lower cancer risk among smokers with higher blood levels of beta-carotene or higher dietary intakes, and on animal studies showing that beta-carotene lowers cancer incidence. In the 1980s, the National Cancer Institute initiated a number of large clinical trials in which beta-carotene supplements were given to test their effect on cancer and heart disease.

In the Alpha Tocopherol and Beta Carotene Study (ATBC), a large randomized controlled study in Finland, supported by the National Cancer Institute, beta-carotene and vitamin E were given to almost 30,000 long-term smokers for about six years and were ineffective in reducing the risk of lung cancer. In fact, there was a modest increase in lung cancer risk in smokers who took beta-carotene. The increase in risk was strongest in subjects who smoked at least 20 cigarettes daily and in those who drank the most alcohol. (Albanes 1996)

In the Carotenoid and Retinol Efficacy Trial (CARET) in the U.S., beta-carotene and high-dose vitamin A were given to a large group of smokers and asbestos workers, and were not effective in reducing the risk of lung cancer. In fact, smokers who took beta-carotene had a somewhat increased risk of lung cancer. (Omenn 1996)

In a third large trial, the Physicians’ Health Trial, more than 20,000 U.S. physicians were given 50 mg of beta-carotene every other day for a period of about 13 years. No benefit was observed against cancer or heart disease in this study. Neither were there any adverse effects. (Hennekens 1996)

These three studies raise a number of questions. Experts who have carefully reviewed the data are cautious about concluding that beta carotene may actually be harmful. Instead, they have urged consideration of several points (CARIG 1996):

- Beta carotene is believed to be protective against the very early stages of lung cancer development. Therefore, giving beta-carotene for only a few years to high-risk lifelong smokers and asbestos workers may have been too late for it to protect against lung cancer.
- Adverse effects in the ATBC trial were primarily seen in men with the greatest intake of alcohol. It is possible that an interaction of beta-carotene, smoking, and alcohol was responsible for the apparent adverse effects.

- Fruits and vegetables contain many carotenoids and other beneficial compounds. In retrospect, it may have been unrealistic to expect a single carotenoid to achieve protective effects on its own. Research should continue on a variety of carotenoids, including beta carotene.

While the debate over the implications of these trials continues, the subjects in the ATBC trial and the CARET trial will continue to be followed for another five to seven years. The Physicians' Health Trial is also being continued, with the addition of vitamin E and multivitamins, so additional data will be forthcoming from all of these sources.

Evaluation of Findings

Drs. Ruth Patterson, Alan Kristal and Marian Neuhouser of the Fred Hutchinson Cancer Research Center in Seattle, Washington, recently pointed out that one of the difficulties in assessing the relationship between nutritional supplements and cancer risk is that most studies have not collected detailed information on the longterm use of supplements. In many cases, participants are asked about supplement use at the beginning or end of a study and there is little probing of exactly what products were taken or whether they were taken throughout the relevant period. This lack of specificity may contribute to the inability to identify an association between supplement use and disease outcomes. Although much more research needs to be done, the researchers offer the recommendations shown below for the general population, based on current evidence. (Patterson 2001)

- The researchers conclude that beta carotene supplements confer no benefit for cancer prevention in the general population, and smokers should not take beta carotene supplements.
- Selenium supplementation would be premature on the basis of current evidence, but if people choose to use selenium supplements, the researchers recommend an organic form such as high-selenium brewer's yeast and a dosage level that does not exceed 200 µg per day.
- "Vitamin C supplementation may reduce the risk of some cancers, particularly those of the GI tract and the bladder." The authors suggest that the level of supplementation not exceed 500 mg per day.
- Vitamin E may reduce the risk of prostate cancer or colon cancer, and may also be protective against cardiovascular disease. The researchers recommend a level of vitamin E in the range of 200 to 400 mg per day.
- "There is some modest evidence that calcium supplements may reduce risk of colon cancer. Given the much stronger evidence that this supplement can prevent osteoporosis, use of calcium supplements in the range of 500-1000 mg/d may be prudent for many Americans."
- There is little evidence on other vitamins and minerals in relation to cancer risk.
- A daily multivitamin and mineral may be beneficial and is unlikely to be harmful.
- Supplements should be understood literally for what they are—supplements and not replacements for a healthy diet.

Bottom Line

There is suggestive evidence of a relationship between some nutrients and the risk of cancer. Because much of the evidence is epidemiologic, it is difficult to pinpoint the exact nutrients that may be responsible for the benefit of certain dietary patterns. Research is continuing, and some scientists believe supplementation with some nutrients may be rational, even while study continues.

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