Over the past 25 years, epidemiological studies have demonstrated diminished risk of chronic disease with diets high in fruits and vegetables. It has been hypothesized that antioxidants found in large quantities in fruits and vegetables may be responsible for this protective effect. Antioxidants may modify risk of chronic disease by reducing oxidative stress generated from free radical formation.

The first article of this series defined free radicals, phytochemicals and antioxidants, and the second article reviewed the research regarding antioxidants and cardiovascular disease. Now, we will consider the research evaluating antioxidants and cancer.

**Free Radicals and Cancer Development**

Excess free radical production has been implicated in several types of cancer. Many theories have been postulated to specify the mechanisms involved. Radicals generated close to DNA may lead to attacks on purines and pyrimidines, which can lead to mutations and eventual cancer. DNA undergoes continual "oxidative damage," requiring repeated corrections.

Damage that is not corrected can eventually lead to cell destruction. Free radicals appear to be involved in both cancer initiation and tumor promotion. Progression of cancer and radiation/chemotherapy side effects have also been associated with reactive oxygen species.

**Antioxidants and Cancer Prevention**

In addition to preventing the damage caused by free radicals (described in Part 1 of this series), antioxidants may also inhibit carcinogenesis by blocking nitrosation, a chemical reaction that forms carcinogens in the body. Antioxidants may suppress carcinogen-induced regulatory proteins and stop the cell division of cancerous growths.

Ascorbic acid has probable additional anti-carcinogenic effects by preventing procarcinogens from converting to carcinogens. Carotenoids may also have anti-carcinogenic effects, which include prevention of DNA damage by free radicals and interference with the metabolic activation of chemical carcinogens.

Lycopene, an open-chain analog of b-carotene, is also a potent free radical scavenger and may protect against cancer. Flavonoids such as catechins and theaflavins, found in green and black tea, may have anti-tumor activity. As mentioned in Part 1 of this series, there are non-antioxidant phytochemicals that may also aid in reducing cancer risk. Sulfur-containing chemicals, found in cruciferous vegetables, may up-regulate enzymes involved in the detoxification of carcinogens; lignans have anti-cancer and phytoestrogen properties and probably have a protective effect against hormone-sensitive cancers.

Whenever free radical development...
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Lung Cancer
Smokers are often used in supplement studies because of their willingness to expose themselves to high levels of free radicals and known carcinogens. Smokers are ideal subjects for some scientists because it is assumed that they will eventually have some type of smoking-initiated cellular damage or cancer development. Fruit and vegetable consumption is associated with a lower risk of lung cancer among those who never smoked, and in some studies, a reduced cancer rate in smokers as well.

Heinonen, et al., conducted a randomized, double-blind, placebo-controlled trial using 29,133 male smokers, aged 50 to 69 years old. The subjects, part of the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, had a daily supplement intake of 50mg a-tocopherol, 20mg b-carotene or a placebo for five to eight years. No changes in lung cancer rates were observed in the tocopherol group. However, the carotene group actually had higher rates of lung cancer. The tocopherol group did show fewer cases of prostate cancer, but it had higher rates of hemorrhagic stroke.

The Finnish Alpha-Tocopherol, Beta Caroten Cancer Prevention Study also followed male smokers on supplements for six years. Results were similar in that the supplements did not seem to help prevent lung cancer, and the b-carotene subjects also had significantly more new lung cancer cases. The trend toward increased cancer with b-carotene supplementation in high-risk subjects was also observed in the Beta-Carotene and Retinol Efficacy Trial.

Data such as these have led some scientists to hypothesize that there are times when b-carotene may act as a pro-oxidant. It is important to note that these three studies provided significantly lower amounts of supplemental b-carotene than would normally be found in the diet from foods.

Although supplements do not seem to protect smokers from lung cancer, it does seem prudent to recommend to your patients an increase in fruit and vegetable consumption if they will not stop using tobacco.

Using data from the National Health and Nutrition Examination III, Wei, et al., categorized 7,873 seemingly healthy adults as smokers or nonsmokers using serum cotinine (a nicotine metabolite) levels. The subjects had completed 24-hour dietary recalls and data on vitamin C, vitamin E, b-carotene and selenium were collected.

Smokers had lower dietary intakes of vitamin C and b-carotene. In addition, the smokers had lower serum vitamin C and b-carotene levels independent of diet, an effect that was thought to be due to the effects of smoking. Smokers appear to have increased antioxidant needs and diets with inadequate antioxidant levels.

Breast Cancer
In a 14-year prospective study of 83,234 women who were 33-60 years old at the start, Zhang, et al., identified 2,697 cases of invasive breast cancer as part of the Nurse's Health Study. During this time, diet and supplement intake was monitored frequently and adjustments were made for age, length of follow-up, total energy intake, parity, age at first birth, age at menarche, family history of breast cancer, alcohol intake, BMI at 18 years and height.

After controlling for confounding variables, the researchers found that intakes of b-carotene from food and supplements, lutein/zeaxanthin (carotenoids), and vitamin A from foods were weakly inversely associated with breast cancer risk in those with a family history...
or those who consumed 15 grams or more alcohol per day. There were no associations between breast cancer risk and these substances in normal healthy women. In addition, this study showed that pre-menopausal women who consumed five or more servings of fruits and vegetables had modestly lower risk of breast cancer than those who had less than two servings daily.

Colorectal Cancer

The data linking reduced risk of colorectal cancer with increased antioxidant consumption is inconclusive. There have been several epidemiological studies that have shown a protective effect of a diet high in fruits and vegetables but almost an equal amount of studies that have been conducted show no benefit to colorectal cancer.

Breuer-Katschinski, et al., compared 105 cases of colorectal adenoma to two different control groups. One control group was chosen randomly from the population, and one was a matched hospital control group. These were individuals that had similar symptoms to the cancer group but had no cancer on further investigation. Lifestyle and dietary habits were obtained from all groups as well as serum levels of vitamins A, C, E and carotene. Only the serum vitamin A was significantly inversely related to colorectal adenoma. This significance was more pronounced when lifestyle confounders were controlled for.

The researchers speculated that variability of serum vitamin A regulation could explain its differences between groups. There were not any significant associations with serum concentrations of vitamins C and E or carotene in this study.

Michel, et al., also did not observe a relationship between fruit and vegetable consumption and colon or rectal cancer rate after controlling for other lifestyle factors. They monitored 88,764 women (Nurses Health Study) and 47,325 men (Health Professionals Follow Up Study) for over a decade. Use of vitamin supplements in this study also was not related to colon or rectal cancer development. The researchers did state, in their review of the data, that a diet high in fruits and vegetables is advisable because of its protective effect on other cancers.

Prostate Cancer

Lycopene is a carotenoid with potent antioxidant properties and is found in high concentrations in tomato products. In a thorough scrutiny of the epidemiological studies of lycopene and cancer, Sanjiv and Rao reviewed 72 studies and found that 57 of these studies showed an inverse relationship between tomato and lycopene intake and risk of many types of cancer.

Thirty-five of these showed a statistically significant inverse relationship. This relationship seems to be most pronounced for prostate and breast cancer. Bioavailability of lycopene is high in processed tomato products and significantly higher when ingested with b-carotene. Because lycopene cannot be converted to vitamin A in the body, it is not considered a nutrient.

The Harvard-based Health Professionals’ Cohort Study demonstrated an inverse association between selenium intake and prostate cancer. Those who had the lowest intakes of selenium had three times the likelihood of developing advanced prostate cancer as those who had the highest intakes. Selenium is a mineral that is a cofactor for glutathione peroxidase, an enzyme that fights free radicals.

Inadequate mineral intake, especially those that are cofactors for the antioxidant enzymes, will result in substandard enzymatic antioxidant defenses. A selenium intake of 55 µg/day is associated with the highest activity of glutathione peroxidase, yet many cancer studies failed to evaluate selenium status. There have been several epidemiological studies that have demonstrated an inverse relationship between selenium intake and cancer mortality.

Summary

It is difficult to make any type of recommendations for encouraging antioxidant supplementation to reduce cancer risk as it appears to be an efficacious approach to minimizing cancer. The reduced risk of cancer observed with increased fruit and vegetable intake could be due to factors other than antioxidant nutrients, such as flavonoids or folic acid.

In its 2000 report on dietary antioxidants and related compounds, the Panel on Dietary Antioxidants and Related Compounds, National Academy of Sciences, emphasized that foods are the preferred sources for nutrients. In addition, a study that appeared in the Journal of the American Medical Association in 2000 showed that those that consumed a balanced diet, based on current dietary guidelines, had lower all-cause mortality without needing supplements. It is probable that the phytochemicals in fruits and vegetables exert a synergistic effect, making food much more healthful than the sum of its individual nutrients.

In an article published in the Journal of the National Cancer Institute, Tom Reynolds summed this data up perfectly when he wrote, “The April 2000 report (National Academy of Sciences’ Institute of Medicine) highlights the chasm of uncertainty between the laboratory and epidemiological evidence suggesting of the benefits of antioxidants on one hand, and the lack of a scientific bases for specific recommendations on the other. So the most consistent advice remains: Eat fruits and vegetables.”

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