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Studies Explore How Antioxidants Prevent DNA Damage, Breast Cancer Metastasis

Two recent studies offer new insights into how antioxidant nutrients prevent cancer-causing DNA (genetic) damage and might even slow the metastasis of existing cancers.

Cancers are distinguished from other tumors by their ability to infiltrate organs, and metastasis refers to the process of how cancerous cells detach from tumors, spread through the bloodstream, and seed new tumors.

Researchers generally believe that most cancers arise from DNA damage caused by free radicals. Each of the 60 trillion cells in the body suffers an estimated 10,000 free radical "hits" daily, but repair mechanisms routinely cleave, or cut away, the damaged sections of DNA. Because the repair mechanisms are not perfect, some DNA damage does not get repaired.

In a study at the Rowett Research Institute, Aberdeen, Scotland, researchers led by Susan J. Duthie, PhD, studied how antioxidant supplements reduced DNA damage in the white blood cells of about 100 smoking and nonsmoking men. About half of the smokers and nonsmokers received daily supplements of 100 mg vitamin C, 280 mg of vitamin E, and 25 mg of beta-carotene for 20 weeks.

Duthie's study had two specific objectives: one, to look for correlations between dietary levels of antioxidants and DNA damage in white blood cells and, two, to determine whether antioxidant supplements could reduce DNA damage.

The effect of antioxidants was measured by counting DNA breaks in samples of white blood cells from all the subjects. Duthie reported in *Cancer Research* (March 15, 1996;56:1291-5) that supplemented smokers and nonsmokers had about one-third fewer DNA breaks than unsupplemented subjects. Furthermore, white blood cells from supplemented subjects were more resistant to free radical damage.

In the other study, Donald C. Malins, PhD, of the Pacific Northwest Research Foundation, Seattle, found that free radical damage promoted the metastasis of breast cancer cells. "Oxidative stress has been implicated as an important factor in metastasis, notably because it results in a loss of cell adhesion which is the prerequisite for cellular detachment and host tissue invasion," Malins and his colleages wrote in the *Proceedings of the National Academy of Sciences of the USA* (March 1996;93:2557-63).

Malins found that the DNA of metastatic cells had twice the free radical damage of nonmetastatic cells. Free radicals are known to cause DNA mutations and, accordingly, the DNA of the metastatic cells had far greater genetic diversity than that of the nonmetastatic cells. In effect, the larger number of DNA mutations favored the creation of metastatic cells.

Surprisingly, most of the free radicals and resulting DNA damage appeared to be created by the cancer cells themselves. The cells produced unusually large amounts of hydrogen peroxide, which breaks down and releases powerful hydroxyl radicals. Malins wrote "that the type of radical reactions previously shown to be associated with DNA damage and cancer would, once a tumor develops, impose additional damage that gives rise to the unique properties associated with metastatic cell[s]..."

Natural Beta-Carotene Looks Good. Could Synthetic Be the Problem?

Smokers who took beta-carotene supplements in recent experiments may have faced a greater risk of lung cancer because they took the *synthetic* form of the nutrient, a new study suggests. The subtle differences between synthetic and natural beta-carotene do appear to influence how the body uses the nutrient.

Synthetic beta-carotene consists of just the "all-trans" isomer of the nutrient, whereas natural beta-carotene consists of two different isomers, "9-cis" and "all-trans." Isomers have the same molecular formula, but a different arrangement of atoms. They're a little like anagrams, in which the letters of one word can be rearranged to form another, such as "star" and "rats."

It turns out that the natural 9-cis isomer is a more potent antioxidant than the all-trans, according to Ami Ben-Amotz, PhD, and Yishai Levy, MD, in the *American Journal of Clinical Nutrition* (May 1996;63:729-34). And the 9-cis isomer is found only in natural beta-carotene.

"I do believe that the results of the CARET study and the other large-scale epidemiological studies could be much different if the researchers had used a natural source of beta-carotene," Ben-Amotz told THE NUTRITION

Continues on next page

REPORTER. "Supplementing with the synthetic product, all-trans beta-carotene, led to the negative results." (The CARET study, announced in January, found that long-term smokers had a slightly increased risk of developing lung cancer when taking synthetic beta-carotene.)

In experiments at Israel's National Institute of Oceanography, Ben-Amotz and Levy gave young, healthy men supplements of either natural beta-carotene from *Dunaliella* algae or synthetic beta-carotene. Blood analyses showed the presence of the all-trans isomer of beta-carotene, but not the 9-cis form found in natural beta-carotene. However, the researchers looked for—and found—9-cis metabolic byproducts, indicating the presence and activity of the natural isomer.

Ben-Amotz and Levy reported that that the natural 9-cis isomer was rapidly used up in quenching free radicals and preventing oxidative damage to essential cell fats. In contrast, much of the all-trans isomer was converted to vitamin A, which is at best a very weak antioxidant.

"However, the most important issue is that at elevated doses of over 5 mg beta-carotene / day, the all-trans beta-carotene [synthetic] acts as a pro-oxidant, while the 9-cis beta-carotene and probably other natural carotenoids function as antioxidants," Ben-Amotz explained to THE NUTRITION REPORTER.

Ben-Amotz and Levy wrote in their article that the differences between natural and synthetic beta-carotene "should provoke a shift in scientific attention to natural sources of carotenoids and their role in cancer prevention." They urged that researchers pay more attention to the different isomers of beta-carotene.

An earlier study, in *Free Radical Biology & Medicine* (1994;17:77-82) also showed that the natural 9-cis isomer is a more potent antioxidant than the all-trans form.

Other researchers have also had difficulty measuring the 9-cis isomer in the blood. The reason might be that the natural 9-cis isomer moves from the blood to the tissues extremely rapidly, according to an unpublished study by Elizabeth Johnson, PhD, Norman I. Krinsky, PhD, and Robert M. Russell, MD, of the USDA Human Nutrition Research Center at Tufts University. After giving 9-cis beta-carotene to two lactating women, the researchers found that 9-cis blood levels were erratic, but 9-cis levels rose consistently in their breast milk. □

Zinc Lozenges Ease Cold Symptoms

Just in time for the next cold season, researchers have confirmed that zinc lozenges can reduce the symptoms and length of the common cold.

Physicians at the prestigious Cleveland Clinic used 99 clinic employees as their subjects. Forty-nine received lozenges containing 13.3 mg of zinc gluconate-glycine, and 50 received look-alike lozenges without the mineral. All of the participants joined the study within 24 hours of developing cold symptoms, and they were instructed to take one lozenge every two waking hours.

People taking the zinc lozenges had significantly shorter colds compared to those taking the dummy lozenges—an average of 4.4 versus 7.6 days, according to a report on the study in the *Annals of Internal Medicine* (July 15, 1996;125:81-8). They also had substantially fewer days with coughing, headache, hoarseness, nasal congestion and drainage, and sore throat. Both groups, however, suffered from fever, muscle aches, and sneezing for about the same amount of time.

"Our study showed that the time to resolution of all symptoms was significantly shorter in the zinc group," wrote lead investigator Michael L. Macknin, MD.

Although Macknin did not investigate why the zinc reduced cold symptoms, he did offer several possible reasons. Zinc prevents the replication of several viruses, including the rhinovirus that causes colds. Zinc might also stabilize cell membranes and promote the body's production of interferon, an anti-viral substance.

Editor's note: THE NUTRITION REPORTER™ recommends two brands of zinc lozenges. One is Cold-Eeze™, the brand used in this study. It's available from the Quigley Corp., of Doylestown, Pa., at 1-800-505-COLD. We also recommend Fast Dry™ Lozenges, marketed by George Eby of Austin, Tx. Eby and his daughter were the first to recognize the benefits of zinc lozenges back in the late 1970s. He can be reached at (512) 442-2933 (8 a.m.-5 p.m. central time zone, USA). □

Zinc Can Improve Taste Sensation

Older people often complain that they've lost the ability to taste food. In fact, an estimated two million Americans suffer from taste and smell disorders. However, relatively few studies have explored why, because the condition is not considered serious.

Zinc has long been reputed to enhance the sense of taste, and in a brief article Catherine A. Heyneman, PharmD, of Idaho State University, reviewed the evidence showing that zinc supplements improve the sense of taste.

Although some of the research cited was inconclusive, zinc supplements did tend to improve the sense of taste in people who were deficient in the mineral, according to Heyneman's article in the *Annals of Pharmacology* (Feb 1996;30:186-7). Daily dosage ranging from 25 to 100 mg improved taste, and the improvement occurred within several months. (Note: high doses of zinc can cause nausea.)

In one study, 82 percent of the people taking zinc supplements improved while 54 percent of those taking dummy pills lost some taste sensation—although both groups were eating zinc-rich foods. □

Free Radicals Age Brain Cells, But Some Go Faster than Others

Free radicals damage and age brain cells, but some regions of the brain seem to age faster than others. That might explain why some people lose their thinking abilities while others lose their physical motor skills, according to Rajindar S. Sohal, PhD, of Southerm Methodist University, Dallas.

Sohal and his colleagues studied the relationship between free radical damage in certain regions of the brain and how they affected the thinking and motor skills of old and young mice. Free radical, or oxidative, damage is considered a major cause of Alzheimer's disease and other age-related brain disorders. One reason is that large numbers of free radicals are generated by brain cells, but these cells do not possess a high level of antioxidant defenses to compensate.

Sohal correlated free radical damage in specific regions of the brain and a loss of the functions controlled by those regions. For example, older mice with extensive free radical damage in the brain's cortex lost cognitive skills and were less able to complete maze tasks. Similarly, mice with free radical damage in the cerebellum suffered a loss of physical coordination. □

Vitamin E = Longer Life Expectancy

Two recent reports add to the evidence that vitamin E slows the aging process and extends lifespan.

Marguerite M. B. Kay, MD, of the University of Arizona School of Medicine, found that large doses of vitamin E dramatically slowed the aging of brain and immune system cells in mice. Her study has direct relevance to people because the mechanism would apply to cells in all mammals.

Kay focused on "band 3" proteins, which are essential for transporting nutrients into cells. Band 3 proteins stop functioning when they are repeatedly attacked and damaged by free radicals. Kay studied brain and immune cells because they influence all other organs in the body and are "most affected by aging," she wrote in the *Proceedings of the National Academy of Sciences of the USA* (May 1996;93:5600-5603.)

The mice were given the human equivalent of 400 IU of vitamin E daily. Kay confirmed that the breakdown of band 3 proteins precipitated age-related declines in brain and immune cell performance—and that the vitamin "delayed or prevented" this decline.

In another study, Katalin G. Losonczy, a doctoral student and an epidemiologist at the National Institute on Aging (National Institutes of Health), analyzed the lifestyle and vitamin supplement habits and causes of death among 11,178 people ages 67-105. Study participants were interviewed each year for six years, and mortality data was obtained for another two to three years.

People who were long-term users of vitamin E supplements were 60 percent less likely to die of coronary heart disease and 59 percent less likely to die of cancer than people who did not take the vitamin, according to Losonczy's artcle in the *American Journal of Clinical Nutrition* (Aug 1996;64:190-6). They were also 29 percent less likely to die at any given age than people who did not take vitamin E.

Short-term users of vitamin E and people who took both vitamins E and C also were less likely to die of coronary heart disease or cancer, but their life expectancy was not as good as those taking just vitamin E. □

More Research: Folic Acid Protects Against Coronary Heart Disease

Another study in the *Journal of the American Medical Association* has tightened the link between low folic acid, a B vitamin, and increased risk of coronary heart disease. (See the Nov 1995 issue of THE NUTRITION REPORTER.)

Howard I. Morrison, MD, of Health Canada, the Canadian government's public health agency, analyzed blood levels of folic acid among 5,056 men and women between the ages of 35 and 79. People with the lowest blood levels of folic acid were 69 percent more likely to die of coronary heart disease, according to Morrison's article in *JAMA* (June 26, 1996;275:1893-6).

Low folic acid levels allow homocysteine to accumulate and attack blood vessel walls. But "normal" levels, it turns out, may be no better than low ones.

"Increased risks were not restricted to individuals with extremely low serum folate levels, but were observed for individuals with normal levels as well, suggesting that current definitions of appropriate serum folate levels be reassessed," Morrison wrote.

He added that "roughly one half of US adults on a given day consume less than the newly lowered recommended dietary allowance for folate [200 mcg/d for men and 180 mcg/d for women], and an estimated 88% consume less than the levels needed to produce low, stable homocysteine levels."

In a related editorial in *JAMA* (275:1929-30), Meir J. Stampfer, MD, and Eric B. Rimm, ScD, urged that human trials with folic acid begin immediately. "Because there is little commercial interest and incentive to test such an inexpensive and nonpatentable intervention as folate...the National Institutes of Health must step in to serve the public's interest to fund such trials. Further delays cannot be justified."

In the *Journal of Nutrition* (March 1996;126:751S-5S), a team of researchers from the Centers for Disease Control and Prevention (CDC) urged that dietary folic acid levels

Continues on bottom of page 4

Quick Reviews of Recent Research

• Beta-Carotene protects against sunburn

Researchers compared the protection afforded by topical sunscreens and a combination of topical sunscreens and oral beta-carotene supplements in 20 young women. The women took 30 mg of beta-carotene daily for 10 weeks. By measuring skin redness and inflammation, the researchers concluded that pre-supplementation with beta-carotene and the use of topical sunscreens was much more protective against sunburn than sunscreens alone.

Gollnick HPM, et al.,*European Journal of Dermatology*, 1996;6:200-5.

• Vitamin C in critically ill patients

Researchers at the University of Leeds, England found that blood levels of vitamin C in critically ill patients averaged less than one-fourth those of healthy subjects. These patients were in hospital intensive care units for a variety of reasons, such as accidental injury, surgery, sepsis, and major-organ failure. The researchers wrote that the antioxidant defenses of these patients were seriously compromised and that their recovery could be impaired by their low vitamin C levels.

Schorah CJ, et al., *American Journal of Clinical Nutrition*, 1996;63:760-5.

• Lead levels and juvenile delinquency

Lead poisoning affects learning and has also been associated with aggressive and difficult-to-manage children. In a study of 301 students, researchers compared teachers' records of behavior to the students' bone levels of lead. There were significant associations with complaints of physical illness, anxiety, depression, social problems, aggressive, and delinquent behavior.

Needleman HL, et al., *JAMA*, 1996;275:363-9.

• Genistein levels in Japanese and American diets

In an analysis of genistein levels in foods, researchers from Japan's National Cancer Center Research Institute found that levels of this isoflavone were higher in fermented soy products, such as soy milk and tofu, than in unfermented products. It is possible that bacterial action during fermentation cleaves (separates) genistein from the larger genistin molecule. Based on food data, individual Japanese consume a range of 1.5-4.1 mg of genistein daily, far more than does the typical American. Higher Japanese consumption of genistein may explain their lower incidence of breast and prostate cancers. Fukutake M, et al., *Food and Chemical Toxicology*, 1996;34:457-61.

• Genistein protects DNA from free radical damage

Free radicals generated from exposure to ultraviolet light and hydrogen peroxide cause oxidative damage to DNA, an early step in the development of many cancers. In experiments, researchers found that genistein significantly inhibited oxidative damage to DNA from ultraviolet light and hydrogen peroxide. The researchers wrote, "The potent inhibition of UV light-induced oxidative DNA damage by genistein suggests its potential anticarcinogenic role in photocarcinogenesis." Wei H, et al., *Carcinogenesis*, 1996;17:73-7.

• More antioxidants better than fewer

In a study of free radicals and antioxidants in the kidney cells of rats, researchers compared the benefits of nine antioxidants to only one or two. Some of the rats were fed diets with vitamin C, acetyl-cysteine, beta-carotene, coenzyme Q10, catechins (a class of flavonoid found in tea), and other antioxidants. Meanwhile, other mice were given either individual antioxidants or a combination of vitamin E and selenium. The researchers found that "increasing the diversity and quantity of antioxidants in the diet provides significantly more protection" against free radical damage.

Knudsen CA, et al., *Free Radical Medicine & Biology*, 1996;20:165-73.

• Ginger inhibits tumor promotion

Ginger is known to have antioxidant and anti-inflammatory properties. Topical application of the spice ginger resulted in significantly fewer skin cancers in mice, compared with mice not given ginger, after they were exposed to a cancer-causing chemical.

Katiyar SK, et al., *Cancer Research*, 1996;56:1023-30.

Folic Acid and Heart Disease...

Continued from page 3

be increased through food fortification. The CDC researchers noted that folic acid was safe, but that anyone with concerns about high levels should also take supplemental vitamin B12.

And most recently, Norman R. C. Campbell, MD, noted in *Archives of Internal Medicine* (Aug 12/26, 1996;156: 1638-44) that folic acid side effects are unlikely (even without B12) as long as people take less than 5 mg (5,000 mcg) daily. □

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