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Alcohol, Synthetic Beta-Carotene, and Hasty Conclusions May Have Made for Study Fiasco

In a re-analysis of two studies showing that beta-carotene increased the risk of lung cancer among smokers, researchers have found that alcohol consumption contributed significantly to the disease process. They also confirmed that former smokers *did* benefit from beta-carotene supplements.

However, the two research teams still failed to adequately address some significant inherent defects in the design and execution of their studies.

Gilbert S. Omenn, MD, of the Fred Hutchinson Cancer Center, Seattle, reported in the *Journal of the National Cancer Institute* (Nov 6, 1996;88:1550-1559) that current, long-term smokers in the Beta-Carotene and Retinol Efficacy Trial (CARET) had a 36 percent greater risk of developing lung cancer when they took a combination of 30 mg of beta-carotene and 25,000 IU of vitamin A daily.

Having three or more alcoholic drinks daily actually doubled the risk of lung cancer compared with smokers who did not take the supplements or drink alcohol.

Meanwhile, *former* smokers taking beta-carotene and vitamin A in the CARET study benefited from a 20 percent decrease in their risk of lung cancer.

Omenn's latest paper contrasted with a reanalysis of the Alpha-Tocopherol Beta-Carotene (ATBC) study, originally published in 1994. When Finnish doctors took another look at ATBC data, they found that subjects taking beta-carotene had a 16 percent increased risk of lung cancer, according to an article in the same issue of *JNCI* (1996;88:1560-1570.

Although the percentage might seem significant, it is generally considered statistically insignificant and would account for less than one new case of cancer in every thousand people. (It's considered statistically insignificant because the increase in cancer deaths was a mathematical extrapolation of cancers in "person-years," not an increase in real cancers.)

The Finnish researchers also determined that smokers consuming about one alcoholic drink daily increased the risk of lung cancer by 35 percent.

But significantly, the researchers found that beta-carotene did *not* increase the risk of lung cancer among people who smoked less than a pack of cigarettes a day and drank little or no alcohol. (The "relative risk" with beta-carotene was 1.03.)

Why did smokers in the CARET study suffer a higher risk of lung cancer compared with people in the ATBC trial? It's possible that the combination of beta-carotene and vitamin A resulted in an overdose of vitamin A. Indeed, some studies have found that a combination of high alcohol and vitamin A can cause liver damage and alter cell behavior. (See Bland J, *Journal of Applied Nutrition*, 1996;48:42-45.)

If that's the case, both studies may have even gotten off to a bad start when researchers decided to use synthetic beta-carotene, which consists of only the all-trans isomer of beta-carotene. In contrast, natural beta-carotene supplements from *Dunaliella* algae are roughly 50:50 all-trans and 9-cis isomers. (Isomers refer to different molecular arrangements of the same compound.)

A recent study by Ami Ben-Amotz, PhD, of Israel's National Institute of Oceanography, suggeted that the natural 9-cis isomer was the more potent antioxidant. He also found that as much as 70 percent of the all-trans isomer is converted to vitamin A. (*American Journal of Clinical Nutrition*, 1996;63:729-34.) That means CARET subjects may have received as much as 60,000 IU of vitamin A daily—an extremely high and potentially dangerous dose.

In his *JNCI* article, Omenn dismissed the differences between synthetic and natural beta-carotene. He stated that while natural beta-carotene supplements contain both the all-trans and 9-cis isomers, the isomers in human circulation are like those from synthethic beta-carotene.

But, in recent experiments, Elizabeth Johnson, PhD, of Tufts University, showed that levels of both the 9-cis and all-trans isomers increased significantly after supplementation with *Dunaliella* algae. (USDA Agricultural Research Service Report No. 37595, 1996.)

Finally, as if to dig in his heels, Omenn has warned that people should not take beta-carotene. He has asked the Food and Drug Administration to re-classify beta-carotene as a carcinogen. (See *Council for Responsible Nutrition News*, July 1996:8.)

But in doing so, Omenn continued to brush aside a salient point in his own research. Although the synthetic all-trans isomer may have limitations or disadvantages, it still reduced the risk of lung cancer in ex-smokers by 20 percent. Beta-carotene still has benefits—but you have to stop smoking and drinking first. □

Research summaries continue on next page

Selenium a Magic Bullet for Cancer Prevention?

Supplementation with a modest 200 mcg of selenium daily reduced the overall risk of cancer by 37 percent and cancer deaths by 50 percent, according to a study published in the *Journal of the American Medical Association* (Dec 25, 1996;276:1957-63).

Half of the 1,312 people in the double-blind study received selenium supplements for an average of 4.5 years, with medical follow up for another 6.4 years. The other half received a placebo. All of the patients had previously been diagnosed with a type of skin cancer.

Larry C. Clark, MPH, PhD, director of epidemiology at the University of Arizona Cancer Center, Tucson, had hoped that the selenium would reduce the incidence of new skin cancers.

While the essential mineral did not protect against skin cancer, its protective role in other cancers was nothing short of dramatic. Patients taking selenium had a 63 percent lower risk prostate cancer, 58 percent lower risk of colorectal cancer, and a 46 percent lower risk of lung cancer.

Patients in the study were recruited from the eastern coastal plains of the United States, where soil and crop levels of selenium are low. Clark noted that such people typically have a higher than average risk of developing cancer.

Selenium is essential for the body's production of glutathione peroxidase, a powerful antioxidant. No cases of selenium toxicity were observed, Clark wrote. □

Citrus Juices, Flavonoids Slow Growth of Breast Cancer Cells

Fresh fruit juices have long been used as an alternative treatment for cancer, and a recent series of experiments suggests that they might have some value.

Kenneth K. Carroll, PhD, a biochemist at the University of Western Ontario, London, Canada, recently investigated the effect of orange and grapefruit juices—and some of the nutritional flavonoids they contain—on breast cancer. The experiments involved either laboratory animals or cell cultures.

Large amounts of orange and grapefuit juice slowed the development of breast cancer in rats exposed to a cancer-causing chemical. In a related experiment, Carroll gave rats the flavonoids naringin or naringenin in amounts comparable to those in grapefruit juice. These citrus flavonoids also slowed the development of breast cancers. Orange juice, containing the flavonoid hesperetin, had a similar effect, according to Carroll's article in *Nutrition and Cancer* (1996;26:167-181.)

In cell-culture experiments with human breast cancer cells, Carroll found that hesperetin and naringenin inhibited the proliferation of breast cancer cells. Furthermore, when each of the citrus flavonoids were combined with quercetin, "they suppressed the proliferation of the cells at much lower concentrations than either compound alone." □

Antioxidant Glutathione Also of Value in Cancer Prevention

Glutathione, a powerful antioxidant produced by the body and found in foods, can prevent cancer by normalizing gene function and blocking angiogenesis. Angiogenesis refers to the growth of blood vessels created by tumors and needed for their expansion.

That's the finding of a recent animal study by Joel L. Schwartz, DDS, of the National Institute of Dental Research, and Gerald Shklar, DDS, of the Harvard School of Dental Medicine.

The researchers exposed the inside cheeks of hamsters to a cancer-causing chemical known as DMBA, then gave glutathione to some of the animals. Hamsters receiving glutathione had fewer—and smaller—tumors than those not given the antioxidant, according to Schwartz and Shklar's article in *Nutrition and Cancer* (1996;26:229-36).

In fact, the overall tumor burden in hamsters receiving glutathione was about one-tenth that of animals not receiving the antioxidant. Microscopic examination showed a significant reduction in precancerous dysplasias, cancers, and invasive cancers.

The reduction in oral cancer was associated with the enhancement of tumor suppression by the p53 gene, which plays an important role in cancer prevention, according to the researchers. "The inhibition of oral carcinogenesis...was also related to a very significant inhibition of tumor angiogenesis," Schwartz and Shklar wrote.

Glutathione is made of three amino acids (cysteine, glycine, and glutamic acid). Various glutathione compounds, such as glutathione peroxidase and glutathione-S-transferase, function as antioxidants in the body. Glutathione levels in the body can be increased by taking the N-acetylcysteine form of cysteine. □

Omega-3 Fish Oils May Be Helpful in Asthma, Behavioral Disorders

The omega-3 essential fatty acids, also known as fish oils, are well known for their benefits to the heart. Two recent studies highlighted their potential benefits in asthma and in behavioral disorders.

Ann J. Woolcock, MD, of the Royal Prince Alfred Hospital, Sydney, Australia, had previously found that regular fish eaters had about one-third the risk of asthma compared to children who did not regularly eat fish. In her latest study, she compared the fish-eating habits of several hundred children age 8-11.

Woolcock found that asthmatic children were about half as likely to consume "oily" fish, which are particularly rich in the omega-3 fatty acids. These fish, which contain more than 2 percent fat, include yellowtail, salmon, tuna, mackerel, and trout.

"Reduced risk of current asthma was associated with the consumption of oily fish, but not with non-oily fish. Fish oil contains the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have anti-inflammatory effects," Woolcock wrote in the *Medical Journal of Australia* (1996;164:137-40). About one oily fish meal weekly was associated with a reduced risk of asthma.

In another study, John R. Burgess, PhD, of Purdue University, investigated 96 boys with and without attention deficit/hyperactivity disorder (ADHD) in northern Indiana. He had teachers and parents complete the Conners' test, a common method of assessing behavioral problems in children, for each of the children. Burgess then compared test results with blood levels of the omega-3 and omega-6 essential fatty acids.

He found that low blood levels of omega-3 fatty acids were significantly associated with hyperactivity, impulsiveness, rebellious and destructive behavior, temper tantrums, sleep disorders, and anxiety. These children also had physical symptoms of a deficiency of essential fatty acids, including thirst, frequent urination, and dry skin.

Burgess wrote in *Physiology & Behavior* (1996;59:915-20) that "more learning and health problems were found in subjects with lower total omega-3 fatty acid concentrations." Forty-four percent of the children with low omega-3 levels also had low levels of omega-6 fatty acids. □

Vitamin E May Protect Against Some Types of Breast Cancer

An estimated 3 million Japanese men and women carry a genetic defect that leaves them vulnerable to breast cancer. But vitamin E might just protect them.

The genetic defect results in abnormally low production of catalase, an enzyme that converts hydrogen peroxide into water and oxygen. Without sufficient catalase, hydrogen peroxide is more likely to generate dangerous hydroxyl free radicals, which can cause breast cancer and other diseases.

If a comparable (0.23) percent of Americans share this genetic trait, more than 6 million people in this country would also suffer from low catalase production, or hypocatalasemia. A smaller number of people suffer from acatalasemia, in which they produce virtually no catalase at all.

In recent experiments, Kunihiko Ishii, MD, of the Okayama University Medical School, Japan, showed that mice with low catalase production in their breast cells were especially prone to cancer, strongly suggesting that free radicals are involved in the disease process.

He then fed three strains of mice—normal, hypocatalasemic, and acatalasemic—diets either enriched or deficient in vitamin E. He used vitamin E because it is a well-known antioxidant, and some studies have found it to protect against breast cancer.

The acatalasemic mice had the highest incidence of breast cancer, following by the hypocatalasemic mice. The normal mice did not develop any breast cancers. Vitamin E-enriched diets reduced the number of breast cancers and greatly delayed their appearance.

"The incidence of mammary tumor in [acatalasemic] mice given the vitamin E-supplemented diet was 47%, while that in mice given vitamin E-deficient diet was 82%," Ishii wrote in the *Japanese Journal of Cancer Research* (July 1996;87:680-4). "Mammary tumors were apparent after 9 months of vitamin E deprivation and after 14 months of vitamin E supplementation."

He added: "Thus, subjects with acatalasemia or hypocatalasemia would have a risk factor of breast cancer, and vitamin E should be effective in preventing mammary tumorigenesis in the high-risk group of subjects with lower catalase activity. It may be concluded, therefore, that vitamin E intrinsically has a protective effect against the development of mammary tumor, and this may apply not only to the acatalasemic mouse, but also to humans." □

Acetyl-L-Carnitine Can Slow Progression of Early Alzheimer's

Acetyl-L-carnitine, a component of protein, can slow the progression of Alzheimer's disease in people under age 65. However, acetyl-L-carnitine supplements may slightly worsen Alzheimer's in older folks.

Leon J. Thal, MD, of the University of California School of Medicine, San Diego, headed a double-blind, placebo controlled study of several hundred patients with probable Alzheimer's disease. Some of the patients received 3 grams daily of acetyl-L-carnitine and others were given a dummy pill. The progression of Alzheimer's was measured with the Alzheimer's Disease Assessment Scale and other cognitive tests.

Patients with early-onset Alzheimer's—when the disease develops before age 65—declined more slowly if they took acetyl-L-carnitine. The resistance to Alzheimer's is significant because early-onset patients generally declined faster than older patients without treatment.

"The results of this study suggest the working hypothesis that early-onset Alzheimer's disease patients are differentiated from late-onset patients by experiencing a more rapid rate of cell and synapse loss," Thal and his colleagues wrote in *Neurology* (Sept 1996;47:705-11).

Continued on bottom of next page

Quick Reviews of Recent Research

• The dangers of mothballs

Most people don't think of mothballs as an oxidative stress. But they are. The key active ingredient in mothballs is naphthalene, and researchers recently investigated its effect on rats, some of which were fed vitamin E succinate. Naphthalene resulted in higher levels of lipid peroxidation (free radical damage to fats) in liver and brain cells, as well as breaks in DNA strands. In animals given vitamin E, liver and brain damage was 39-46 percent less. Only about half as many DNA breaks occurred in mice given vitamin E.

Vuchetich PJ, et al., *Free Radical Biology & Medicine*, 1996;21:577-90.

• Sulfur dioxide induces oxidative stress

Sulfur dioxide, one of the most common chemicals in air pollution, is absorbed through the lungs and enters tissues throughout the body. Researchers exposed guinea pigs to 10 parts per million of sulfur dioxide for one hour daily for 30 days. Several markers of oxidative stress increased significantly. These indicators of oxidative stress were lower in animals given vitamins C and E.

Etlik O, et al., *Environmental Research*, 1995;71:25-8.

• Diabetes, birth defects, and vitamin E

Women with diabetes are at high risk of delivering infants with severe birth defects. To model what happens, researchers induced diabetes in rats with the toxin streptozotocin. In animals given vitamin E, the rate of embryo malformations decreased. Furthermore, the embryos increased in size and matured normally, "supporting a role for free radicals in the teratogenic effects of diabetes."

Viana M, et al., *Diabetologia*, 1996;39:1041-6.

• Vitamin E and heart disease in post-menopausal women

Most studies show that vitamin E supplements are far superior to dietary levels of the vitamin when it comes to preventing coronary heart disease. However, researchers recently reported that even small dietary levels of vitamin E, such as those found in margarine can make a difference. Post-menopausal women eating approximately 10 IU of vitamin E daily had about half the risk of death from heart disease, compared with women who consumed substantially less vitamin E.

Kushi LH, et al., *New England Journal of Medicine*, 1996;334:1156-62.

• Beta-carotene enhances natural killer cells

Beta-carotene enhances immune function in part by stimulating activity of natural killer (NK) cells. These cells, produced by the immune system, kill cancer cells and virus-infected cells. Researchers found that 50 mg (83,000 IU) of beta-carotene daily enhanced NK cell activity in elderly men. Men not taking beta-carotene had much lower levels of NK cells.

Santos MS, et al., *American Journal of Clinical Nutrition*, 1996;64:772-777.

• Arrhythmias and fish oils

Researchers fed rats diets with fish oils (omega-3 fatty acids), saturated fats, or low fat. Only the fish oils prevented the initiation and reduced the severity of arrhythmias in the animals' hearts.

Pete S and McLennan PL, *Journal of Nutrition*;1996;126:34-42.

• Manganese and lipid peroxidation

High dietary levels of polyunsaturated fats without antioxidants increase the rate of lipid peroxidation. In an animal study, researchers found that high levels of manganese protect against this damage to cellular fats. The manganese increased levels of manganese-superoxide dismutase, a powerful antioxidant.

Malecki EA and Grefer JR, *Journal of Nutrition*, 1996;126:27-33.

Alzheimer's continued from page 3

"Agents that prevent or retard synapse loss would be effective in slowing the progression of Alzheimer's disease that is characteristic of fast decliners."

The strongest predictor of how fast Alzheimer's would progress was the age of the patient and the severity of the disease at diagnosis.

Acetyl-L-carnitine transports long-chain fatty acids through the cell, where they are burned for energy, and they also remove toxic fatty acid byproducts. It is composed of two amino acids, lysine and methionine.

"This study suggests that a subgroup of patients, aged 65 or younger, may benefit from treatment with acetyl-L-carnitine," wrote Thal. But he added that "a cautionary note must also be sounded since our subanalysis suggests a slightly but not significantly faster rate of decline in late-onset patients treated with acetyl-L-carnitine. "

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