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Selenium: More Than Just a Micronutrient Mineral

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ABSTRACT

Selenium is a micronutrient mineral found mainly in soils. Studies on selenium have increased rapidly worldwide especially after it has been shown to reduce the risk of certain types of cancer in humans and animals. The exact mechanism of action on how selenium inhibits diseases, in particular cancer, is still unknown. To date, the use of selenium in preventing or treating diseases is limited. However, many aspects about the biochemistry of selenium have been identified. This article reviews a number of key clinical, experimental and epidemiological studies on selenium as an anti-carcinogenic agent for some types of cancers. Some nutritional information on selenium and its recommended intake are also included. More clinical and experimental studies are needed to confirm previous findings on the role of selenium as an anti-carcinogenic agent.

INTRODUCTION

The word selenium is derived from a Greek word Selene which means moon. In 1817, Berzelius and Gahn discovered selenium while examining the sediment from a sulfuric acid plant at Gripsholm in Sweden, as quoted by Whanger (2002). At first, selenium was thought to be toxic. In 1856, Madison, who was an army surgeon at Fort Randall in South Dakota, USA, described a fatal disease as "alkali disease" affecting horses grazing in areas near the Fort (Whanger, 2002). Subsequently, in 1934, the toxic component in the plants fed to the horses was identified as selenium (El-Bayoumy & Sinha, 2004).

Nelson, Fitzhugh & Calvey (1943) and his team found that selenium caused liver tumours in rats and they concluded that selenium was a carcinogenic agent. However, Schwarz and Foltz (1957) found that selenium was more potent than vitamin E in protecting the animal liver from necrosis in rats fed torula yeast diets. Frost and Shamberger (1969) stimulated research interests on selenium in cancer prevention. The biochemical basis for the role of selenium in the glutathione peroxidase enzyme was established by Rotruck *et al.* (1973). Schrauzer, White & Schneider (1977) reported that selenium is a potential human cancer protective agent. Since then, selenium as an anticarcinogenic agent has been the subject of many studies worldwide.

Selenium is a micronutrient mineral that plays an important role in health. Implicated as an anti-carcinogenic agent, selenium affects oxidative stress, DNA methylation, DNA repair, inflammation, apoptosis, cell proliferation, carcinogen metabolism, hormone production, angiogenesis and immune function (Taylor, 2004). The functions of selenium are believed to be carried out by selenoproteins, in which selenium is incorporated as the amino acid called selenocysteine.

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Selenoproteins are responsible for selenium functions in biologic systems (Raymond, 2001). These include glutathione peroxidase, thioredoxin reductase and seleno-protein P.

The purpose of this communication is to present key scientific evidence for selenium as an anti-carcinogenic agent.

SELENIUM IN PLANTS AND FOODS

Selenium occurs naturally in soil. It flows through the food chain from soil to plants and then to humans and animals. Thus, the selenium content of food varies from one region to another, depending on the selenium content of the soil in which it is grown. In general, selenium is found in fish, meat, poultry, eggs, diary products and grains. Brazil nuts have a high concentration of selenium.

It is known that selenium is similar to sulfur in terms of chemical and physical properties. Most plants are known to convert inorganic selenium in soil to organic selenium compounds through the sulfur pathway. In the 1990s, researchers worked on enriching soil with selenium. They also tried to enrich plants, such as garlic, onion, beets, tomato, broccoli and cabbage, with selenium by fertilising the crops with water-soluble selenite salt. After harvesting and processing, the selenium-enriched plants are usually lyophilised and milled to a powder.

The amount of selenium varies markedly in plants grown on seleniferous soils. Vegetables such as potatoes, beets, tomatoes, beans, carrots, cabbage and cucumbers contain no more than 6 µg selenium per gram even when grown on seleniferous soils. In contrast, other vegetables such as asparagus and onions have been found to contain up to 17 µg selenium per gram grown on the same type of soil (Whanger, 2002). With the introduction of HPLC–ICP–MS (High Performance Liquid Chromatography with Inductively Coupled Plasma–Mass Spectrometry), more than 17 seleno-compounds have been identified so far.

Selenium occurs in two forms, organic and inorganic. Selenite is the most predominant inorganic form found in both plant and animal tissues, while selenomethionine is the major organic seleno-compound in cereal grains, grassland legumes and soybeans (Whanger, 2002). Se–methylselenocysteine is the predominant form present in selenium enriched plants such as garlic, broccoli, onions and sprouts (Clement *et al.,* 2000; Cai *et al.,* 1995; Finley *et al.,* 2001). At low concentrations of selenium, Se-methylselenocysteine is the major form present in plants, but at elevated concentrations, γ–glutamyl-se-methylselenocysteine is the predominant form of selenium and it serves as a carrier of se–methylselenocysteine (Dong *et al.,* 2001).

Clement, Lisk & Stoewsand (1992) reported that selenium-enriched garlic, which yielded 3 µg selenium per gram of diet, significantly reduced the mammary tumour incidence in rats from 83% to 33%. Similar to garlic, selenium-enriched broccoli also reduced incidence of mammary tumours from 90% to 37% (Finley *et al.,* 2001). Selenium-enriched garlic was shown to be twice as effective as selenium-enriched yeast in the reduction of mammary tumours (Clement *et al.,* 2000). The total number of tumours and the incidence of tumours were reduced to a greater extent by selenium-enriched garlic than selenium enriched yeast. In general, selenium-enriched yeast, mushroom, garlic, onion and leek are used as dietary supplements owing to claims for their anti–oxidative and anti–tumour effects (Clement, Dong and Ganther, 2002).

In some parts of China where the soil is depleted of selenium, Keshan disease (cardiomyopathy) and Kaschin–Beck disease (arthritis) result from selenium deficiency (Yang, Zhu and Liu, 1984). These diseases occur when selenium

intake is 10 µg per day or less. The Daily Reference Intake (DRI) of United States for selenium is set at 55 µg per day for adults with adjustments for women who are pregnant or lactating, and for babies and children. Selenium becomes toxic at levels of 800–1000 µg per day (8–10 ppm) (Jacobs and Frost, 1981). It has been suggested that the dietary selenium intake (100–500 µg per day) above the DRI is required for selenium's anti-carcinogenic effects (Rotruck *et al.*, 1973; Clement, 1998; El-Bayoumy, 2001). Selenium is available as a dietary supplement, either singly or in combination with other vitamins such as vitamin E. Doses of 20 µg inorganic forms (sodium selenite or sodium selenate) and 50 to 200 µg organic selenium in the form of selenised yeast or selenium–methylselenocysteine, are available in pharmacies.

SELENIUM AND DISEASES

Experimental, epidemiological and clinical studies have shown that selenium can reduce the risk of certain types of cancer.

Experimental studies

Worldwide, several animal studies on selenium as an anti-carcinogenic agent have been conducted. Combs and Combs (1986) estimated that more than 100 animal studies in which tumour production and/or preneoplastic endpoints had been measured, two thirds of these studies revealed reductions in the incidence of such outcomes, with half showing reductions of 50% or more. They observed that only a few studies have found selenium to be ineffective, and concluded that the preponderance of results, from animal studies involving inductions of tumours by chemical or viral agents or by transplantation, indicated that high level exposure to at least some selenium compounds can be anti-carcinogenic. In animal modules, selenium inhibits carcinogenesis during both the initiation and later stages of carcinogenesis, and that it inhibits both chemically and virally induced tumours (Combs and Grey, 1998). The effects of selenium appear to be reversible, in that the anti-carcinogenic effect is reversed when selenium is withdrawn.

Dorado, Porta & Aquino (1985) found that dietary exposure of either 4 or 6 µg sodium selenite /g of diet to rats treated with diethyl nitrosamine after partial hepatectomy and later promoted with Phenobarbital, showed modest reductions in the incidence of hepatic tumours, and nearly twice the incidence of renal tumours. Also, the studies of Thirunavukkarasu and Sakthisekaran (2003a, b, c) in N-nitroso-diethylamine initiated and Phenobarbital promoted rat hepatocarcinogenesis treated with dietary sodium selenite (4 ppm) (parts per million), indicated selenium's role as an essential micronutrient in cancer chemo-preventive therapy.

More recently, Björkhem *et al.* (2005) showed that daily dietary exposure of 1 to 5 ppm sodium selenite to rats treated with diethyl nitrosamine and promoted later with 2-AAF (2-acetylaminefluorene), showed that the carcinogenetic process may be prevented by selenium supplementation both during the promotion and the progression phases. They concluded that selenium is a potent cancer preventive agent.

Epidemiological studies

A number of studies have shown that cancer patients generally have lower selenium status, on average, than healthy controls (Combs, 1997). In 1971, Shamberger and Willis reported that mortality due to lymphomas and cancers of the gastrointestinal tract, peritoneum, lung and breast is lower for men and women residing in areas of the United States that have either moderate or high concentra-

tions of selenium in forage crops than for those residing in low areas forage selenium. In Japan, a prospective study of 4,857 patients followed serum selenium levels in those who developed cancers of all types over a 3-year period (Ujiie, Itoh and Kikuchi, 1998). Those who developed cancers during the trial period had significantly low serum selenium levels at baseline than those who were free of cancer.

In Finland, Knekt, Aromaa and Maatela (1990) reported that a prospective study of 39,268 Finnish men and women showed that risk for several cancers, particularly stomach, pancreas and lung, was significantly higher in men who had the lowest level of serum selenium. In China, where soil selenium content varies from region to region and people tend to live in a single area all their lives, Yu *et al.* (1985) measured the selenium content of blood stored in blood banks in 30 different regions of China, and used this data to classify the regions as high, medium or low selenium. The regions were divided equally into 3 groups (10 regions per group). Then they looked at total death rates from cancer in the low, medium and high selenium groups of provinces. They found that the death ratio was 3 to 2 to 1, respectively, which means that the cancer death rate in the high selenium region was only one third that of the low selenium region. In another study in China, researchers demonstrated a significant inverse association between the incidence of primary hepatocellular carcinoma and plasma selenium levels (Li, Blot and Taylor, 1995).

Clinical studies

The most important clinical study on selenium and cancer is probably the study of Clark and his team (Clark *et al.,* 1996). The study, started in 1983 and completed in 1993, was a randomised double-blind study with 1321 older (average age 63) Americans (75% men and 25% women) with a history of basal and/or squamous cell carcinomas of the skin. Briefly, individuals were divided into two groups, one group received placebo, and the other received 200 µg selenium-enriched yeast per day. The major aim of this study was to determine whether selenium could lower the incidence of skin cancers. Clark and his colleagues found no reduction in skin cancer but found instead dramatic declines in the incidence of other cancers in the selenium group. They found 50% lower total cancer deaths, 37% lower total cancer incidences, 63% fewer prostate cancers, 58% fewer colorectal cancers and 46% fewer lung cancers compared with the placebo group. There was no sign of selenium toxicity seen in Clark's study.

From the scientific point of view, Clark's study was criticised by other researchers including Colditz (1996), who highlighted several points regarding Clark's study with selenium. Firstly, due to a relatively small proportion of women (25%) in the study, the results showed no consistent reduction in breast cancer and other cancers that are specific to women with higher selenium intake, and thus, Colditz concluded that the applicability of the results to women remains to be established. Secondly, Colditz wondered about the reasons for the inconsistent results of selenium: is it the result of the dose of selenium, the form of selenium or the specific cancers? Finally, Colditz observed that selenium showed reductions in some cancers such as lung and prostate but not for all types of cancer. Despite this setback, it was noted that the number of selenium studies, both in vitro and in vivo, increased manifolds after Clark's study.

In Qidang (Shandong province in China), where 15% of adults carry the hepatitis B surface antigen and are 200 times more likely to develop hepatocellular carcinoma (Yu, Zhu and Li, 1997), Yu and his team conducted two studies in this area. The first study involving 2,474 family members who had developed liver

cancer, was randomised to receive either 200 µg of selenium- enriched yeast daily or placebo over a period of 2 years. They found that 13 of the 1030 controls developed liver cancer as compared to 10 of the 1,444 subjects receiving selenium. Thus, the incidence of liver cancer was 45% lower in the selenium treated group. The second study in Qidang was over a 7-year period involving the use of a tablet salt fortified with 15ppm selenium as sodium selenite. Yu and his team reported that liver cancer incidence among villagers provided selenium fortified salt dropped from 54.8 to 34.5 per 100,000 cases whereas rates in control villagers remained high at 54 – 65 per 100,000.

In Italy, 304 patients with metachronous polyps of the large bowel were given 200 µg selenium as L-selenomethionine daily plus zinc and vitamins A, C and E for 5 years and compared with those taking placebo. Patients with prior resected adenomatous polyps were used in a randomised trial and new adenomatous polyps were noted. The incidence of metachronous adenomas was only 5.6% in the treated group and 11% in the control group (Bonelli *et al.,* 1998).

In India, 149 patients with precancerous lesions in the oral cavity were supplemented with a mixture of four nutrients (vitamin A, riboflavin, zinc and selenium) 100 µg daily for 6 months and 50 µg in the final 6 months as selenium enriched yeast and compared to controls (also 149 patients) who received placebo. The frequency of micronuclei and DNA adducts were significantly reduced in the treated group at the end of the one-year study. The adducts decreased by 95% in the treated group with all categories of lesions and by 72% in subjects without lesions. No such effects were noted in the control group (Prasad, Mukunda and Krishnaswamy, 1995).

There are two large ongoing clinical trials that examine the effect of selenium alone or combined with vitamin E on the risk of prostate cancer, namely, SELECT (Selenium and Vitamin E Cancer Prevention Trial) and APPOSE (Australian Prostate Cancer Prevention Trial Using Selenium). SELECT, which began in 2001, involves more than 35,000 men from the United States, Puerto Rico and Canada so far. The amounts of selenium and vitamin E used in this study are 200 µg and 400 IU (International Units), per day, respectively. APPOSE, which is conducted in Australia in a population of men who are at increased risk because of first-degree relatives with prostate cancer, aims to use daily supplementation with selenium to reduce prostate cancer incidence. The results of these two clinical trials are expected to be available in the next few years.

CONCLUSIONS

Selenium is an important mineral found mainly in fish, meat, poultry, eggs, diary products and Brazil nuts. The intake of 55 µg selenium per day is recommended in US to support general health. Selenium intake is considered safe (provided not exceeding 800 µg per day). Clinical, experimental and epidemiological studies indicate selenium's role as an anti-carcinogenic agent. However, more studies are needed to confirm findings of previous studies of selenium as an anti–cancer agent.

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