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Selenium and Cancer Prevention

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Epidemiologic and preclinical studies provide evidence that the essential nutrient selenium has chemopreventive potential. In particular, the results of a clinical intervention trial have shown strong protective effects of selenium-enriched yeast (200μg/day) for cancers of the lung, colon and prostate. While serum, plasma or toenail selenium concentrations are often utilized to predict exposure, it is not known if exfoliated cells would be a better sample for the accumulation and activity of selenium in target tissues. The cancer protective activities of selenium, like other biological effects of selenium, depend on the concentration as well as the chemical form provided. Genetic differences as well as interactions with other nutrients may also contribute to variation in the response to selenium. Selenium has been shown to modify a number of specific molecular targets involved with the cancer process. It appears to exert its chemopreventive effects via changes in selenoprotein production, immune function, carcinogen metabolism, DNA methylation, cell proliferation, apoptosis and/or angiogenesis. Which targets are modified will depend on the concentration and chemical species of selenium. Various clinical trials are currently being conducted in the United States to further investigate the effect of selenium on prostate, lung and colon cancer prevention. The SELECT or Selenium and Vitamin E Cancer Prevention Trial is a randomized phase III trial to determine the effectiveness of selenium and vitamin E, either alone or together, in preventing prostate cancer. Four smaller prostate cancer prevention studies are also being conducted. Volunteers are also being recruited for a randomized phase III trial to determine the effectiveness of selenium in preventing the development of second primary lung tumors in patients who have undergone surgery to remove stage I non-small cell lung cancer. Finally, a phase II randomized study is being conducted on the effect of celecoxib, a COX-2 inhibitor, and selenium and/or their combination on colonic adenoma recurrence. All of the current studies are in the recruitment phase of the trials.

Key Words: Selenium (se), Cancer prevention, SELECT, National Cancer Institute (NCI)

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Evidence for the Cancer Protective Effect of Selenium

Substantial evidence indicates that selenium, an essential trace element and normal constituent of diets, can be protective against cancer. Evidence for the cancer-protective effects of selenium in humans was initially obtained by means of ecological and correlation studies. Geographic correlation data in different regions worldwide and in the U.S. have noted an inverse association between selenium levels in forage crops or diet and cancer mortality in the same area.[1~4] Subsequently, a number of case-control studies indicated that selenium levels in blood, serum, hair or toenails is usually lower in cancer patients than in controls.[5~10] In prospective studies, low selenium status has been associated with significant increased risk of cancer incidence and mortality. For example, low plasma selenium was associated with a higher risk of prostate cancer.[11] Compared with the lowest quartile of selenium, the odds ratio of the second, third and fourth quartiles was 0.15, 0.21 and 0.24, respectively. Thus showing low plasma selenium is associated with a four to five-fold increased risk of prostate cancer.

Laboratory animal model studies support the epidemiologic evidence and demonstrate that selenium supplementation in the diet or drinking water inhibits initiation and/or post-initiation stages of liver, esophageal, pancreatic, colon and mammary carcinogenesis. However, the chemopreventive effect of selenium will depend on its chemical form.

Not all forms of selenium are metabolized the same or have the same biological effects (Fig. 1). Selenium-enriched yeast and many foods contain primarily selenomethionine. Selenomethionine may substitute for methionine in general body proteins and is the most effective form of selenium for increasing the concentration of selenium in organs and tissues. Selenomethionine can also undergo trans-sulfuration to form selenocysteine which can be metabolized by a specific lyase to hydrogen selenide. Many supplements contain selenium in the form of selenite or selenate which can be reduced to form hydrogen selenide. Hydrogen selenide is the precursor for selenium incorporation into selenoproteins.

Hydrogen selenide can be methylated to form methylselenol. The formation of methylselenol is believed to be necessary for selenium to exert its anticarcinogenic effects.[12] Some foods, such as garlic and broccoli, contain selenium primarily as Se-methyl-selenocysteine, which can be directly metabolized to methyl selenol. A number of studies have shown that selenium-enriched garlic is an effective anticarcinogen and that the cancer protective effect of selenium-enriched garlic is superior to that of natural garlic or other chemically defined sources of selenium such as selenite or selenomethionine.[13,14] Similar results have been obtained for selenium-enriched broccoli.[15~18]

All of the above-mentioned human studies have analyzed either serum, plasma, hair or toenail selenium to assess status. However, the relationship between the concentration of selenium in these samples and in the target tissues where selenium has

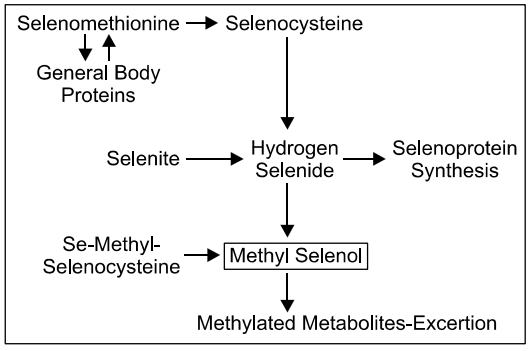

Fig. 1. Metabolism of different chemical forms of selenium. Selenomethionine is incorporated into general body proteins or converted to selenocysteine. Selenocytseine is metabolized to hydrogen selenide. Selenate and selenite combine with glutathione to form hydrogen selenide. Hydrogen selenide can either be utilized as a precursor for the synthesis of selenoproteins or undergo a series of methylation steps to form methyl selenol. Se-Methyl-selenocysteine is a direct precursor of methylselenol.

been shown to be protective against cancer is unknown. Exfoliated cells, such as colonic epithelial cells obtained from stool samples or from gastric lavage, lung epithelial cells from bronchoalveolar lavage or in sputum, mammary epithelial cells obtained by ductal lavage, from nipple aspirate fluid, or from breast milk, bladder urothelial cells present in urine samples, and buccal mucosal cells in mouth washings, might actually be better samples for monitoring site-specific exposure to selenium. Furthermore, selenomethionine, particularly during methionine deficiency, can accumulate in tissues in exchange for methionine in body proteins where it does not exert any specific biological effects related to selenium. Measuring selenium concentrations in blood constituents or other body fluids may not indicate the role that specific selenium compounds are having on molecular targets that are important for cancer protection in specific tissues.

There have been few intervention trials looking at selenium supplementation without supplementing other nutrients. In an intervention trial conducted in China, a community of about 21,000 was supplemented with selenite-fortified salt and residents of the community experienced a 35% drop in the incidence of primary liver cancer.[19)]

The Nutritional Prevention of Cancer Trial, carried out by Clark and coworkers in the U.S. was the first double-blind, placebo-controlled intervention trial in a western population, designed to test the hypothesis that selenium supplementation would reduce the risk of cancer.[20)] This study involved 1312 patients who were recruited because of a recent history of basal cell and/or squamous cell carcinoma of the skin. Supplementation of 200μg selenium/day as selenium-enriched yeast did not significantly affect the incidence of basal cell or squamous cell skin cancer; however, selenium supplementation significantly reduced total cancer mortality, and incidences of lung, prostate and colorectal cancers.[20)] However, not everyone benefitted from selenium supplementation. The protective effect of selenium was confined to males and was most pronounced in former smokers.[21)] Furthermore, participants with baseline plasma selenium concentrations in the lowest two tertiles (＜121.6 ng/ml) experienced reductions in total cancer incidence, whereas those in the highest tertile showed an elevated incidence.[21)]

Genetic variability may also determine how a person responds to selenium supplementation. Glutathione peroxidase is a selenium-dependent enzyme that participates in the detoxification of hydrogen peroxide. A nucleotide polymorphism at codon 198 of human glutathione peroxidase, resulting in a substitution of leucine for proline, has been associated with an increased risk for lung cancer.[22)] Individuals with one copy of the mutant allele were at 80% greater risk for lung cancer and individuals with two copies of the mutant allele were at 130% greater risk for lung cancer compared with individuals with the normal genotype. Although the activity of the enzyme has been shown not to differ among the different genotypes,[23)] the effect of dietary selenium supplementation on protecting people with the mutant allele from lung cancer is not known. Furthermore, there may be other, yet unidentified, polymorphisms that may relate to individual variability in the response to supplemental selenium.

Mechanisms for the Cancer Protective Effects of Selenium

Many potential mechanisms appear to be involved in the chemopreventive effects of selenium (Fig. 2). During selenium deficiency, addition of small amounts of selenium to the diet increases glutathione peroxidase and other selenoproteins such as thioredoxin reductase. However, many investigators believe that changes in the activity of selenoproteins may not be an important mechanism for the cancer protective effects of selenium because the amount of selenium needed for chemoprevention is usually much larger than the amount of selenium needed to maximize glutathione peroxidase activity.[24)] Despite these data,

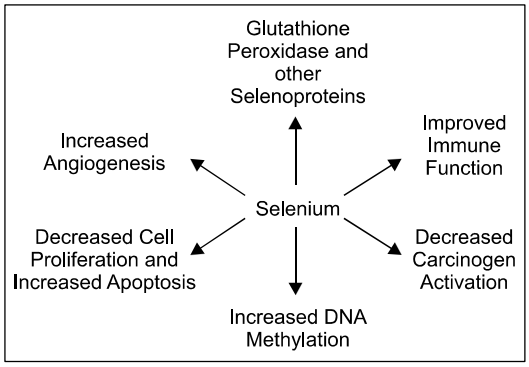

Fig. 2. Mechanisms for the chemopreventive effects of selenium.

there is increasing evidence that selenoproteins may indeed play a role in chemoprevention. First, while glutathione peroxidase activity does plateau at a fairly low intake of selenium, thioredoxin reductase activity can be influenced by chemopreventive levels of selenium.[25] For example, using rats fed a moderately high level (1μg Se/g) of selenium as selenite, thioredoxin reductase activity increased approximately two-fold in some tissues (lung, liver and kidney) but not in others, in comparison with rats fed a normal selenium level (0.1μg Se/g). In contrast to thioredoxin reductase, glutathione peroxidase activity was not increased by the high selenium level in any tissue.[26] Also, there is increasing evidence that many of the putative effects of selenium on cell cycle control and apoptosis are mediated via reactive oxygen species, and intracellular reactive oxygen species are regulated by several selenoproteins including thioredoxin reductase and the glutathione peroxidase family of proteins. Protein kinase C can also be influenced by selenoprotein status because its activity depends on reduction of sulfhydryls of surface cysteine residues by reduced thioredoxin, and thioredoxin reductase is the only known enzyme capable of reducing thioredoxin.[27]

Selenium also improves immune function. Several studies have found that supranutritional levels of selenium stimulate the cytotoxic activities of natural killer cells and lymphokine-activated killer cells.[28] The mRNAs of several T-cell-associated genes (CD4, CD8, HLA-DR) have open reading frames resembling that of selenoprotein P and potential stem-loop RNA structures with consensus SeCys-insertion sequences,[29] raising the possibility that they may encode functional selenoproteins yet to be identified. Furthermore, Beck[30] has observed using a mouse model of coxsackievirus-induced myocarditis, that a host deficiency in selenium leads to a change in viral phenotype, such that an avirulent strain of the virus becomes virulent and a virulent strain becomes more virulent. This change in pathogenicity was due to mutations in the viral genome.[31] Once these mutations occurred, even mice with normal selenium nutriture developed disease from the mutated virus.

Selenium may also regulate the activity of enzymes involved in the metabolism of carcinogens. Several studies have demonstrated that selenium supplementation can inhibit carcinogen-DNA adduct formation. For example, supplementation with either selenite or selenate but not selenomethionine resulted in significantly fewer 3,2'-dimethyl-4-aminobiphenyl (DMABP)-DNA adducts in the colon, but not in the liver, than in rats fed a selenium-deficient diet.[32] This reduction in DMABP-DNA adduct formation in the colon correlated with a reduction in DMABP-induced aberrant crypt foci.[33] Similarly, selenium has been shown to inhibit 7,12-dimethylbenz (a) anthracene (DMBA)-DNA adduct formation in the mammary gland but not in the liver and this has correlated with decreased mammary tumor development.[34,35] However, the protective effect of selenium against DMABP-DNA adducts appeared to occur between selenium deficiency and selenium adequacy, whereas the protective effect of selenium against DMBA-DNA adducts appeared to occur between selenium adequacy and selenium supplementation. This suggests that the protective effect of selenium against carcinogen-DNA adduct formation will depend not only on the chemical form and concentration of selenium, but also the carcinogen utilized and the target tissue examined.

During selenium deficiency, there also appears to be decreased DNA methylation, which is an epigenetic event associated with cancer susceptibility. During tumor progression, the DNA becomes paradoxically hypomethylated, despite the presence of regional hypermethylation and an increase in DNA methyltransferase (Dnmt1) activity. Rats fed a selenium-deficient diet had significantly hypomethylated liver and colon DNA compared with rats fed diets supplemented with selenite or selenomethionine.[36] HT-29 colon adenocarcinoma cells cultured in the absence of selenium had significantly hypomethyldated DNA but significantly more Dnmt1 protein expression that cells cultured in the presence of selenium.[37] Other dietary constituents may modify the effect of selenium on DNA methylation. Dietary folate and selenium appear to have interactive effects on DNA methylation, 1-carbon metabolism and cancer susceptibility.[38]

In contrast, selenium supplementation, at the levels observed in cancer chemoprevention trials, probably exerts its chemopreventive effects by different pathways including decreased cell proliferation and increased apoptosis. Selenium has been shown to inhibit cancer cell proliferation in many different model systems. Dong *et al.*[39] utilized microarray analysis to profile the gene expression changes in response to methylseleninic acid in PC-3 human prostate cancer cells. Of a total of 12,000 genes screened, over 2,500 were identified to be responsive to selenium treatment.[39] This demonstrates that selenium appears to exert its effects by multiple mechanisms. Furthermore, the literature suggests that four different pathways relating to cell proliferation and apoptosis are activated depending on the specific chemical form of selenium and that many of these pathways may be either p53-dependent or p53-independent.[40] First, selenium in the reductive pathway to selenide, especially seleno-diglutathione and hydrogen selenide induce irreversible apoptosis with DNA strand breaks. Second, methylated forms of selenium appear to induce cell cycle arrest and/or apoptosis independent of DNA strand breaks. Third, selenite and methylseleninic acid may induce global changes in the mitogen activated cell signaling pathway. Fourth, some forms of selenium such as the synthetic organoselenium compounds benzylselenocyanate (BSC) and 1,4-pheynylenebis (methylene) selenocyanate (*p*-XSC) may be directly cytotoxic.

Selenium, in the form of selenomethionine, has also been shown to be a determinant of basal p53 activity.[41] Selenomethionine reduces the cysteines in the p53 tumor suppressor protein, leading to an increase in the efficiency of DNA excision repair.[41] Thus suggesting another mechanism for the cancer protective effects of selenium.

In addition to affecting the intitiation and promotion stages of carcinogenesis, selenium may affect tumor promotion by inhibiting angiogenesis and metastasis. Jiang *et al.*[42] reported that methylseleninic acid and methylselenocyanate but not selenite or selenide inhibited matrix metalloproteinase-2 activity in human umbilical vein endothelial cells in a concentration-dependent manner. Likewise, methylseleninic acid but not selenite decreased cellular and secreted vascular endothelial growth factor protein levels in human prostate and breast cancer cells.[42] This demonstrates that the chemical form of selenium will also determine its effect on angiogenesis.

Current Selenium Cancer Prevention Studies in the United States

Many cancer chemoprevention trials are currently being conducted in the United States to further investigate the effect of selenium supplementation on cancer risk. The SELECT, or Selenium and Vitamin E Cancer Prevention trial, is a phase III, randomized, double-blinded, prospective 2×2 factorial clinical trial which will randomize 32,400 healthy men with normal prostate specific antigen to one of four study arms: a placebo, 200μg selenium as selenomethionine, 400 mg vitamin E as -tocopherol acetate or both the selenium and vitamin E supplements.[43] The objectives of the study are to compare the effect of

selenium and vitamin E on prostate cancer incidence and the incidence of lung cancer, colorectal cancer and all cancer combined in participants in this study. In the first 12 months of recruitment (August 2001-August 2002) 13,951 men were randomized; this is 43% of the total. Study agents will be taken orally for a minimum of 7 and a maximum of 12 years with assessments of general health, incident prostate cancer and toxicity performed at 12 month intervals.[43)]

Four smaller randomized, placebo-controlled clinical trials are also being conducted to further investigate the role of selenium in prostate cancer prevention. The first is for 1,165 men who are at greatly elevated prostate cancer risk by virtue of having been diagnosed with high grade prostatic intrepithelial neoplasia (HGPIN). Subjects will be randomized to either 200 μg/day selenomethionine or placebo. After randomization, each subject will be supplemented for 3 years and then followed for an additional 7 years. The primary endopoint of this study is prostate cancer. Secondary endpoints will include evaluation of cell proliferation and apoptosis in the prostate. The second study is for men with elevated prostate specific antigen but a negative biopsy. The study endpoints are prostate cancer, high grade prostatic intraepithelial neoplasia, prostate cell proliferation and apoptosis. The third study is for men with cancer, dosed with selenium between diagnosis and prostatectomy; the study outcomes are change in prostate selenium level, tissue glutathione peroxidase activity, proliferation and apoptosis. The fourth is for men with low-grade, organ-confined tumors who have elected watchful waiting; the study outcome is disease progresssion. In all four studies, men are being randomized to receive either selenium as selenomethionine or a placebo.

The National Cancer Institute is also conducting a study to determine the efficacy of selenium in terms of reducing the incidence of second primary lung tumors in participants with previously resected stage I non-small cell lung cancer. A total of 1,960 participants will be randomized to receive selenium-enriched yeast or a placebo for 4 years, with continued follow-up for the duration of the 10-year study. A second objective of this study is to compare the incidence of specific cancers, mortality from cancer, and overall survival of participants treated with selenium versus those treated with placebo.

A large clinical study is also being conducted to investigate the effect of selenium supplementation on colon cancer. In this study, participants will be randomized to receive celecoxib, a COX-2 inibitor, and/or selenium as selenium-enriched yeast in a factorial design. They study outcome is adenoma recurrence. All of the clinical trials are currently in the recruitment phase and no results have been obtained.

Summary

The trace element selenium has been shown to have chemopreventive potential by a converging body of evidence from epidemiologic, clinical and experimental studies. Despite similar selenium intakes, the absolute response of an individual to selenium may reflect complex interactions occurring with other nutrients such as methionine and folate and with genetic factors. There are various molecular targets for selenium; however, which targets are important will depend on the chemical form of selenium, concentration of selenium and disease site. Credentialing or understanding which genetic or epigenetic targets are most important for bringing about a phenotypic change will be necessary in future selenium and cancer prevention studies. Currently, the National Cancer Institute in the United States is sponsoring several large intervention studies to further investigate the role of selenium in prostate, lung and colon cancer.

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