Micronutrients: To Supplement, Or Not To Supplement?

Tell a smoker to eat a carrot a day and he’ll keep the doctor away, but give him regular beta-carotene supplements—the major antioxidant nutrient found in carrots—and you may increase his risk of developing lung cancer. Why? Doctors aren’t entirely sure what the difference is between dietary intake and micronutrient supplementation, but they do know that any diet–cancer association is far more complex than simply supplementing the diet with a few micronutrients.

When a person ingests micronutrients as part of a natural everyday diet, he or she receives more than just a single nutrient. A slice of whole-grain bread, for example, might provide fiber, iron, vitamin E, and folate. The body breaks down and uses all the micronutrients in the slice, which may interact in different biologic pathways and systems.

Micronutrients ingested in supplement form are often pharmacologically or synthetically produced. People who ingest a tablet of vitamin E typically ingest vitamin E in isolation, without the concomitant interactions of other nutrients. Supplement tablets or capsules often contain much higher doses than the level of micronutrients someone would receive in a typical day’s diet.

Scientists hypothesize that nutrients taken as supplements act differently or activate different biologic pathways in the body than nutrient intake as part of a natural diet. For instance, a certain micronutrient in isolation may have no ability to prevent metastasis, but when combined with other nutrients, it may form a compound that limits metastasis. Also, evidence would suggest that certain nutrients can be beneficial as cancer preventives or for combating other health risks, but only at specific levels. Whereas 5 mg of beta-carotene might increase
activation of a certain biochemical pathway, 20 mg may flood the pathway and decrease its beneficial activity.

In this issue of the Journal (p. 245), Richard B. Hayes, Ph.D., of the National Cancer Institute, and colleagues examined the effects of dietary and supplemental antioxidant use on prostate cancer risk among participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. They found that intake of antioxidants—from either dietary or supplement sources—was not associated with prostate cancer risk, but they noted that in specific population subgroups, supplementary vitamin E or beta-carotene could reduce prostate cancer risk.

There have not been many studies that have looked directly at the difference between dietary intake and supplementation, but limited evidence has pointed to possible clues for several micronutrients. Here are a few that have been studied to date.

**Beta-Carotene**

Perhaps the most well-known story of micronutrient supplementation is that of beta-carotene, a nutrient tested for cancer prevention in two trials that ended more than a decade ago. The trials—the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study and the Beta-Carotene and Retinol Efficiency Trial (CARET)—tested the effect of beta-carotene on cancer incidence based on evidence that suggested that people with a high dietary intake of carotenoids (rich in beta-carotene) or high circulating blood levels of beta-carotene did not develop cancer as frequently. Both trials showed that the beta-carotene supplements given to participants, most of whom were smokers, put them at an increased risk of lung cancer and increased their overall mortality.

Demetrius Albanes, M.D., who led the ATBC study, explains what may have happened to participants in the trials who experienced negative effects of beta-carotene supplementation.

“Within the normal dietary range, you have a beneficial impact of beta-carotene on important metabolic pathways, but taking the level of beta-carotene too high could lead to harmful alterations in some of the same systems.” Albanes suggests that a negative interaction between betacarotene and other molecules may have occurred in smokers, whose smoking habit introduces carcinogens in the body and increases the body’s oxidative stress. “This [combination] may have altered [specific enzyme regulation] as well as retinoic acid receptor signaling.”

**Folic Acid**

Folic acid came into the spotlight in 1992 when the U.S. Public Health Service recommended that all menstruating women take in 400 μg of folic acid a day in supplementary or dietary form to prevent neural tube defects in a developing fetus, including defects such as spina bifida. The recommendations led to grain fortification with folate, making folic acid deficiency virtually nonexistent. Epidemiology studies have indicated that folic acid intake may also be associated with a decreased risk of certain cancers, particularly colorectal cancer and breast cancer. However, recent studies on colorectal cancer in rodents suggest that the timing of when an animal receives folic acid can change whether folic acid promotes or prevents cancer growth. When folic acid is given before tumor development, it appears to stop colorectal tumor formation. Given after tumor development, folic acid seems to promote colorectal cancer growth.

The highest levels of folic acid intake generally come from supplementation. “When you eat folate that’s found naturally in foods, you absorb about half of it,” said Rachael Stolzenberg-Solomon, Ph.D., of the National Cancer Institute. “Supplemental folic acid is much more biologically available. You absorb 100% of it.” Despite folic acid’s ability to guard against neural tube defects, some nutritionists worry about both folic acid supplementation and even enriched grains because of the association with increased risk of colorectal cancer in mice. “It’s a confusing and controversial topic,” Stolzenberg-Solomon said.

**Vitamin E**

Vitamin E is an antioxidant found in foods such as whole grains, seeds, nuts, and vegetable oils. With a typical dietary intake, a person will absorb about 5–10 mg of vitamin E daily. Many studies of average daily dietary intake of vitamin E have not found an association between intake of the nutrient and cancer incidence.

However, results from the ATBC study suggested that supplementary intake of vitamin E at a dose of 50 mg a day did affect biologically relevant systems. “We noticed that the vitamin E [supplements] did lead to a reduction in androgen levels, including testosterone and androstenedione, [and] we saw a reduction in [vascular endothelial growth factor] in response to the supplementation,” Albanes said. “Such biochemical effects may not be evident at a lower dietary range of intake.” The ATBC study did find an association between vitamin E intake and a reduced incidence of prostate cancer.

That study led to the creation of a new trial in 2001, still ongoing today, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is testing the association between supplemental selenium and vitamin E intake and the risk of prostate and other cancers. Selenium has, in the past, been associated with a reduced risk of a wide range of cancers.
Vitamin D

A person’s body makes 15,000–20,000 IU of vitamin D after standing in the sun for a half an hour. Doctors recommend that people get 1,000 IU of vitamin D a day, but with warnings about UV light and skin cancer, increased amount of time spent indoors, and decreased consumption of dairy products (a major dietary source of vitamin D), many people don’t get enough vitamin D exposure and are deficient for the nutrient.

Higher levels of vitamin D have been associated with a reduced risk of colon cancer. Observational studies have found higher rates of colon cancer among people living at northern latitudes, where people aren’t exposed to as much sunlight, and among African Americans, for whom melanin in their skin blocks synthesis of vitamin D.

Walter Willett, M.D., Dr.P.H., of the Harvard School of Public Health, thinks the answer for many lies in vitamin D supplements, though he cautions that standard supplements contain only 400 IU of vitamin D—just a “drop in the bucket.” People should take a supplement containing 1,000 IU of vitamin D, he says.

Calcium

Calcium intake of 700–1,000 mg per day, an amount equivalent to about two servings of milk, has been associated with a slightly reduced risk of colorectal cancer and with a reduced risk of breast cancer in observational studies.

However, calcium intake through supplementation can be much higher than 1,000 mg per day, and increased daily dosage has been associated with an increased risk of prostate cancer. Too much calcium can suppress the active form of vitamin D, potentially increasing a person’s risk of prostate cancer. Says Willett, “Until further data becomes available, caution seems warranted.”

Other Nutrients

Other nutrients—either in the diet or as supplements—have also been studied in association with cancer. Some observational studies have suggested that eating tomatoes or tomato products stops the development of prostate cancer, whereas lycopene supplements have no effect. No studies have found an association between vitamin C intake and increased or decreased cancer risk. Other nutrients, such as flavonoids, have been studied as potential anticancer agents, particularly in lung cancer or in addition to certain chemotherapy drugs.

Although solid conclusions are hard to come by in dietary research, researchers admit that studies of micronutrients have presented some interesting surprises. Albanes says studies looking at dietary intake versus supplementation are “part of the big challenge we have today. We must disentangle [the] multiple possible impacts of dietary intakes and dietary modifications versus lower and higher doses of specific nutrient supplements.”

—Ariel Whitworth

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