Dynamic Chiropractic

VITAMINS / SUPPLEMENTS

Selenium: Important for Colon Cancer Prevention

James P. Meschino, DC, MS

Selenium is an essential nutrient for humans; it fulfills the physiological requirements for more than 13 human enzymes and proteins.[1] Its most well-known function relates to the activation of the enzyme glutathione peroxidase, which accounts for selenium's antioxidant role in the reduction of hydrogen peroxide to water and organic hydroxyperoxides to alcohol. The form of selenium in all selenoproteins is an amino acid, L-selenocysteine. Both inorganic (e.g., selenite and selenate) and organic (seleno amino acids) forms of selenium have shown impressive cancer chemopreventive effects in humans and in animal models.[2]

The nutritional requirement for selenium for the synthesis of L-selenocysteine is considered to be 55 micrograms per day. However, selenium consumed as a dietary supplement (up to 200 mcgs per day) beyond levels attainable from food is associated with reduced incidence of lung, colorectal and prostate cancer in humans. Animal studies also strongly indicate that supraphysiological levels of selenium significantly reduce cancer incidence in various test models.[1]

Mechanism for Cancer Prevention

Many cancer researchers now propose that the level of selenium intake required to reduce cancer risk exceeds the intake level (55 mcgs) required to maximize the synthesis of L-selenocysteine, upon which the RDA is based. At supraphysiological levels of intake, selenium has been shown to exhibit a number of anti-cancer properties beyond the activation of the antioxidant enzyme glutathione peroxidase. These general mechanisms include:

- Apoptosis - programmed cell death of cancer cells.
- Growth-inhibitory effects of cancer cells.
- Induction of p53 tumor suppressor gene, which gives rise to proteins that arrest cell cycle division when DNA mutations occur, allowing DNA repair enzymes to correct the error.
- Protects against DNA damage.
- Anti-promotional agent, discouraging cancer cell division.

The induction of apoptosis (a very important chemopreventive function) is detectable toward the upper limit of plasma selenium concentrations (approximately 5 micromoles per liter)[3-5] The present view is that selenium metabolites (i.e., methylated forms of selenium), rather than simply the saturation of L-selenocysteine synthesis alone, are key factors in selenium's cancer preventive effects.[5] At physiological levels of intake, dietary selenium (inorganic and organic forms) is reduced to hydrogen selenide (H2Se). From H2Se, selenium is phosphorylated and incorporated into proteins such as L-selenocysteine.

During periods of supraphysiological intake (supplementation), once L-selenocysteine levels are saturated, H2Se is rapidly methylated to dimethyl selenide and other methylated forms, including the monomethylated form, and trimethylselenonium. Experimental studies highlight the fact that

these methylated forms of selenium (metabolites) possess direct and indirect chemopreventive effects not attainable by the action of glutathione peroxidase acting alone.

Thus, selenium supplementation (100-400 mcg per day) increases the levels of methylated selenium metabolites that appear to account for many of selenium's cancer preventive effects.[1-5] Note that under toxic conditions, this methylation metabolic pathway becomes rate limiting and dimethyl selenide is eliminated by pulmonary excretion, giving rise to garlic breath.[1]

As reported by Combs B, et al., selenium plasma levels of approximately 120 ng/ml (1.5 umol/ml) may be optimal for cancer prevention in general. The most recent estimates suggest that women require a minimum of 96 micrograms per day and men require at least 120 micrograms per day to support plasma levels at 120 ug/ml. These levels are 175 percent and 218 percent, respectively, of the revised RDA.[6]

Selenium for Colon/Rectal Cancer: Animal and Human Studies

A lesser-appreciated fact among health professionals is the extensive research that suggests that the mineral selenium may be a highly protective micronutrient in the prevention of colon and rectal cancers. Selenium is an essential trace mineral found in soils and crops and has been shown to prevent chemically induced colorectal cancer in animals.

In one study, rats were fed a cancer-causing agent known to cause colon cancer. The rats whose diets were supplemented with selenium had a tumor incidence of only 3 percent, whereas the rats that received no selenium supplementation had a 29 percent tumor incidence. Other animal studies have shown that selenium supplementation reduces the incidence of intestinal tumors by 50 percent compared with rats given the cancer-causing agent without selenium supplementation.[17-20]

Human observation studies are equally as impressive. For example, areas with low soil and crop selenium content have higher rates of colon and rectal cancers. Other studies demonstrate that lower blood levels of selenium are associated with an increased risk of developing colon cancer.[21-25]

In a study of U.S. veterans, blood levels of selenium were measured, in subjects with colorectal cancer and those free from colon cancer. The results demonstrated that subjects with blood selenium levels below 128 micrograms per liter were 4.2 times more likely to have one or more cancerous polyps.[22]

In a clinical trial using selenium to reduce risk of skin cancer 1,312 subjects were given either 200 micrograms of selenium or a placebo. Although selenium was not found to be protective against skin cancer, subjects taking the selenium experienced a 58 percent reduction in colon and rectal cancers compared with subjects taking the placebo pill.[24]

More recently, a study by Dr. Mark Russo and associates at The University of North Carolina (Chapel Hill) further supported a role for selenium in the prevention of colon and rectal cancers. In their study, patients who were referred for a colonoscopy assessment also had blood tests performed. Lower blood levels of selenium were associated with multiple cancerous lesions in the colon. The average blood level for patients with cancerous lesions was 107 micrograms per liter vs. 120 micrograms per liter for the cancer-free subjects.[25]

The authors conclude that this data support a protective effect of selenium against colon and rectal cancers after adjustments for possible confounding factors such as smoking, alcohol intake, use of

dandruff shampoo (which contains selenium), vitamin E intake, vitamin C intake, iron intake, fat intake and fiber intake: "Our results demonstrate that individuals with high plasma (blood) selenium levels are at a decreased risk for colorectal adenomas (cancerous lesions)." An increase of 30 micrograms per liter in blood selenium level was associated with a 50 percent reduction in risk of colon cancer lesions.

As noted, there are several ways that selenium is thought to reduce cancer risk. Selenium enhances antioxidant defenses by increasing activity and levels of the powerful antioxidant enzyme known as Glutathione Peroxidase, considered a strong anticancer agent within the body. Selenium supplementation also decreases the formation of certain cancer permissive eicosanoids of the prostaglandin E2 series. Prostaglandin E2 has been shown to increase the rate of cell division of various cancer cells. Animal studies have demonstrated these effects quite extensively.

Selenium metabolism itself may initiate changes that lead to programmed cell death of cancer cells and pre-cancerous cells.[26-27, 31-32] It is important to note that other human studies also reported, a two- and threefold increased risk for colon and intestinal cancer respectively, in patients presenting with low blood selenium levels when compared to patients with higher blood levels of selenium.[28-29] In line with these observations is the emerging evidence that selenium metabolites (methylated forms) exert a broad range of anti-cancer influences on the cell, including colonic epithelial cells, and that higher levels of selenium intake is required to produce protective levels of these methylated selenium compounds.[3-5].

Current Trends and Practical Application

The average intake of selenium from food sources is shown to be between 50-70 micrograms daily. Is that adequate? The evidence suggesting that selenium can reduce the risk of certain cancers indicates that ingesting additional selenium from a supplement may be a prudent strategy. Many health-conscious physicians now recommend a supplement containing 50-200 micrograms of selenium daily as part of a preventative health strategy.[30,33]

As for safety, toxicity of selenium begins at doses starting at 1,000 micrograms per day, but doses as high as 2,000 mcgs per day have been shown to be nontoxic is some individuals.[6,30,33-34] Most clinical applications have used 100-500 mcg of selenium per day [28, 34]

Ingesting a safe level of selenium from a vitamin and mineral supplement may have other health benefits as well. For instance, the National Research Council has stated, "A large accumulation of evidence indicates that supplementation of the diet or drinking water with selenium protects against tumors induced by a wide variety of chemical carcinogens" in animal studies. Significant protection was demonstrated against the development of breast, colon, liver, and skin cancers.[35]

In humans, epidemiological studies have linked lower selenium intake to a higher incidence of leukemia and cancers of the colon, rectum, pancreas, breast, ovary, prostate, bladder, skin and (in the male) lung.[36] As a result of these studies, a number of clinical trials are underway which are testing selenium as a cancer preventive agent. In the Linxian China study, the combination of selenium, vitamin E and beta-carotene was shown to reduce the incidence of stomach and esophageal cancers by 16 percent and 17 percent, respectively, in a very high-risk population.[37] Studies using selenium have also suggested it plays a role in strengthening the immune system, reducing inflammatory conditions and reducing risk of heart disease and stroke.[38-40]

In conclusion, the mineral selenium demonstrates very promising chemopreventive capabilities as reported in a number of animal and human studies. At recommended supplemental doses (100-500 micrograms per day), it is extremely nontoxic. Moreover, it appears that selenium supplementation may be the only viable means to provide sufficient concentrations to enable the body to generate protective levels of methylated selenium metabolites, which are now considered to be important bioactive agents that account for much of selenium's anti-cancer effects.

It may be prudent to initiate a selenium supplementation early in life. As a rule of thumb, selenium supplementation at 1.5 micrograms per pound of body weight is reported to be a safe intake level that can be applied to children and young adults.[34] The best food sources of selenium include wheat germ, oats, whole wheat bread, bran, tuna, swordfish, oysters, turnips, barley, garlic, brown rice and red Swiss chard.[30,34]

As cancer of the colon and rectum now affects one in 20 people in the population at some point in their lifetime, using proactive nutrition and supplementation strategies to defend against this disease should be encouraged by primary health care professionals. In addition to a low-fat, high-fiber diet, the body of evidence is highly suggestive that certain micronutrients, including not only selenium but also vitamin C, vitamin E, beta-carotene, calcium and vitamin D, exert significant chemopreventive effects in regards to colon and rectal cancers. As a matter of public health policy, health practitioners should be engaged in the process of educating patients as to the much-underrated relationship between nutrition and cancer. This is especially true in regards to colorectal cancers, as up to 90 percent of these cases are considered to be preventable through better nutrition and lifestyle practices.

References

1. Spallholz, J.E., et al. Dimethyldiselenide and methylseleninic acid generate superoxide in an in vitro chemiluminescence assay in the presence of glutathione: implications for the anticarcinogenic activity of l-selenomethionine and L-Se-methylselenocysteine. *Nutrition and Cancer*;40(1):34-41.
2. Woo Youn, B., et al. Mechanisms of organoselenium compounds in chemoprevention: effects on transcription factor-DNA binding. *Nutrition and Cancer*;40 (1): 28-33.
3. El-Bayoumy, Karam, et al. Multiorgan sensitivity to anticarcinogenesis by the organoselenium 1, 4-phenylenebis (methylene) selenocyanate. *Nutrition and Cancer*;40 (1):18-27.
4. Fleming, J, et al. Molecular mechanisms of cancer prevention by selenium compounds. *Nutrition and Cancer*;40 (1):42-49.
5. Kim, Y.S., Milner, J. Molecular targets for selenium in cancer prevention. *Nutrition and Cancer*;40 (1):50-54.
6. Combs, Jr., Gerald F. Impact of selenium and cancer-prevention findings on the nutrition-health paradigm. *Nutrition and Cancer*;40(1):6-11.
7. Doll R., Peto R. *The Causes of Cancer*. Oxford, Oxford University Press; 1981.
8. Mendeloff A. Dietary fiber and gastrointestinal disease. *American Journal of Clinical Nutrition*, 1987;45:1267-70.
9. Doll R., Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Instit*, 1981;66:1191-1308.
10. Burkitt, DP. Epidemiology of cancer of the colon and rectum. *Cancer*, 1971;28:3-13.
11. Potter, JD, and McMichael, AJ: Diet and cancer of colon and rectum: a case-control study. *J Natl Cancer Instit*, 1986;76:557-569.
12. Wattenberg, LW: Inhibition of neoplasia by minor dietary constituents. *Cancer Res*, 1983;43:2448s-2453s-2453s.
13. Shekelle, RB, Lepper, M, Liu, S, Maliza, C, Raynor, et al. Dietary vitamin A and risk of cancer

in the Western electric study. *Lancet*, 1981;28:1185-1191.
14. Narbonne JF, Cassand P, Decoudu S, and Leveque F. Effect of fat soluble vitamins on chemical carcinogenesis in rat liver. *Int J Viam Nutr Res*, 1990;60:188.
15. Silverman J, Katayama S, Zelenakas K, Lauber J, et al. Effect of retinoids on the induction of colon cancer in F344 rats by N-methyl-N-nitrosourea or by 1,2-dimethylhydrazine. *Carcinogenesis*, 1981;2:1167-1172.
16. Alabaster, O, Tang, ZC, Frost, A, and Shivapurkar, N: "Effect of Beta-Carotene and Wheat Bran Fiber on Colonic Aberrant Crypt and Tumor Formation in Rats Exposed to Azoxymethane and High Dietary Fat." Carcinogenesis 16, 127-132, 1995
17. Soullier, B, Wilson, P, and Nigro, N: "Effect of selenium on azoxymethane-induced intestinal cancer in rats fed a high fat diet." Cancer Lett 12, 343-348, 1981
18. Jacobs, M: "Selenium inhibition of 1,2-dimethylhydralyzine-induced colon carcinogenesis." Cancer Res 43, 1646-1649, 1983
19. Fiala, E, Joseph, C, Sohn, O, El-Bayoumy, K, and Reddy, B: "Mechanism of benzylselenocyanate inhibition of azoxymethane-induced colon carcinogenesis in F344 rats." Cancer Res 51, 2826-2830, 1991
20. Reddy, B, Tanaka, T, and El-Bayoumy, K: "Inhibitory effect of dietary p-methoxybenzeneselenol on azoxymethane-induced colon and kidney carcinogenesis in female 344 rats: J Natl Cancer Instit 74, 1325-1328, 1985
21. Clark, L, Cantor, K, and Allaway, W: "Selenium in forage crops and cancer mortality in US counties." Arch Environ Health 46, 37-42, 1991
22. Virtamo J, Valkeila E, Alfthan G, Punsar S, Huttunen J, et al. Serum selenium and risk of cancer: a prospective follow-up of nine years. Cancer, 1987;60:145-148.
23. Clark L, Hixson L, Combs G Jr, Reid M, Turnbull B, et al. Plasma selenium concentration predicts the prevalence of colorectal adenomatous polyps. *Cancer Epidemiol Biomarkers Prev*, 1993;2:41-45.
24. Clark L, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. *JAMA*, 1996;276:1957-1964.
25. Russo MW, et al. Plasma selenium levels and the risk of colorectal adenomas. *Nutrition and Cancer*, 1997;28(2):125-129.
26. Reddy B, Rivenson A, Kulkarni N, Upadhyaya P, El-Bayoumy K. Chemoprevention of colon carcinogenesis by the synthetic organoselenium compound 1,4-phenylenebis(methylene)selenocyanate. *Cancer Res*, 1992;52:5635-5640.
27. Lanfear J, Fleming J, Wu L, Webster G, Harrison PR. The selenium metabolite selenodiglutathione induces p53 and apoptosis. *Carcinogenesis*, 1994;15:1378-1392.
28. Willett WC, Polk PF, Morris JS, Stampfer MJ, Pressel S, et al. Prediagnostic serum selenium and risk of cancer. *Lancet*, 1983;2:130-134.
29. Salonen J, Alfthan G, Huttunen J, Puska P. Association between serum selenium and the risk of cancer. *Am J Epidemiol*, 1984;120:342-349.
30. Hendler S. *The Doctor's Vitamin and Mineral Encyclopedia*. Simon and Schuster, 1990.
31. Thompson CD, et al., Effect of prolonged supplementation with daily supplements of selenomethionine and sodium selenite on glutathione peroxidase activity in blood of New Zealand residents. *Am J Clin Nutr*, 1982;36:24-31.
32. Lavender OA, et al., Bioavailability of selenium to Finnish men as assessed by platelet glutathione peroxidase activity and other blood parameters. *Am J Clin Med*, 1983;37:887-897.
33. Mutanen M, Bioavailability of selenium. *Annals Clin Res*, 198 6;18:48-54.
34. Murray M. *Encyclopedia of Nutritional Supplements*. Prima Publishing, 1996
35. National Research Council: *Diet and Health. Implications for Reducing Chronic Disease Risk*. National Academy Press; Washington, D.C.: 1989:376-379.
36. Clark L. The epidemiology of selenium and cancer. *Fed Proc*, 1985;44:2584-2589.
37. Clot WJ, et al. The Linxian trials: mortality rates by vitamin-mineral intervention group. *Am J*

Clin Nutr, 1995;62 (suppl):14245-14265.
38. Kiremidjian-Schumacher L, et al. Supplementation with selenium and human immune cell functions, II, effect on cytotoxic lymphocytes and natural killer cells. *Bio Trace Elem Res*, 1994;41:103-114.
39. Tarp U, et al. Selenium treatment in rheumatoid arthritis. *Scard J Rheumatol*, 1985,14:364-368.
40. Salomen JR. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. *Lancet*, 1982;2:175-179.