Selenium Biochemistry and Cancer: A Review of the Literature

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Abstract

In recent years, the role of selenium in the prevention of a number of degenerative conditions including cancer, inflammatory diseases, thyroid function, cardiovascular disease, neurological diseases, aging, infertility, and infections, has been established by laboratory experiments, clinical trials, and epidemiological data. Most of the effects in these conditions are related to the function of selenium in antioxidant enzyme systems. Replenishing selenium in deficiency conditions appears to have immune-stimulating effects, particularly in patients undergoing chemotherapy. However, increasing the levels of selenoprotein antioxidant enzymes (glutathione peroxidase, thioredoxin reductase, etc.) appears to be only one of many ways in which selenium-based metabolites contribute to normal cellular growth and function. Animal data, epidemiological data, and intervention trials have shown a clear role for selenium compounds in both prevention of specific cancers and antitumorigenic effects in post-initiation phases of cancer.

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Introduction

Selenium's unique role in human physiology has been found to include the prevention of atherosclerosis, specific cancers, arthritis, diseases of accelerated aging, central nervous system pathologies, male infertility, and altered immunological function.[1] Selenium is active in a variety of selenoproteins that include, but are not limited to, the glutathione reductases.[2] Other selenoproteins have roles that support immune function and, through specific cellular pathways, may play a preventive role in both the initiation and promotion of specific cancers.[3]

Human Selenium Biochemistry

At least 25 selenoproteins have been identified in human biochemistry. The functions of selenium are believed to be carried out by selenoproteins, in which selenium is specifically incorporated as the amino acid selenocysteine.[2] In addition to incorporation as selenocysteine, selenium can replace sulfur in methionine, forming selenomethionine. This compound can be incorporated non-specifically into proteins in place of methionine. Finally, selenium can be tightly bound by certain proteins, known as selenium-binding proteins, to distinguish them from true selenoproteins.[2]

The first true selenoprotein identified was glutathione peroxidase, which catalyzes the oxidation of reduced glutathione and allows for the reduction of hydrogen peroxide to water, preventing lipid peroxidation and cellular damage.[4] There are basically five forms of glutathione peroxidase (GPx) that have been identified in human tissue: classical GPx (found only in the cell cytosol), gastrointestinal GPx (found in the liver and gastrointestinal tract), plasma glutathione peroxidase, phospholipid-hydroperoxide GPx (PHGPx), and sperm nuclei GPx.

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Table 1. Selenium-containing Enzymes[12]

Selenoenzyme	Location
Glutathione peroxidase (GSHPx)	plasma, thyroid
Gastrointestinal GSHPx	GI tract
Glutathione peroxidase (classic)	cytosol
Phospholipid hydroperoxide glutathione peroxidase (PHGPx)	cell membrane
Sperm nuclei glutathione peroxidase	sperm nuclei
Thioredoxin reductase	tissues, skin, thyroid
Selenoprotein P	blood, thyroid
Type I iodothyronine deiodinase	liver, kidneys, thyroid
Type II iodothyronine deiodinase	brain

Phospholipid-hydroperoxide GPx is found in cell nuclei, mitochondria, and the cytosol, and specifically acts to prevent lipid peroxidation in cell membranes. This is a unique function of this antioxidant enzyme, as most antioxidant enzymes cannot reduce phospholipid hydroperoxides inside cell membranes.[5] This particular form of GPx is found in high concentrations in spermatozoa, and is involved in sperm maturation and the prevention of cellular apoptosis. The ejaculate of infertile men contains significantly lower amounts of PHGPx compared to men with normal sperm counts and motility indexes.[6] As a class of enzymes, the PHGPx regulate eicosanoid production and cell signaling by reactive oxygen species. GPx levels in the blood and liver are responsive to early dietary selenium deficiency; whereas, the phospholipid-rich tissue membranes that contain PHGPx appear to be less affected by mild selenium deficiency.[6]

Selenoprotein P, the majority of the selenium found in the bloodstream, also acts as an antioxidant enzyme and a selenium-transporter and appears to be very sensitive to dietary selenium.[7]

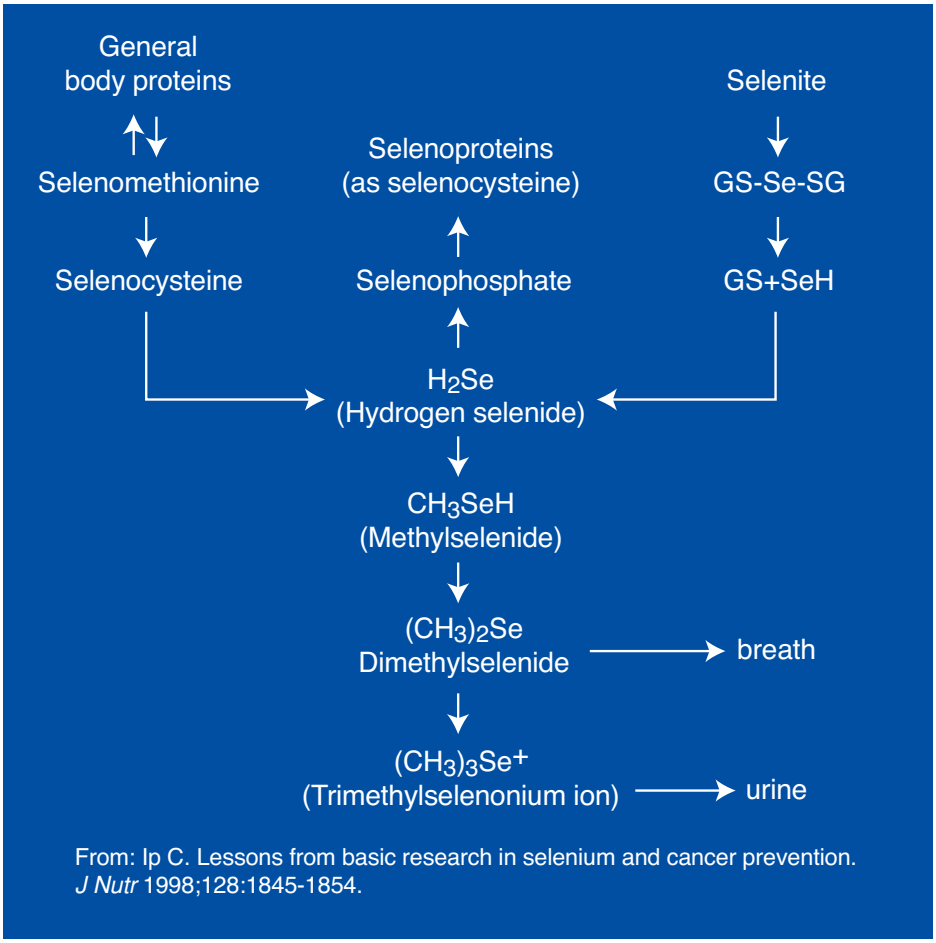
Thioredoxin reductase, another selenoenzyme that acts as an antioxidant, is found in all tissues. As a major component of the antioxidant system, thioredoxin reductase is responsible for degrading peroxides and hydroperoxides outside cell membranes. Peroxides and hydroperoxides have been shown to cause cell death, DNA damage, and tissue atrophy.[8] Thioredoxin reductase also recycles lipoic acid and vitamin C, regulates the metabolism of vitamin K3, and acts to regulate cell growth and the activity of tumor-suppressing protein p53.[9] This selenocysteine-encoding enzyme exists in large concentrations in keratinocytes and melanocytes, where it is believed to provide the initial line of defense against ultraviolet light-generated free radical damage.[10] Thioredoxin reductase is responsive to increased levels of selenium in the cellular environment. Adding selenium at a low 1 microM concentration, a level easily achievable in humans by supplementation, increases the antioxidant activity of thioredoxin reductase by 40-fold in epithelial cell lines.[11] Table 1 summarizes the selenium-containing enzymes.

Selenium Bioavailability

Selenium is stored in the tissues in varying density: 30 percent of tissue selenium is in the liver, 15 percent in the kidney, 30 percent in muscle, 10 percent in the plasma, and the remaining 15 percent throughout other organs.[13] Because selenium binds to mercury and is deposited in tissue in an inert complex with a 1:1 molar ratio, this selenium-mercury complex is unavailable for metabolism. When free non-mercury-bound selenium is determined in specific tissues, tissue concentrations are greatest in the kidney cortex and pituitary gland, followed by the thyroid gland, liver, spleen, and cerebral cortex.[14]

There is no homeostatic control mechanism for selenium absorption and selenium is highly absorbable. Selenium occurs naturally in plants as selenomethionine, Se-methylselenomethionine, selenocysteine, and selenocystine.[15] Selenite (commercially available as sodium selenite) is greater than 80-percent bioavailable and selenomethionine or selenate can be greater than 90-percent bioavailable.[15] Absorption from food is also efficient and adult human exposure to selenium via diet ranges in different parts of the world from 11-5,000 mcg/day. Average dietary intake usually falls within the range of 20-300 mcg/day.[16] This range is broad enough to create a difference between normal tissue glutathione peroxidase and subnormal levels. Selenium deficits, correlated with serum selenium concentrations less than 85-90 mcg/L, are common in parts of China where juvenile cardiomyopathy (Keshan disease) and chondrodystrophy (Kaschin-Beck disease) result from selenium deficiency.[17] In the United States, however, most soils are selenium replete, and whereas low serum selenium levels of 11-20 mcg/L in parts of China are common, serum levels in South Dakota and Maryland have been reported to be as high as 133-197 mcg/L.[18]

Figure 1. Selenium Metabolism[2]



From: Ip C. Lessons from basic research in selenium and cancer prevention. *J Nutr* 1998;128:1845-1854.

Metabolism of Selenium Compounds

Selenomethionine is the major organic seleno-compound in cereal grains, grassland legumes, and soybeans, as well as in selenium-enriched yeast used for selenium supplementation.[19] In several animal studies measuring the distribu-

tion of supplemental selenium, tissue storage of selenium was shown to be higher with selenomethionine compared to selenocysteine, selenate, and selenite. Selenomethionine is generally thought to be the most bioavailable form of selenium.[2] Selenomethionine, however, may substitute in tissue proteins for methionine, and changing the methionine content of the diet will alter how much selenomethionine is used to satisfy methionine requirements.[2,20]

Selenoproteins can be produced in the body from a variety of selenium sources (Figure 1).[21] Selenomethionine competes with methionine for absorption on the gut surface, and is incorporated and stored in body proteins that contain methionine. It may also be converted through transulfuration to selenocysteine and degraded to hydrogen selenide via the beta-lyase enzyme. Selenite is also metabolized to hydrogen selenide via a pathway in which it is complexed with glutathione. Hydrogen selenide acts as a precursor for selenoprotein synthesis and is also the form of selenium excreted; it is methylated and excreted through urine and breath. This is why one of the symptoms of selenium toxicity is referred to as "garlic breath" – the odor of dimethylselenide excreted through the lungs.[2] More than 90 percent of animal chemoprevention studies have used either sodium selenite or selenomethionine as the test agent.[2]

Selenium Toxicity

The U.S. Environmental Protection Agency (EPA) limit for selenium based on projected lifetime exposure is 5 mcg/kg body weight/day. The low adverse effect level (LOAEL), the lowest level of selenium at which any adverse effect may be seen in humans, has been calculated at 1540 ± 653 mcg/day. The no adverse effect level (NOAEL), the level at which no adverse effects will be expected, has been calculated at 819 ± 126 mcg/day.[22]

Combs, however, reports that human selenium toxicity states seen in China require daily intakes on the order of 2 mg daily.[14] No evidence of selenium toxicity was seen in the Nutritional Prevention of Cancer Trial at doses of 400 mcg selenium daily in 424 persons for 1,220 person years of observation. None of the seven people in the selenium group who withdrew from the study complained of symptoms of selenosis (changes in hair, nails, or skin, or garlic breath).[14]

A further trial of selenium in biopsy-proven prostate cancer in which patients were randomized to 1,600 or 3,200 mcg/day selenized yeast for 12 months did not report any selenium-related toxicity signs or symptoms.[23]

Selenoproteins and the Thyroid Gland

Although there is inconsistent data concerning the role of low selenium levels in thyroid cancer, the role of selenium in thyroid metabolism is complex, and an understanding of selenium's free-radical protective effects are crucial to understanding the role selenium may play in thyroid cancers.

The human thyroid gland contains one of the highest selenium contents of any tissue in the body.[24] Selenium is present in thyrocytes and follicular tissue in the form of glutathione peroxidase, selenoprotein P, and thioredoxin. Abundant amounts of extracellular glutathione peroxidase are present in thyroid tissue to act as an antioxidant defense system against significant amounts of hydrogen peroxide resulting from thyroid hormone production.[25] Glutathione peroxidase in thyroid tissue also controls thyroglobulin iodination. Type I iodothyronine deiodinase, a selenium enzyme that requires selenocysteine, catalyzes the conversion of thyroxine (T4) to triiodothyronine (T3) in the liver,[25] and type II iodothyronine deiodinase catalyzes the same reaction in the brain.[26] These enzymes are not found in thyroid tissue in large amounts, but have effects on circulating thyroid hormone levels due to their role in T3 production.[27] The deiodinase selenoenzymes also catalyze the breakdown of T4 to reverse T3, degrade T4 to T2, inactivate T3, and regulate the pituitary-hypothalamic-thyroid axis.[28]

Thyroid metabolism is sensitive to the selenium content in the diet. Significant depressions in T3/T4 ratios have been observed in elderly subjects on low-selenium diets.[29]

A depression in selenoenzyme activity, with subsequent lowering of T3/T4 ratios, has also been documented in a population previously receiving selenium-rich wheat from Canada and switched to selenium-poor grain from Europe.[30] In areas of China where both soil selenium and iodine differ significantly depending on the region, inhabitants with subclinical hyperthyroidism had lower levels of serum selenium (82.6 mcg/L) compared to controls (87.3 mcg/L).[31] Normal controls also demonstrated an inverse relationship between TSH and serum selenium: when serum levels were below 80 mcg/L, TSH levels were correlated at 2.1 mU/L, significantly higher than in those with serum selenium above 80 mcg/L who demonstrated median TSH levels of 1.28-1.29 mU/L. Serum selenium was also inversely correlated with thyroid autoantibody levels. Those with thyroperoxidase antibody (TPO Ab) levels > 600 IU/mL had a mean serum selenium of 83.6 IU/L, while those with TPO Ab levels lower than 600 had mean serum selenium levels between 92.9 and 95.6 mcg/L.[31]

Selenium Replacement in Hypothyroidism

Selenium replacement studies in hypothyroidism have focused on areas of the world where both selenium and iodine deficiencies are endemic. Studies using 50 mcg selenium daily in goiter-endemic areas in Zaire have resulted in significant improvement of symptoms, while serum levels of T4 and reverse T3 dropped to normal range, serum total T3 improved, and serum TSH levels stayed within normal ranges.[32] Because of the interaction of iodine and selenium in thyroid metabolism, and the fact that iodine replacement increases oxidative metabolism in thyroid tissue, it is recommended that in situations where both selenium and iodine are deficient, replacement of both minerals is necessary for the normalization of thyroid function.[33]

The results of rat studies have led to the assumption that selenium supplementation in humans will invariably lead to increased serum T3 levels. Human studies, however, show that may not always be the case.[34] Short-term effects of selenium supplementation on thyroid function reveal a more complex picture of thyroid/selenoprotein interactions. Studies of iodine-replete men given either daily doses of 300 mcg selenium from high-selenium foods or kept on a selenium-deficient diet of 14 mcg daily have shown responses that illustrate the unique effect of selenium on human thyroid metabolism.[28] After 99 days, the high selenium group had a significant drop in serum total T3 levels and a compensatory increase in TSH levels. The low-selenium group had a rise in serum total T3 levels. Because selenium can be stored in thyroid tissue, even in a state of selenium deficiency, it is not clear if the low-selenium diet had a direct effect on thyroid tissue levels of selenoproteins or whether deiodinase enzyme levels were affected. This study is important because it indicates selenium supplementation is more complex than has been presumed, and longer trials will indicate whether these alterations in hormone levels with selenium supplementation are temporary or long-term.

Selenium and Thyroid Cancers

Studies of selenium tissue levels in thyroid tumors are not consistent. One study of tissue samples from 135 patients found a slightly lower level of selenium in both benign and malignant tumors compared to normal tissue, but also found significant elevations of silver, cobalt, mercury, and rubidium in both benign and malignant thyroid tissue compared to normal tissue.[35]

Another study sampled 43 persons who developed thyroid cancer an average of 4.8 years after blood samples were taken.[36] Compared to matched controls, cases were significantly lower in serum selenium than controls. Those with cancer who had serum levels less than or equal to 1.25 microM/L had a 7.7-times greater risk for thyroid cancer compared to controls. Those with higher levels of serum selenium – 1.26-1.64 microM/L – had a 6.1-times greater chance of having thyroid cancer. Levels greater than or equal to 1.65 microM/L were associated with no increased risk of thyroid cancer.

Other studies, however, have failed to find links between selenium and thyroid carcinogenesis. A study investigating tissue selenium found no difference in selenium, tissue selenoenzyme levels, tumor levels of selenium, glutathione peroxidase, or other selenoproteins compared to those in normal thyroid tissue.[37]

On the other hand, low selenium levels and lower selenoenzyme activity levels have been documented in parathyroid adenoma tissue and C-cell carcinoma tissue – medullary thyroid carcinoma – when compared to goiter, autoimmune disease, or differentiated thyroid cancer.[38] Mean zinc and selenium levels in thyroid tissue of patients with thyroid carcinoma were found to be significantly lower than that of patients with non-cancerous thyroid disorders.[39] The ratios of copper/zinc, copper/selenium, and zinc/selenium were significantly higher in those with thyroid carcinomas than controls or those with other thyroid disorders.

Epidemiological Studies of Selenium and Cancer Risk

Erythrocyte, serum, plasma, and urine selenium levels have been found to be lower in a variety of cancer diagnoses compared to both matched and unmatched controls.[40-44] The majority of epidemiological studies also provide evidence for selenium as a chemopreventive agent for specific cancers: prostate,[45,46] lung,[47-49] colorectal,[50,51] stomach,[52] and multiple cancers.[42,53-54] The study of plasma selenium and non-melanoma skin cancers that led to the Nutritional Prevention of Cancer Trial, a 10-year prospective study of 1,738 Americans detailed below, found initial plasma selenium levels inversely correlated to both non-melanoma skin cancer and colonic adenomatous polyps.[55] Those with plasma levels below the U.S. population median of 128 ng/mL plasma were four times more likely to have one or more polyps than those with levels above 128 ng/mL.

In a prospective study of 39,268 men and women in Finland, risk for several cancers was significantly elevated in men who had the lowest level of serum selenium – for cancers of the stomach, pancreas, and lung specifically.[56] The mean levels of serum selenium found in those who developed cancer – 53-63 mcg/L – would be considered low in the United States.[57]

A prospective study of 4,857 Japanese patients followed serum selenium levels in those who developed cancers of all types over a 36-month period.[58] Those who developed cancer during the trial period had significantly lower serum selenium levels at baseline than those who were cancer free. Studies in China's Qidong Province demonstrated a significant inverse association between the incidence of primary hepatocellular carcinoma and plasma selenium levels.[59] In an eight-year retrospective trial in Washington County, Maryland, those with low plasma selenium had a two-fold increased risk for bladder cancer.[60] A U.S. study of 11,000 hypertensives followed for five years showed a two-fold increase in risk for all cancers in those in the lowest (< 115 ng/mL) quintile compared to those in the highest quintile (> 154 ng/mL) of plasma selenium.[42]

A meta-analysis of large prospective studies has shown a consistent relationship between low prediagnostic levels of serum selenium in cancer patients compared to cancer-free controls.[61] The meta-analysis examined nine studies that assessed prediagnostic levels of antioxidants and 10 specific types of cancer. The levels of serum selenium in those who developed cancer of the stomach, pancreas, lung, and bladder were significantly lower than controls. The difference was most pronounced for pancreatic cancer.

Several studies have demonstrated no protective association between selenium and cancer risk.[62,63] Some studies that found no relationship between selenium and cancer risk used toenail selenium as a marker for selenium intake.[63] This method of assessing dietary selenium exposure and assuming toenail selenium as a reflection of tissue stores has been questioned by Schrauzer[64] when there is insufficient difference among quintiles of toenail selenium, raising concerns about toenail selenium being an imprecise tool in determining selenium status.

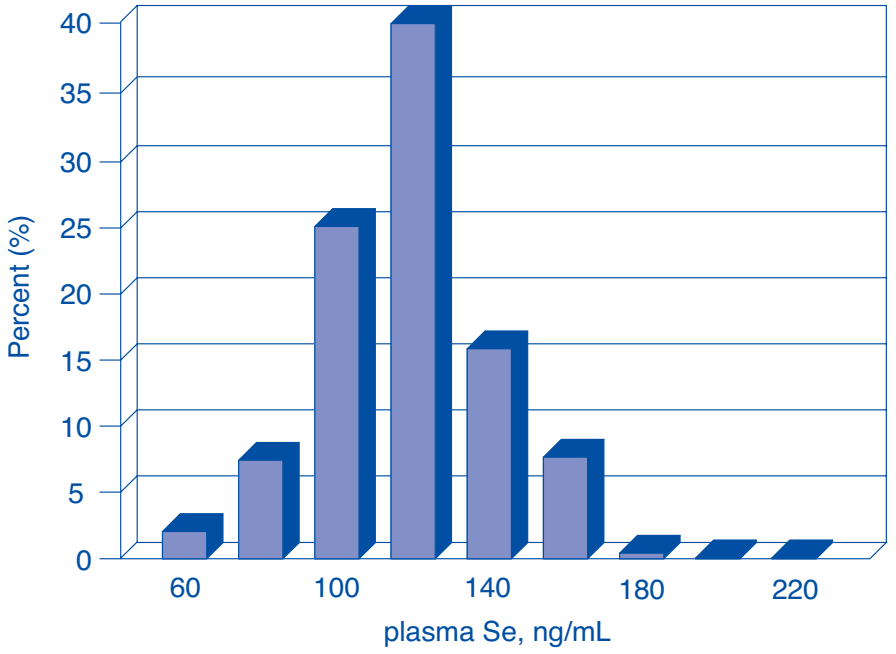
The Nutritional Prevention of Cancer Trial

In 1985, Clark published geographical data on the selenium content of food crops by U.S. county, showing an inverse association of total cancer mortality with local forage plant selenium levels.[65,66] An inverse association was found with the incidence of lung, rectal, bladder, esophageal, and cervical cancer in rural counties, and lung, breast, rectal, bladder, esophageal, and uterine cancers in all counties. Clark also published data showing that in case-control studies in North Carolina, those with squamous cell carcinoma or basal cell epithelioma had significantly lower plasma selenium levels compared to controls.[67] When compared to cancer-free controls, those with the lowest levels of plasma selenium were 5.8 times more likely to have either cancer.

These data encouraged a study of the effects of selenium supplementation in cancer prevention and led to the now well-known Nutritional Prevention of Cancer Trial (NPC Trial).[68] The NPC Trial is the only prospective double-blind, placebo-controlled, randomized trial in the Western world to test a selenium supplement on a large population and measure cancer incidence.

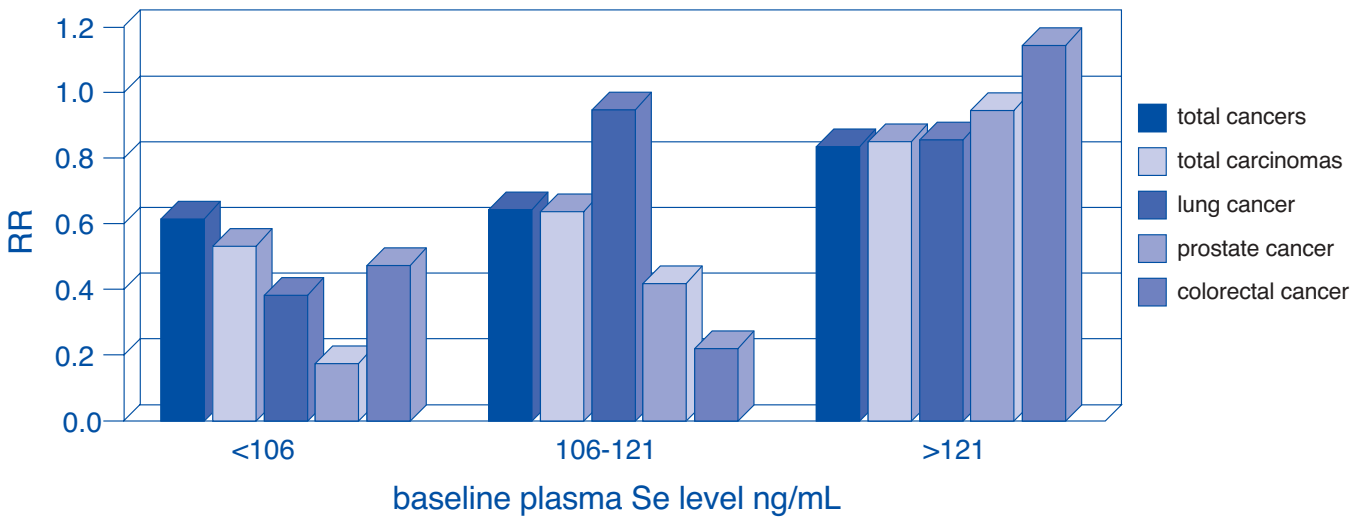
The study originally attempted to assess the ability of selenized yeast containing 200 mcg of elemental selenium to prevent recurrences of non-melanoma skin cancer in 1,312 residents of the southeastern United States, where soil selenium levels are the lowest in the nation. Because of unexpected results, the trial was unblinded early; i.e., selenium supplementation significantly decreased the total cancer incidence by 50 percent, and specifically dropped the incidence of lung cancer by 48 percent, prostate cancer by 63 percent, and colorectal cancer by 58 percent.[69] Analysis of more extended data from the original trial found the protective effect of selenium, although still impressive, decreased to a statistically significant 25-percent reduction in total cancer incidence, a 42-percent reduction in prostate cancer incidence, and a 51-percent reduction in total cancer mortality. In this follow-up report the decrease in lung cancer incidence was no longer statistically significant, while a 54-percent reduction in colorectal cancer incidence was marginally significant (p=0.057).[70] Because 75 percent of the trial group was male, the effects were confined to males and were most prominent in smokers and those with baseline plasma selenium levels below 121.6 ng/mL. Those who entered the trial with plasma selenium levels less than 106 ng/mL showed both the greatest protection from selenium and the highest rates of subsequent cancer in the control group (Figures 2, 3, and 4).[3]

Figure 2. Plasma Levels of Selenium on Entry in NPC Trial[3]



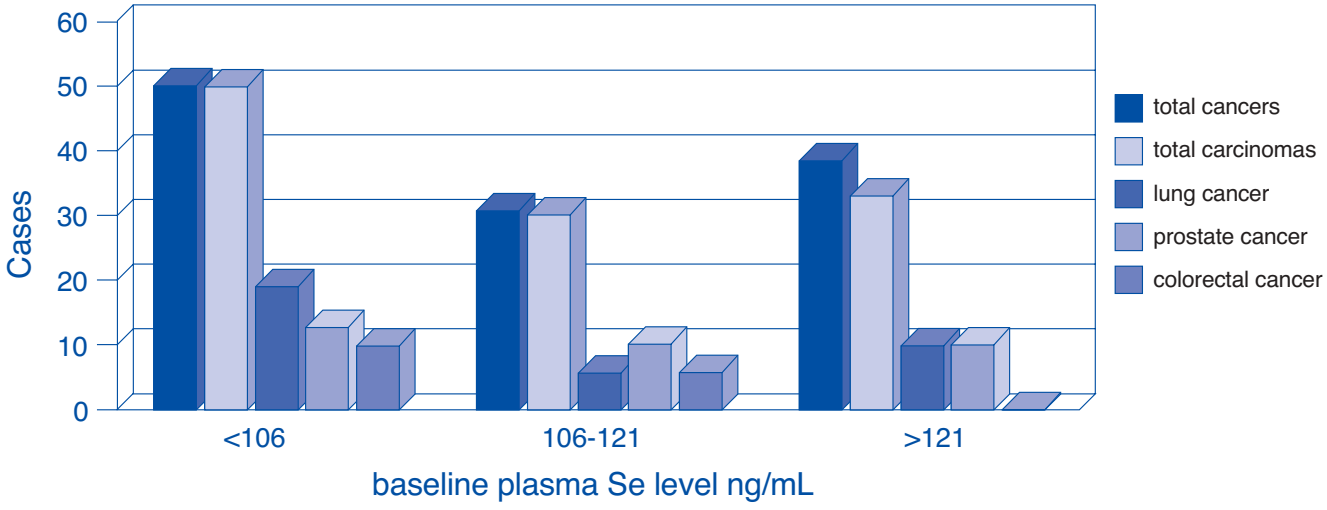
From: Combs GF. Impact of selenium and cancer prevention findings on the nutrition-health paradigm. *Nutr Cancer* 2001;40:6-11.

Figure 3. Protective Effect of Selenium on Subjects in NPC Trial in Lowest Tertile of Selenium[3]



From: Combs GF. Impact of selenium and cancer prevention findings on the nutrition-health paradigm. *Nutr Cancer* 2001;40:6-11.

Figure 4. Cancer Incidence in Placebo Group by Baseline Selenium Level[3]



From: Combs GF. Impact of selenium and cancer prevention findings on the nutrition-health paradigm. *Nutr Cancer* 2001;40:6-11.

Those in the highest tertile of baseline selenium – over 121.6 ng/mL – actually had a non-significant increased total cancer incidence and did not appear to benefit from selenium supplementation at 200 mcg daily. The breast cancer incidence data in this trial demonstrated that the female subjects in the study taking selenium actually experienced an increase in the incidence of breast cancer, but as authors of the NPC Trial data point out, the incidence is not significant and may be irrelevant due to an inadequate numbers of females.[70] The same insignificant increase was true for other sites, including melanoma, esophagus, bladder, brain, leukemias, and lymphomas.[70] Finally, an evaluation by one of the principal investigators in the NPC Trial reported that, derived from the data, 96-300 mcg of elemental selenium daily as selenomethionine is indicated for both adequate antioxidant defense and tumor inhibition.[3]

The Qidong and Linxian Studies

The other large clinical intervention trials involved two Chinese provinces where selenium deficiency and chronic hepatitis B are endemic. The first, a trial giving 30-50 mcg of daily elemental selenium from sodium selenite to 20,847 inhabitants of Qidong Province, resulted in a statistically significant 50-percent drop in the incidence of primary liver cancer.[71] In a subset of this population at high risk for primary liver cancer, 2,474 families received 200 mcg elemental selenium daily from a high-selenium yeast or placebo. At the end of the two-year study, those receiving selenium had a statistically significant 35-percent reduction in the incidence of primary liver cancer.[71]

In Linxian Province, the mortality from esophageal cancer is the highest in the world. An antioxidant intervention trial followed different groups taking antioxidant supplements for five years, during which time cancer mortality from stomach and esophageal cancer accounted for 32 percent of all cancer deaths in the control population. In the group supplemented daily with beta-carotene, vitamin E, and 50 mcg elemental selenium from high-selenium yeast, total cancer mortality was reduced by 13 percent, a statistically significant drop.[72] Follow-up data found a significant inverse association between baseline serum selenium and mortality from esophageal squamous cell carcinoma and gastric cardia cancer.[73] The effect of selenium in this trial may, in large part, have resulted from the treatment of selenium deficiency and normalization of selenoprotein levels, including glutathione peroxidase. The mean serum selenium concentration in the study population was 73 mcg/L; deficiency in this study was defined as any level below 78 mcg/L.

Animal Chemoprevention Studies: The Search for Active Metabolites of Selenium

In the NPC Trial, only six of the 1,312 subjects had initial plasma selenium levels below 80 ng/mL.[70] This is considered the minimum level of plasma selenium necessary in the bloodstream for maximum production of selenoproteins (glutathione peroxidases, thioredoxin reductase, etc.).[74] In other words, the chemoprevention observed in the NPC Trial was not the result of increased levels of the glutathione peroxidases or other selenoproteins. This hypothesis, that the antitumorigenic effect of selenium works via pathways other than selenoprotein production, has been supported in more than 100 studies of animal models of selenium chemoprevention.[75]

Animal studies have consistently shown a beneficial effect of high selenium levels in the prevention of cancer.[75] Of these studies, the majority have shown a clear antitumorigenic/chemopreventive effect of selenium in mammary gland, liver, skin, pancreas, esophagus, and colon cancers.[21] At least half of these studies have shown a reduction of tumor yield by more than 50 percent with selenium supplementation of 1-2.5 mg/kg in addition to an already selenium-replete diet.[3] Reviews of these studies have concurred that high-level exposure to specific selenium compounds is antitumorigenic.[76] The studies show dose-dependent responses at levels that do not show toxicity (Table 2). This high level of supplementation,

however, has not been replicated in human studies as it would necessitate levels significantly higher than those currently used in human research.

Although the mechanisms have not yet been clearly outlined, it has been shown in animal models that selenium inhibits tumorigenesis during both the initiation and later stages of carcinogenesis, and that it inhibits both chemically and virally induced tumors. The effects of selenium appear to be reversible, in that the anticarcinogenic effect is reversed when selenium is withdrawn.[77] Selenium also alters carcinogen metabolism, inhibits tumor cell proliferation, enhances apoptosis, and suppresses tumor angiogenesis.[21] Supranutritional levels of selenium supplementation, exceeding that necessary to make adequate levels of glutathione peroxidase, have also been shown to increase the cytotoxic activities of natural killer cells and macrophages, and up-regulate the expression of interleukin-2 receptors.[78] This immune-enhancing effect has been demonstrated both in animal[79] and human studies,[80] where eight-week doses of 200 mcg yeast-based selenium in humans significantly increased cytotoxic lymphocyte and macrophage activity.[81] Because the antitumorigenic effects of selenium in rodent studies occurred at levels of 100 mcg/kg body weight (average human selenium intake is 1-4 mcg/kg body weight worldwide), research has focused on the metabolically active forms of selenium that would allow for nontoxic levels of selenium supplementation.[69]

Antitumorigenic activity has been observed in metabolites of naturally occurring forms of selenium: selenomethionine, selenocysteine, methylselenocysteine, and inorganic selenium salts – selenite and selenate metabolized to selenodiglutathione.[19] The selenized yeast used in the NPC Trial contained only 20-percent selenomethionine. The remaining selenocompounds were selenocysteine, Se-methylselenocysteine, selenoethionine, selenoglutathione, selenodiglutathione, and selenite.[21,82] Ip and colleagues[83] compared sodium selenite to selenomethionine and demonstrated that selenite was more effective in preventing chemically induced mammary tumors, even though tissue levels of selenium were significantly higher in those given selenomethionine. These data, showing the effects of selenium compounds were not based on tissue levels but on the specific metabolic fates of different forms of selenium, have initiated research on selenium metabolites as chemopreventive agents.

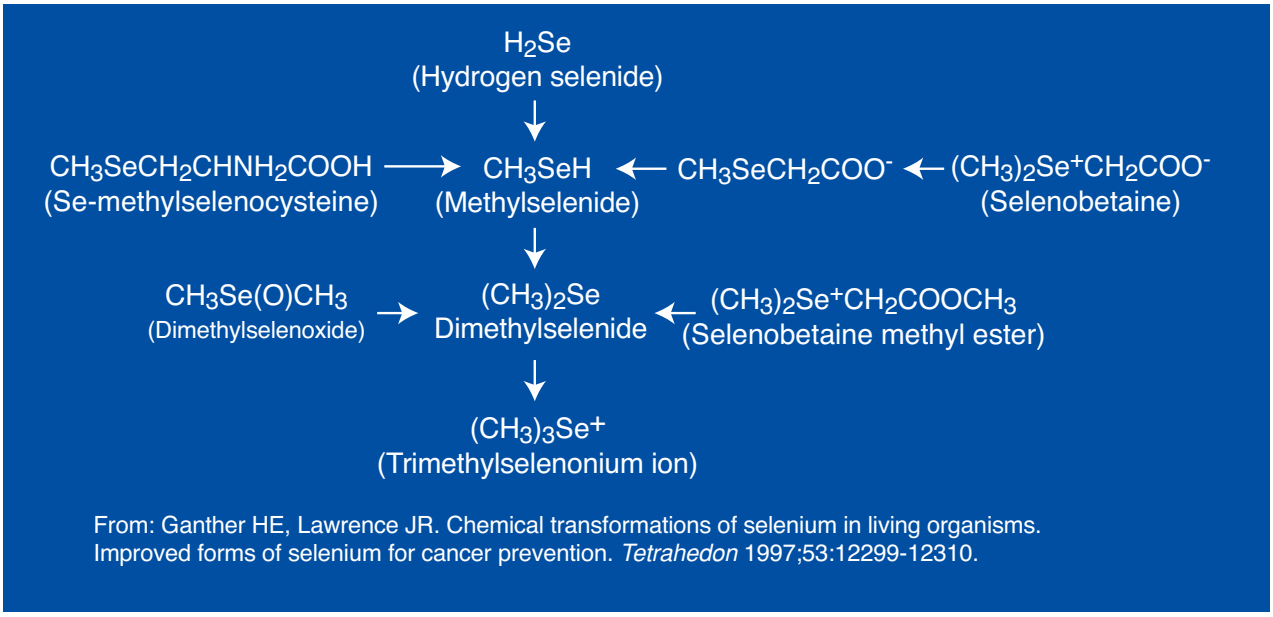
Earlier studies found low-molecular weight forms of selenium not used in synthesis of selenoproteins are instrumental in the metabolism of selenium. These methylated selenium compounds are found in plants and in the metabolic breakdown of sodium selenide in humans, and were ultimately found to be responsible for the chemopreventive effect of selenium (Figure 5).[84] In one study, the methylated selenium compound selenium methylselenocysteine was found to be more effective in suppressing mammary tumors than either selenite or selenomethionine in the dosage range of 1-3 ppm.[85]

Table 2. Antitumorigenic Effect of Different Selenium Compounds

Compound	Dose of Selenium for 50% inhibition (ppm)
Se-methylselenocysteine	2
Selenobetaine	2
Selenobetaine methyl ester	2-3
Selenite	3
Selenomethionine	4-5
Selenocystine	4-5

From: Whanger PD. Selenocompounds in plants and animals and their biological significance. *J Am Coll Nutr* 2002; 21: 223-232.

Figure 5. Methylated Selenium Compounds and their Entry into the Inorganic Selenium Pool



From: Ganther HE, Lawrence JR. Chemical transformations of selenium in living organisms. Improved forms of selenium for cancer prevention. *Tetrahedon* 1997;53:12299-12310.

Sources of Se-methylselenocysteine

Se-methylselenocysteine occurs naturally in plants. It is found in high levels in Astragalus and in selenium-enriched garlic, broccoli, leeks, and onions.[86,87] Astragalus species may accumulate 1,000-10,000 mcg selenium/g, 80 percent as Se-methylselenocysteine.[88] These plants also accumulate selenium as selenopeptides, selenocystathionine, and other selenium compounds. There are no or very little measurable amounts of selenium occurring as selenite in these accumulator plants.[19] Selenium-enriched yeast has been found to contain from six- to 20-percent Se-methylselenocysteine and 85-percent selenomethionine (Table 3).[89] Accumulator plants produce methylated forms of selenium as a way to detoxify inorganic selenate. Methylated forms of selenium, such as Se-methylselenocysteine, have a toxicity equal to selenomethionine, a minimally toxic form of selenium.[90]

Selenium and Breast Cancer

Human Epidemiological Studies

In four studies, plasma, serum, or erythrocyte levels of selenium were found to be significantly lower in breast cancer cases compared to healthy controls.[91-94] A study of Japanese women using toenail selenium revealed a significant difference between the levels in newly diagnosed breast cancer patients and those of healthy women.[95] The nail levels in the healthy women correlated with an apparent protective effect of selenium at daily intakes of 200-300 mcg. Selenium toenail levels in the breast cancer patients, conversely, correlated with a selenium intake of roughly one-half of this amount, which is closer to the intakes observed in Western industrialized countries. However, other epidemiological studies show no relationship between toenail selenium levels,[96-99] serum selenium levels,[98,100] or dietary selenium[99] and breast cancer risk or incidence.

The well-publicized trial of 62,641 women in the Nurses' Health Study also showed no protective effect of selenium on breast cancer.[97] This study involved assessing selenium intake as reflected in toenail clippings and found a relative risk for breast cancer of 1.1 for those in the lowest quintile of selenium and no trends for increasing protection across rising quintiles of toenail selenium levels. Unfortunately, toenail selenium measurements in this study were found to be a poor method of measuring selenium: the correlation

Table 3. Variations in Selenocompounds in Various Yeasts

Sources of Yeast	Percentage of Distribution		
	SeCys	SEM	Other
SUNY-Albany	2.1	62.6	35.2
Norwich England	6.6	23.3	70.0
Nutrition 21	10.6	16.0	81.5

SeCys and SEM, respectively, indicate selenocysteine and selenomethionine but no SeMCYS was found in any of these yeasts.
From: Whanger PD. Selenocompounds in plants and animals and their biological significance. *J Am Coll Nutr* 2002; 21:223-232.

coefficient for two measurements of toenail selenium was only 0.48, and the measurement of one sample of toenail selenium would only account for 25 percent of the variability in toenail selenium levels.[101] As criticized by Clark, lead investigator of the Nutritional Prevention of Cancer Trial, the Nurses' Health Study use of toenail selenium as a measurement, "suggests the potential for considerable misclassification in the exposure variable that could result in a substantial attenuation of the observed relative risk."[102] In other words, the negative findings of the Nurses' Health Study could be a result of using a method of measuring selenium that does not correlate with subsequent measurements or selenium intake, and would result in inadequate data on selenium and breast cancer risk.

Breast Cancer Animal Studies

The mammary gland has been the most studied of all the organs in which tumorigenesis is affected by selenium.[90] Selenium has been shown to inhibit many different mammary tumor models: mouse virus-induced mammary tumors, chemical carcinogen-induced mammary tumors, and spontaneous mammary tumors in the mouse. The research of Medina and colleagues[90] found that Se-methylselenocysteine, selenobetaine, and a garlic-based form, Se-allylselenocysteine, are the most efficacious forms of selenium in mammary tumor prevention in animal models. For an in-depth review of selenium and mechanisms of action in mammary tumor chemoprevention see Medina et al.[90]

Methylselenocysteine, a metabolite of selenomethionine, is twice as active as selenomethionine at suppressing mammary tumors in rodents at 2 mcg Se/g diet.[103] Adding selenium-enriched garlic at the dosage of 3 mcg/g diet reduced mammary tumor incidence in rodents from 83 percent to 33 percent, while plain garlic alone reduced the incidence to 60 percent. Se-allylselenocysteine was also effective at reducing tumor yield, indicating the naturally occurring form of selenium found in garlic may also be part of a chemoprevention strategy.[90] Both Se-methylselenocysteine and Se-allylselenocysteine have no toxicity, low body accumulation, and greater *in vivo* efficacy, as opposed to selenite or selenate.[21,90]

One animal study, however, did show selenium supplementation (4 mcg/mL drinking water) actually increased fibroadenoma incidence by adenovirus type 9 in rats.[104] The same study showed that the same amount of selenium also inhibited the incidence of carcinogen-induced large bowel cancers, while facilitating the incidence of carcinogen-induced small bowel cancers. No explanation was given for the differing effects of selenium in these carcinogenic states.

Selenium and Colon Cancer

Epidemiological Studies of Selenium in Colorectal Cancer

It is expected that 50 percent of the population in Western countries will develop at least one colorectal tumor by age 70.[105] Epidemiological studies have found an inverse association between dietary intake of selenium and colon cancer risk.[65] Colorectal cancer patients were found

to have significantly lower serum selenium (41.8 mcg/mL) and significantly higher serum manganese and iron levels compared to controls.[106,107] Studies of selenium status in patients with stomach and colorectal cancer found that both plasma levels of selenium, erythrocyte selenium, and plasma glutathione-peroxidase levels were significantly lower than healthy subjects.[108] On follow-up in 2002, the Nutritional Prevention of Cancer Trial[70] showed a marginally significant preventive effect of selenized yeast supplementation on the incidence of colorectal cancer (p=0.057). This trial also included an active colorectal screening program. Of 1,312 randomized subjects in the trial, 599 underwent endoscopic screening for colorectal cancer during the time of the blinded trial. Those on selenium experienced a borderline significant decrease in risk of incident colorectal polyps.[23]

Animal Studies of Selenium in Colorectal Cancer

Although there is an epidemiological association in humans between increased dietary selenium and decreased incidence of colon cancer, dietary selenomethionine does not appear to have a chemopreventive effect in animal studies of colorectal cancer.[109]

Selenium-enriched broccoli has been used as a food source of Se-methylselenocysteine. A study using this source of selenium in rodents with preneoplastic colon tumors found it was statistically more effective at reducing premalignant changes and colon tumor incidence than equivalent concentrations of low-selenium broccoli, selenite, selenate, or selenomethionine.[110] Rats fed the high-selenium broccoli received 1 mcg/g diet and demonstrated a significant 50-percent reduction in the incidence of two types of preneoplastic lesions (p=0.01; p=0.02). The selenomethionine-fed animals had no reduction in the incidence of tumors and, although the standard selenomethionine, selenate and selenite diets showed higher levels of glutathione peroxidase in the liver, they were not effective at reducing the incidence of colon tumors.

The multiple-intestinal neoplasia mouse, a genetic model for human intestinal cancer and familial adenomatous polyposis, has responded in trials to dietary additions of selenium-enriched broccoli with significant decreases in both small and large intestinal tumors.[111] The mice were fed high-selenium broccoli, the equivalent of 2.1 mcg selenium/g food for 10 weeks. The tumors that did occur were significantly smaller, and even though there was only a minimal increase in liver and plasma selenium levels, the increase correlates negatively with tumor number.

Selenium and Prostate Cancer

An epidemiological, case-control study of 33,737 men followed for six years compared toenail selenium levels and incidence of advanced prostate cancer.[112] When those with the highest level of selenium were compared to those with the lowest, the former had a 65-percent reduced risk of getting advanced prostate cancer. The range of toenail selenium levels was reflective of a large range of dietary selenium intakes and reflected the differences that would be found in the diets of residents of Boston, Massachusetts (0.74 mcg/g), an area of low-selenium soil content, and South Dakota (1.17 mcg/g), an area of relatively high-selenium soil content.[113]

A similar study followed 10,456 men for six years and evaluated those diagnosed with prostate cancer during that period.[114] The men who had plasma selenium levels and plasma alpha- and gamma-tocopherol levels above the median had a 50-percent reduced risk of prostate cancer. These data correspond to other work showing a protective effect of selenium and vitamin E against prostate cancer.[115]

The NPC Trial reported a 63-percent lower incidence of prostate cancer in individuals taking selenium and, as a result, there has been heightened interest in research exploring mechanisms for selenium in prostate chemoprevention.[68] A follow-up of the trial, including three additional years of treatment (1993-1996), saw the incidence remain significantly less at 52 percent (p=0.005).[70] There are currently four trials in progress examining the effect of selenomethionine or high-selenium baker's yeast on specific populations of prostate cancer patients.[116]

The first, the Negative Biopsy Trial, will evaluate 700 men with persistently elevated prostatic specific antigen (PSA) and recent negative biopsy. The hypothesis is that selenium may prevent the progression of cancer in the 25 percent of men in this population who have early cancer missed by biopsy. They will be randomized to 200 or 400 mcg selenium from high-selenium yeast or placebo for 57 months.

The HGPIN Trial (High-Grade Prostatic Intraepithelial Neoplasia) will evaluate 470 men with high-grade prostatic intraepithelial neoplasia who are at risk for subsequent prostate cancer, but have not been treated with surgery or irradiation. If these men are biopsy-negative for cancer, they will be given either placebo or 200 mcg selenium as selenomethionine and will be followed for three years. This study will evaluate the ability of selenium to prevent the transformation of neoplasia to invasive cancer.

The Preprostatectomy Trial will evaluate 110 men with prediagnosed, localized prostate cancer who choose treatment with prostatectomy. Further treatment will consist of either 200 or 400 mcg selenium from high-selenium yeast or placebo for 6-8 weeks prior to surgery. This trial will evaluate biomarkers of inflammation and tissue selenium levels.

The Watchful Waiting Trial will evaluate 264 men with localized cancer and low-grade tumors and a life expectancy of less than 10 years who have elected not to participate in standard treatment. Watchful waiting with no treatment is considered an acceptable alternative in this population. They will be given 200 or 800 mcg high-selenium yeast or placebo. More information about these and other selenium trials is available at http://clinicaltrials.gov/

In a preliminary trial with a design similar to the Watchful Waiting Trial, 24 men with biopsy-proven prostate cancer were given either 1,600 or 3,200 mcg selenized yeast for an average of 12 months.[117] Although subjects on 3,200 mcg daily reported side effects, they did not correspond to plasma selenium levels and all subjects in the study had normal blood chemistries for the duration of the study.

Mechanisms of selenium in prostate cancer have not been fully explained, but there is evidence that selenium induces apoptosis in prostate cancer cells, while having no detrimental effect on normal prostate epithelium. This apoptotic action may be prevented by arachidonic acid and the 5-lipoxygenase products formed from arachidonic acid metabolism.[118] This knowledge may lead to recommendations that high fat diets containing arachidonic acid should be avoided in those on selenium-containing protocols for the treatment of prostate cancer.

Studies of Selenium Supplementation with Chemotherapy

The use of selenium repletion in cancer patients to normalize selenoprotein levels and act as an immune-augmentive strategy has been studied in several cancer types. One study, using both zinc and selenium, was conducted with patients beginning chemotherapy for the treatment of colorectal carcinoma, gastric adenocarcinoma, or esophageal carcinoma.[119] All patients had received 60 days of chemotherapy and had significantly low serum selenium and zinc levels at initiation of treatment. Thirty were given nutritional supplementation of 200 mcg/day selenium in addition to 21 mg/day zinc during the course of chemotherapy; 30 controls were given no selenium or zinc. At the end of the chemotherapy course, 70 percent of those given the nutritional supplements showed no sign of further decline in nutritional status and actually had an improvement in appetite and energy level. Their serum selenium and zinc levels rose significantly, although not to the level of cancer-free controls (Table 4). Eighty percent of those on chemotherapy without the supplements, however, had a significant worsening in nutritional status (prealbumin, albumin/globulin ratio, transferrin, cholesterol, total protein) and symptoms related to malnutrition.

Selenium supplementation was evaluated in 62 women diagnosed with ovarian cancer currently undergoing chemotherapy.[120] The patients had previously undergone surgery and one cycle

of intravenous therapy with cisplatin and cyclophosphamide. Half were given an antioxidant formula daily: 60 mg beta-carotene, 800 mg vitamin C, 144 mg vitamin E, 18 mg riboflavin, 180 mg niacin, and 200 mcg selenium from yeast in divided doses. The remaining 31 patients received only chemotherapy. While the control group had a consistent decline in selenium hair and serum levels during chemotherapy, the supplemented group had an increase in both parameters in addition to an increase in erythrocyte glutathione peroxidase levels and a significant stabilization of neutrophil count compared to controls. After two and three months, the supplemented group had a significant decrease of hair loss, flatulence, abdominal pain, weakness, malaise, and anorexia.

Table 4. Serum Zinc and Selenium Levels in Chemotherapy Patients and Controls

	0 days A	60 days B	Control C
Selenium (µg/dL)	55.7 ± 7.3*	62.4 ± 9.3**	65.0 ± 12.0
Zinc (µg/dL)	78.9 ± 7.8*	84.2 ± 5.4***	87.5 ± 9.70
Copper (µg/dL)	110.9 ± 16*	101.1 ± 12.8**	95.5 ± 13.2

* P < 0.01 A vs C; ** P < 0.05 B vs A; *** P < 0.02 B vs A
From: Federico A, Iodice P, Federico P, et al. Effects of selenium and zinc supplements on nutritional status in patients with cancer of the digestive tract. *Eur J Clin Nutr* 2001;55:293-297.

Advanced squamous cell carcinoma of the head and neck is associated with significant immunosuppression and has a poor prognosis with surgery or chemotherapy. Patients with this type of cancer who had previously received no chemotherapy were given 200 mcg sodium selenite starting on the first day of surgery or radiation treatment and followed for 60 days.[121] Compared to a placebo group with the same staging who also received radiation or surgical interventions, the selenium-supplemented group demonstrated a significant increase in immune activity: tumor cytolysis by cytotoxic lymphocytes, lymphocyte proliferation, and response to phytohemagglutinin, a mitogen that stimulates T lymphocyte responses. Those who received selenium or placebo, but no treatment, showed no improvement in immune parameters.

Conclusion

Adequate selenium is necessary for normal functioning of the immune system and thyroid gland. Selenium deficiency has been associated with thyroid disease and a variety of cancers. In numerous animal studies, selenium has demonstrated cytotoxic activity against tumor cells and significant immune-enhancing properties. Selenium is the basis of several key selenoprotein enzymes that have antioxidant effects. The doses of selenium used in animal and human chemoprevention studies have been greater than doses necessary for the maximal production of these enzymes, and it has been hypothesized the activity of selenium at these levels is due to other selenium compounds such as Se-methylselenocysteine, selenobetaine, and Se-allylselenocysteine. The benefit of using selenium in conjunction with chemotherapy or radiation therapy in specific cancers appears worthy of further investigation.

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