

BY HANK GEORGE

In 1996, Larry C. Clark, M.D., of the Arizona Cancer Center, was lead author of a 16-contributor report from the Nutritional Prevention of Cancer Study Group. That report detailed the results of a study involving 1,312 patients who had a history of forming nonmelanoma skin cancers. These patients were followed at seven dermatology clinics, located in the eastern United States.

Study participants were selected at random to receive either 200 micrograms of the mineral selenium or a placebo. They were “treated” in this manner for an average of 4.5 years and followed altogether for just under 6.5 years.

The authors had hypothesized that administering selenium might reduce the risk of new basal and squamous cell skin carcinomas.

They were wrong.

The rest of this story, however, was totally unexpected and led to the publication of these findings in the prestigious *Journal of the American Medical Association*.

What they discovered was that subjects randomly selected to receive selenium experienced a dramatic reduction in cancer mortality (29 cancer deaths, vs. 71 in controls who received the placebo). The incidence of new cancers—excluding skin lesions—was also appreciably lower in the selenium group (77 cases) than in the placebo group (119 new tumors). There were particularly significant reductions in new lung, colorectal, and prostate malignancies.

By the end of the follow-up period, the selenium group had 21 percent lower all-cause mortality. Furthermore, the safety of selenium supplementation in this dosage (200 micrograms) was affirmed. There wasn't a single case of “selenosis” (the term for selenium toxicity; manifested mainly by nails sloughing off, loss of hair, and skin lesions).

Commenting on these unexpected results, Dr. Edward Giovannucci of Harvard Medical School said that the findings “. . . provide strong support for a cause-and-effect relation” between selenium supplementation and the reduction in cancer. “The evidence now available . . .” he went on to say, “indicates that substantial increases in the consumption of selenium . . . may have a striking impact on prostate-cancer rates.”

SELENIUM

The Supplement That Shocked The World

The mineral selenium vaulted into prominence after a 1996 cancer research study showed a very unexpected outcome when this mineral was given as a dietary supplement to a large group of skin cancer patients. What do we really know about selenium? What are the implications of its future use?

What Is Selenium?

Selenium is a trace element. It was discovered in 1818 and is part of the periodic table, where its closest relative is sulfur. Selenium readily forms compounds with sulfur-containing amino acids, including methionine, an amino acid essential to normal metabolism.

Virtually all selenium is found in proteins called selenoproteins. Some 35 selenoproteins have been described to date. Most are enzymes that control oxidation/reduction reactions.

Glutathione peroxidase, a powerful antioxidant, is the best known and most studied selenoprotein. Dr. Margaret Rayman, writing on "The Importance of Selenium to Human Health" in the July 2000 issue of the British journal *The Lancet*, said that glutathione peroxidase's key functions involve maintaining the integrity of cell membranes and limiting oxidative (free radical) damage to lipids, lipoproteins, and DNA. Such damage has been shown to increase the risk of chronic diseases, especially cancer and atherosclerosis.

Other selenoproteins also serve as efficient free radical scavengers. Two of these are selenoprotein P (which protects endothelial cells) and prostate epithelial selenoprotein (which may confer protection against prostate carcinogenesis).

Selenium constitutes just 0.00001 percent of the earth's crust, but it's not distributed evenly around the globe. Some areas have abundant selenium in the soil; others are deficient.

In China, for example, a marked selenium deficiency in one region has been shown to cause endemic forms of heart muscle disease (cardiomyopathy) and deforming arthritis. In the United States, no overt selenium deficiency disorders have been documented. However, the Pacific Northwest, the Atlantic coastal states, and some of the states around the Great Lakes are known to have relatively low selenium soil content.

Dietary sources of selenium include unrefined grains (especially those grown in regions with high selenium soil content), organ meats (kidney, liver), and brazil nuts. Fish and shellfish contribute some selenium as well. The fact is, many well-nourished people rarely eat foods that are high in extractable selenium content.



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this author can't resist
speculating that
there may come a time,
in the very near future, when
forward-thinking
life insurers
will extend a "credit"
—against adverse mortality risk factors—
to individuals
who indulge in ongoing
selenium
supplementation.

Selenium was recognized as an essential nutrient in the late 1920s. The official RDA (recommended daily allowance) is 55 micrograms a day. It also stipulates that intake should not exceed 400 micrograms, which is approximately twice the dose found in typical commercial supplements. Smoking and alcohol intake have been shown to be potent depressants of plasma selenium levels.

Selenium is quite inexpensive. Though it's readily toxic in high doses, it has been shown again and again to be safe in what would likely be supplemental quantities.

Most North Americans get enough selenium from their diet to satisfy the RDA. The question is, would there be therapeutic benefit from supplementing this level of selenium, as was done in the aforementioned cancer study?

Selenium and Cancer

Epidemiologic evidence for links between selenium and cancer has been accumulating for three decades. Animal studies have shown that supranutritional levels (i.e., those equivalent to supplementation doses in humans) reduced the incidence of tumor formation. As of 1986, more than 100 such studies had been published and two out of three revealed a positive effect for selenium against cancer.

Studies in the United States and Canada have shown that selenium soil content varies inversely with cancer incidence in both countries. There's also an inverse relationship between selenium blood levels and cancer rates. A 27-country study revealed that total cancer mortality attributable to leukemia and carcinomas of the colon, rectum, breast, ovary, and lung varied inversely with calculated per capita dietary selenium intake.

In Linxian, China, there are epidemic rates of squamous cell esophageal carcinoma and adenocarcinoma of the upper portion of the stomach. Mark et al. have demonstrated that selenium supplementation significantly decreases the risk of both of these highly lethal malignancies.

Willett found that the risk of cancer in the lowest selenium quintile was twice that of the highest quintile. This was further impacted by vitamin E and retinol (vitamin A). The highest cancer risk was in those subjects in the lowest tertile for all three micronutrients, suggesting that at least some selenium benefits may be synergistic with those provided by other antioxidants.

The Health Professionals Followup Study investigated the association between the risk of prostate carcinoma and levels of selenium as measured in toenail clippings. In 1987, 33,737 subjects had clippings taken. By 1994, 181 new cases of advanced prostatic cancer were recorded among study subjects. The risk of such tumors in the highest selenium quintile was barely one third of that seen in the lowest quintile. This was true after adjusting for other risk factors thought to influence the risk of prostate cancer, such as lycopene intake (from tomatoes), calcium intake, family history, and geographic region of residence.

Hepatitis B is an endemic disease in Taiwan. It's the leading cause of liver cancer in that country. Ming-Whei Yu et al. report-

ed that the odds of developing hepatocellular carcinoma were significantly lower in higher quintiles of selenium intake, as compared to the lowest quintile. Results were U-shaped, with a somewhat greater risk in the highest quintile than in the third and fourth quintiles. This outcome was attributed more to chance than to any possibility that selenium was in any way contributory to cancer at the highest levels. These authors called for further studies combining selenium with other micronutrients to see if there were any additive effects in preventing liver carcinogenesis in both hepatitis B carriers and people with chronic hepatitis C.

Most recently, Helzlsouer and coworkers measured toenail and plasma selenium, alpha-tocopherol and gamma-tocopherol levels in 10,456 males from Washington County, Maryland. Selenium was shown to exert a protective effect against new prostate tumors. That effect, however, was overshadowed by the impact of the two forms of vitamin E. Gamma-tocopherol had the greatest net impact, in terms of reduced prostate cancer risk. This is further evidence of possible synergy between antioxidants.

How Does Selenium Work?

Selenium is a powerful antioxidant and the role of oxidative damage has been convincingly implicated in carcinogenesis, especially in the early stages that culminate in a fully invasive malignant tumor. But it may be the immune effects of selenium that play an equal or even greater role in ultimately inhibiting malignancy.

Reduction in prostate cancer incidence was said to have become evident in the Clark study within two years of initiating selenium supplementation. It's argued that this means the selenium was influencing late stages (tumor promotion and progression) of carcinogenesis. One researcher has postulated that selenium induces cancer cell death by a mechanism known as apoptosis.

Dr. Rayman explained that "deficiency in selenium is accompanied by loss of immunocompetence," which affects both arms of the immune system (T-cell anti-tumor surveillance and B-cell antibody production). Selenium supplementation, even in people with normal dietary selenium intake, causes "marked immunostimulating effects." This could explain how selenium optimizes its anticancer effects, blocking further development of incipient premalignant lesions.

In a detailed 1998 report on selenium, Combs and Gray con-

clude that “it is clear from a fair body of epidemiological studies that it is plausible to consider selenium compounds as possible chemopreventive agents. . . .”

Further studies are now being undertaken to confirm the findings in the Clark study and expand our knowledge of the impact of selenium supplementation as a possible anti-cancer prophylaxis. The PRECISE (Prevention of Cancer by Intervention with Selenium) Study is being done in the United Kingdom and Europe, with 33,000 subjects. The SELECT (Selenium and Vitamin E Cancer Prevention Trial) is going forward under the auspices of the National Cancer Institute in the United States, with 32,000 randomly selected males to receive 200 micrograms of selenium plus vitamin E, or placebo. The outcome will be measured in terms of new prostate carcinomas. When the results of these studies are available, the role of selenium as an anticancer micronutrient will be more clearly established.

Selenium and Other Disorders

Selenium inhibits the HIV-1 virus in vitro. Many studies have shown that as plasma selenium levels decline, AIDS progresses. Baum et al. have labeled selenium an “independent predictor of survival for those with HIV infection.”

The role of selenium in heart disease remains unclear. Some studies have shown a benefit; others have not. Jean Neve (Brussels) has reviewed selenium’s function as a possible cardiovascular risk factor. Selenium deficiency is known to cause heart damage, as in the endemic cardiomyopathies mentioned earlier. The question is whether selenium supplementation can evoke cardioprotective benefits.

Free radicals play a clear role in atherogenesis. Selenium is a potent antioxidant.

In animal studies, selenium deficiency promotes endothelial dysfunction, a type of artery injury that facilitates atherosclerosis and its complications. Selenium also inhibits platelet aggregation, the clumping together of platelets that plays a pivotal role in intra-arterial blood clot formation and, thus, heart attacks and strokes. Finally, selenium acts against heavy metals such as mercury and cadmium, which are known cardiotoxins.

Selenium levels have been favorably linked to improved left ventricular ejection fraction (a key determinant of heart function). Further studies in this regard are now underway.

Brain selenium content in patients with Alzheimer dementia is only 60 percent of that seen in dementia-free subjects. Selenium has been shown to reduce the severity of seizure activity in children with epilepsy. Selenium supplementation, in the range of 100-200 micrograms per day, reportedly can decrease depression, anxiety, and fatigue while increasing confidence and composure. All of these findings suggest a possible role for selenium supplementation in certain neurologic and psychiatric impairments.

A study of rheumatoid arthritics showed that 200 micrograms of selenium, taken for three months, significantly lessened pain and joint involvement. British studies have docu-

mented similarly impressive beneficial effects of selenium supplements on adult asthmatics and in patients with chronic pancreatitis, an insidious disease of high mortality.

Conclusion

It’s perhaps premature for physicians to advocate widespread use of selenium as a dietary supplement, especially for individuals at increased risk for cancer and other diseases. That may change once the aforementioned new studies are completed.

As a life insurance underwriter, this author can’t resist speculating that there may come a time, in the very near future, when forward-thinking life insurers will extend a “credit”—against adverse mortality risk factors—to individuals who indulge in ongoing selenium supplementation. The precedent for this approach has already been set; progressive carriers now give favorable consideration, during risk selection, to such things as “aspirin-a-day” prophylaxis and use of hormone replacement therapies by postmenopausal females.

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