

Reduction of Cancer Risk by Consumption of Selenium-Enriched Plants: Enrichment of Broccoli with Selenium Increases the Anticarcinogenic Properties of Broccoli

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ABSTRACT

Plant-based diets and phytochemicals present in plants are associated with decreased risk of cancer. *Brassica* species, and broccoli in particular, are associated with reduced risk of several important cancers. Selenium (Se) is an essential nutrient that is covalently bound in a number of different chemical forms found in plants. Broccoli accumulates Se many-fold beyond the concentration of Se in the soil, and the chemical form of Se in broccoli is similar to the chemical form in high-Se garlic, a food with unique chemoprotective properties. Se from broccoli grown to accumulate more than 500 µg Se/g did not accumulate in rat tissues or increase glutathione peroxidase enzyme activity to the same extent as Se salts or seleno-amino acids. Se from high-Se broccoli decreased the incidence of aberrant crypts in rats with chemically induced colon cancer by more than 50%, compared with controls. Se from high-Se broccoli also decreased the incidence of mammary tumors in rats treated with 7,12-dimethylbenz(a)anthracene (DMBA) and tumor number and volume in APC^{min} mice. These results suggest that development of methods to increase the natural accumulation of Se in broccoli may greatly enhance its health-promoting properties.

INTRODUCTION

MANY PLANTS CONTAIN bioactive substances, often called phytochemicals, that have medicinal properties, and protection against cancer is often associated with dietary consumption of phytochemicals. Phytochemicals have many different biochemical actions, including functioning as antioxidants and acti-

vating detoxification pathways.¹ Selenium (Se) is a nutritionally essential mineral that also has been associated with protection against several important cancers.² Se is incorporated into most plant tissues in direct proportion to the amount of Se available from the soil, but some plants actively accumulate Se well beyond the concentration in the soil.³ Different plant species often contain different chemical forms

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of Se, and the chemical form of Se often determines its bioactivity.⁴ This review focuses on the bioactivity of Se from broccoli; broccoli may contain Se in a form that is especially chemoprotective against certain cancers.

Schwarz and Foltz⁵ demonstrated in 1957 that Se was a component of factor 3, an organic compound that protects pigs and rats against liver necrosis. There are many known biological functions of Se, including its essentiality for the synthesis of selenoproteins such as glutathione peroxidase (GSH-Px) and thioredoxin reductase,⁶ optimal function of the immune system,⁷ optimal neuropsychological function,⁸ as an antioxidant,⁹ and as a regulator of metabolism.^{10,11} One of the most studied functions of Se is cancer protection. Clark et al.² fed human subjects for 10 years a placebo or 200 μg of Se per day and reported that Se decreased the incidence and mortality of prostate cancer by 70%, lung and colorectal cancer by 50%, and total cancer incidence and mortality by 50%. In an intervention trial in Linxian, China, cancer rates were significantly decreased with a combination of β -carotene, vitamin E, and Se.¹² The prediagnostic concentration of Se in toenails has been significantly and inversely associated with prostate cancer incidence.¹³ The population of Great Britain has a history of low Se intakes, and an editorial in the *British Medical Journal* entitled, "Dietary Selenium—Time to Act: Low Bioavailability in Britain and Europe Could Be Contributing to Cancers, Cardiovascular Disease, and Subfertility," argued that the available evidence is sufficient to recommend increased Se intake in Great Britain.¹⁴ Popular interest in Se supplementation is demonstrated by the presence of more than 20,000 sites on the World Wide Web that are devoted to Se supplements or health benefits.

Se occurs in many inorganic and organic chemical forms.¹⁵ Inorganic Se is often in the form of salts of selenite or selenate. Se can be covalently bound in organic molecules such as Se-substituted analogs of sulfur-amino acids (e.g., selenomethionine [SeMet], selenocysteine), amino acid derivatives (e.g., selenohomocysteine, selenocystathione), and methylated forms (e.g., methyl selenol, dimethyl selenide, selenium methyl selenocysteine [SeMSC]). Other exotic forms are primarily

generated in the laboratory (e.g., benzyl selenocyanate, dibenzyl diselenide).

The chemical form of Se partially determines its metabolism (Fig. 1) and may affect the ultimate physiological outcome and health benefit.^{15–17} For example, SeMet may substitute for methionine⁶ and accumulate in methionine-containing proteins in the body, and selenite readily incorporates into specific selenoproteins in Se-deficient animals.¹⁸ Methyl selenol, a metabolite produced in the excretory pathway,¹⁵ may be especially efficacious for reducing the risk of cancer. Therefore, forms of Se, such as SeMSC, that can easily be transformed to methyl selenol may be more chemoprotective than others forms of Se.¹⁹

Different foods contain different amounts²⁰ and different chemical forms⁴ of Se, so it is reasonable to assume that Se from different foods may be metabolized by different routes. Therefore, the health benefits of Se from food may depend on both the total amount and the chemical form of Se in the specific food consumed. When total Se concentrations were determined in different brands of identical food products purchased from the same grocery store (Table 1), Se varied as much as tenfold.²⁰ Such variation was probably a consequence of the origination of the raw agricultural commodities from areas of low or high soil Se content.

SELENIUM IN PLANTS

Plants containing Se may be grouped into two broad categories: those that accumulate Se in direct proportion to the amount of Se available from the soil (e.g., wheat) and those that actively accumulate Se orders of magnitude greater than the Se concentrations in the soil (e.g., *Astragalus* spp.).³ The Se concentration of wheat may vary from an average of 0.2 μg Se per gram of plant tissue to 50 $\mu\text{g}/\text{g}$ for wheat grown in seleniferous areas.²¹ However, *Astragalus* plants collected from an area with high soil Se contained in excess of 2,000 $\mu\text{g}/\text{g}$, while wheat growing in close proximity contained only 8 $\mu\text{g}/\text{g}$ (Table 2).²²

Se is sequestered in accumulator plants primarily in methylated forms such as SeMSC, γ -glutamyl SeMSC, selenocystathione, seleno-

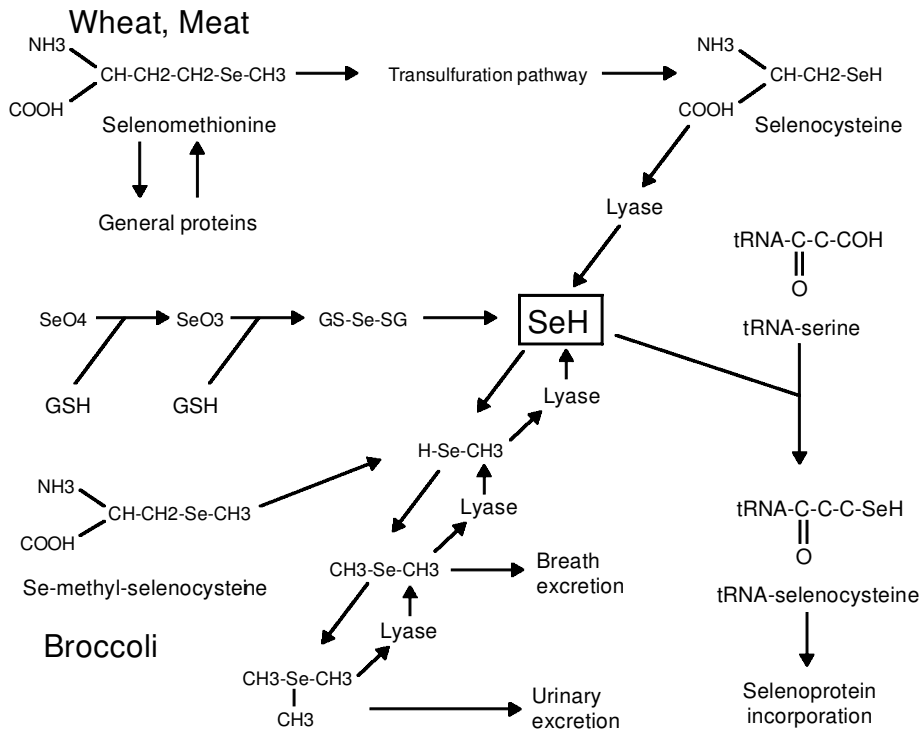


FIG. 1. A generalized schematic diagram of Se metabolism, showing the unique pathways that may be followed by Se from broccoli, wheat, and meat. Formation of methyl selenol (Se-CH₃) may be a crucial event in protection against carcinogenesis.

mocysteine, γ -glutamyl selenocystathione, and methyl selenol.²³ These forms of Se can be safely stored in membrane-bound structures within the plant, and Se-accumulating plants also have a much smaller fraction of their total Se sequestered in the protein fractions of the plant.³ A key enzyme necessary for synthesis of many of these methylated compounds is selenocysteine-specific methyltransferase. Insertion of the gene for this enzyme into a species of *Astragalus* that does not accumulate Se confers to the plant the ability to accumulate Se.^{24,25}

SELENIUM IN BROCCOLI

Broccoli is an Se accumulator, and broccoli that was grown in a synthetic soil-free mixture (peat moss/vermiculite) with added sodium selenate accumulated almost 1,000 μg Se per gram of dry plant tissue.²⁶ Limited work has been conducted to determine the chemical form of Se in broccoli. Cai et al.⁴ reported that broccoli contained large amounts of SeMSC, a finding recently confirmed by Roberge et al.²⁷ Se from broccoli does not accumulate in the rat²⁶

TABLE 1. CONCENTRATION OF SELENIUM IN SIMILAR FOODS OF DIFFERENT BRANDS PURCHASED FROM A LOCAL GROCERY STORE

Food/brand	Selenium concentration ($\mu\text{g}/\text{g}$)	% of Daily recommended Intake in a 100-g serving
Tortilla, corn, Brand A	0.03 \pm 0.002	5
Tortilla, corn, Brand B	0.35 \pm 0.03	64
Corn masa mix, Brand A	0.047 \pm 0.006	8
Corn masa mix, Brand B	0.50 \pm 0.008	91
Ground beef, SW Missouri	0.06 \pm 0.001	11
Ground beef, North Dakota	0.37 \pm 0.009	67

From Finley et al. (1996).²⁰

TABLE 2. SELENIUM CONTENT OF PLANT AND ANIMAL MATERIAL FROM A HIGH-SELENIUM AREA IN SOUTH DAKOTA

Item	Selenium concentration ($\mu\text{g/g}$)
Wheat	9.0 ± 1.0
Ground beef (raw)	0.64 ± 0.5
Princess plume	$2,843 \pm 170$
Astragalus plant	$1,658 \pm 122$
Astragalus flower	$3,178 \pm 500$

From Finley (1999).²²

or human²⁸ to the same extent as other forms of Se do, presumably because the SeMSC is metabolized directly to methyl selenol²⁹ and enters the excretory pathway.¹⁵

There is experimental evidence that methylated forms of Se are more chemoprotective than other forms.³⁰ Ip and coworkers developed a system for growing garlic that contains as much as 1,000 μg Se per gram of dry garlic powder. When the garlic was fed to rats, the Se did not accumulate in rat tissues as well as Se from Brazil nuts did.³¹ The chemical form of Se in garlic that contains more than 200 $\mu\text{g/g}$ is primarily SeMSC⁴; however, garlic with Se concentrations lower than 200 $\mu\text{g/g}$ contains primarily γ -glutamyl SeMSC.²³

A series of reports has demonstrated that Se from high-Se garlic, but not from high-Se onions, is a potent chemopreventive agent.³² High-Se garlic has been demonstrated to be especially effective against mammary cancer in rats induced by 7,12-dimethylbenz(a)anthracene (DMBA).^{33,34} Se, and not other compounds in garlic, was reported to be primarily responsible for the anticarcinogenic effect. An aqueous extract of garlic also has been demonstrated to be protective.³⁵

SELENIUM FROM HIGH-SELENIUM BROCCOLI IS METABOLIZED IN A UNIQUE MANNER

Broccoli is an important vegetable in the Western diet, and consumption of broccoli in the United States has increased sevenfold in the last 30 years. Numerous studies have shown an inverse correlation between the incidence of many cancers and consumption of cruciferous

vegetables.³⁶ Broccoli intake has been directly associated with reduced risk of bladder cancer.³⁷ The most studied chemoprotective compounds in broccoli are glucosinolates—secondary plant compounds that induce phase II enzymes.³⁸ More recently, an article in *Medical Hypotheses* presented the argument that the addition of Se to brassicas could provide even greater protection against cancer.³⁹

The retention, distribution, and excretion of Se from broccoli were studied in rats that were made Se-deficient and then refed adequate amounts of dietary Se as selenite, selenate, selenomethionine, or high-Se broccoli. Se from high-Se broccoli did not accumulate in most rat tissues or increase the activity of glutathione peroxidase (GSH-Px) as well as Se from salts or SeMet did (Fig. 2).²⁶ The incorporation of Se from different food sources into selenoproteins was studied by polyacrylamide electrophoresis. Radioactive Se from broccoli grown hydroponically in the presence of selenium 75 (⁷⁵Se) and fed to Se-deficient rats was not incorporated into specific selenoproteins with the same efficiency as was ⁷⁵Se from meat.⁴⁰ A stable Se isotope incorporated into hydroponically grown broccoli and fed to healthy young men was not accumulated as well as stable Se in the form of selenate.²⁸ Inefficient retention of Se from broccoli implies that a large proportion of the Se is moved into the excretory pathway and thus may be available for protection against carcinogenesis.

SELENIUM FROM BROCCOLI IS EFFICACIOUS FOR THE PREVENTION OF COLON CANCER

The anticarcinogenic potential of Se from broccoli was evaluated in rats by using chemically-induced aberrant colonic crypts as the model.⁴¹ Aberrant crypts are precancerous lesions in the colon that are highly correlated with the eventual number of colonic tumors. Rats were assigned to dietary treatments (0, 0.1, or 2 mg Se per kilogram of diet as selenate, selenite, or SeMet) for 3 weeks, and cancerous lesions were induced by injecting the animals with a carcinogen (either 2,3-dimethyl-4-amino biphenyl or dimethyl hydrazine). Rats con-

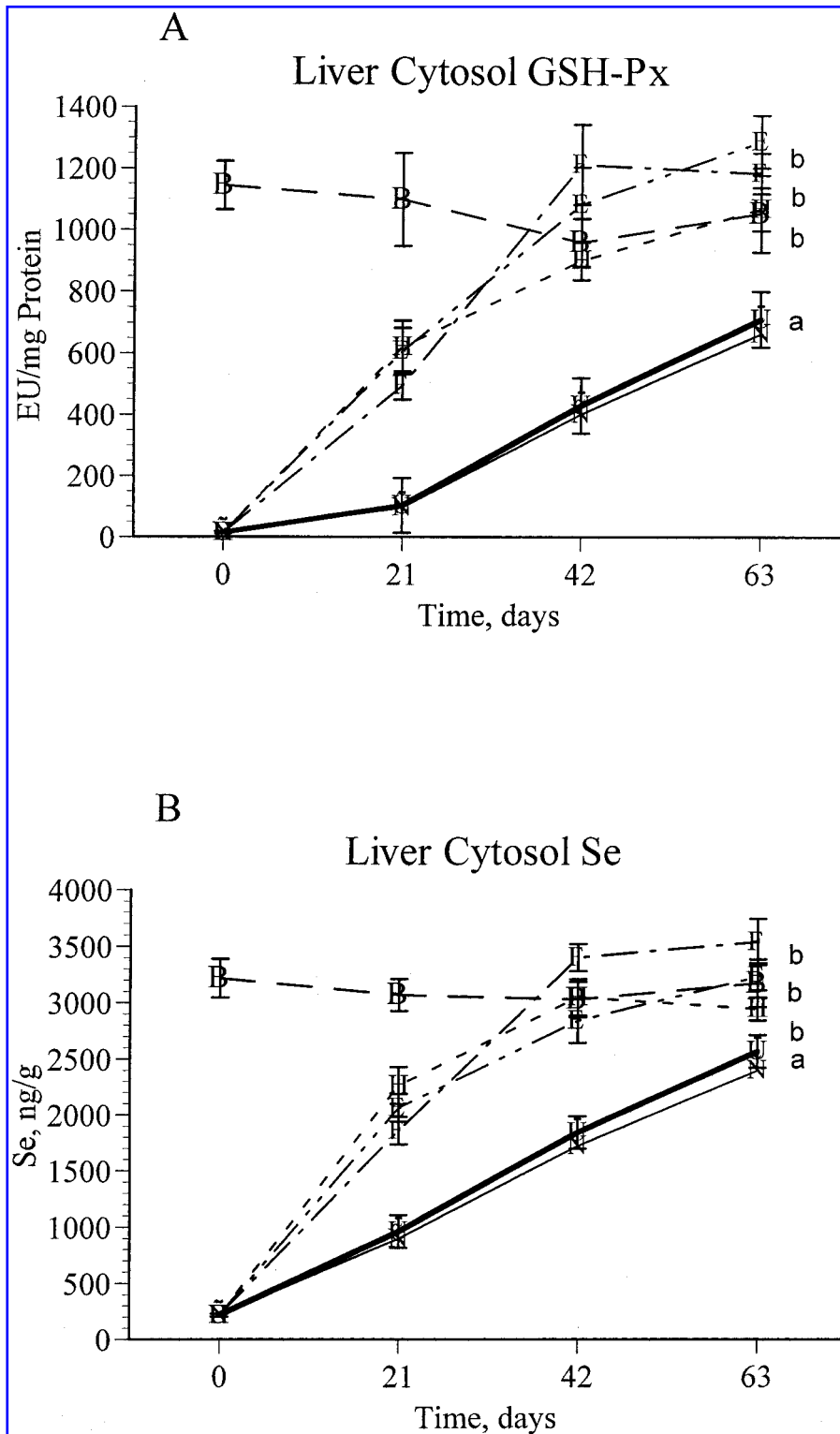


FIG. 2. Se from high-Se broccoli does not accumulate in liver cytosol or activate GSH-Px activity as well as Se from selenate, selenite, or selenomethionine. Rats made Se-deficient by consumption of a Se-deficient diet for 6 weeks were refeed adequate Se ($0.1 \mu\text{g}$ per gram of diet) as selenate, selenite, or selenomethionine (*dashed lines*) or as high-Se broccoli (*solid lines*). Activation of GSH-Px in liver cytosol (**A**) and accumulation of Se in liver cytosol (**B**) were monitored for 63 days after refeeding of Se-adequate diets.²⁶

sumed the assigned diets for 8 additional weeks before they were killed and their colons were prepared for microscopic evaluation. Aberrant crypts were significantly decreased in a dose-dependent manner by selenate and selenite, but not by SeMet.⁴¹

The anticarcinogenic potential of Se from high-Se broccoli was determined by adding sufficient high-Se broccoli to diets to supply 0.1 or 1.0 μg Se per gram of diet. In our model, diets containing 0.1 $\mu\text{g}/\text{g}$ were representative of human diets that are adequate in Se for normal health, and those containing 1.0 $\mu\text{g}/\text{g}$ were representative of the supplemental levels of Se that have been shown to protect against cancer in humans. Because broccoli itself is anticarcinogenic, all diets contained the same amount of broccoli; the low-Se diets utilized broccoli grown without added Se. Compared with rats fed selenate or selenite (found to be effective against aberrant crypts in the initial experiment), rats fed high-Se broccoli had approximately 50% fewer aberrant crypts (Fig. 3).⁴² Broccoli sprouts contain higher concentrations of phytochemicals than broccoli florets do, but broccoli sprouts grown to contain high concentrations of Se ($>500 \mu\text{g}/\text{g}$) were not more chemoprotective than broccoli florets alone.⁴³

High-Se broccoli has been proven to be protective against cancer in other tumor models. The APC^{min} mouse is a murine model for the human disorder familial adenomatous polyposis. The APC^{min} mouse model is unique in that tumors appear spontaneously in the gastrointestinal tract, rather than as a result of induction by a carcinogen. Mice fed high-Se broccoli (2 μg Se per gram of diet) showed significantly fewer total tumors and a lower total tumor burden (by almost 50%) than mice fed low-Se broccoli and 0.1 $\mu\text{g}/\text{g}$ Se.⁴⁴ In the DMBA-induced rat mammary tumor model, high-Se broccoli significantly reduced tumor incidence, total tumor number, and the percentage of animals with tumors to about 30% of the values in control animals fed adequate Se (0.1 $\mu\text{g}/\text{g}$) without broccoli.⁴³

Broccoli also can accumulate relatively high concentrations of Se when grown under standard agricultural conditions. The aquifers in some of the vegetable-producing regions of California pass through seleniferous rock lay-

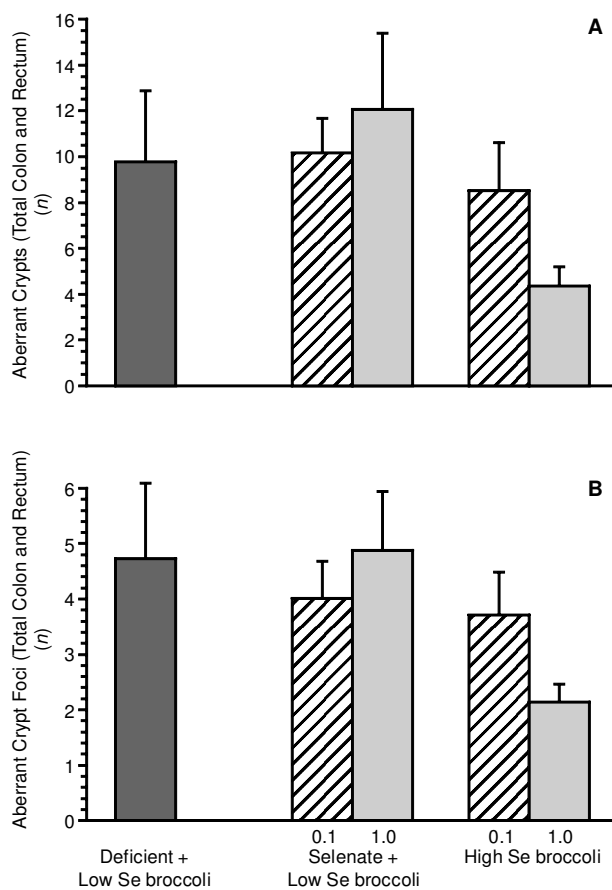


FIG. 3. Se from high-Se broccoli is more effective than broccoli alone or selenate + broccoli for the reduction of aberrant crypts (A) or aberrant crypt foci (B). Aberrant crypts and aberrant crypt foci are both markers of colon cancer and are highly correlated with the ultimate number of colonic tumors. Rats were fed either a Se-deficient diet + low-Se broccoli, a diet containing 0.1 or 1.0 μg Se per gram as selenate + low-Se broccoli, or a diet containing 0.1 or 1.0 μg Se per gram as high-Se broccoli. All diets had equal amounts of broccoli, and diets were fed for 13 weeks before the animals were killed and their colons were examined for aberrant crypt foci.⁴²

ers, and broccoli irrigated with this water may accumulate high concentrations of Se (1–5 mg/kg; G. Banuelos, personal communication). Broccoli has been used as a phytoremediation agent to remove Se from seleniferous soils in these areas of California.⁴⁵ The anticarcinogenic potential of this broccoli has not been studied.

The effectiveness of Se in broccoli against cancer, the inclusion of many other anticancer compounds, and the general acceptability of broccoli by the public should make this vegetable an excellent source of supplemental dietary Se. However, there have been no long-

term human studies using high-Se broccoli. The Se content of naturally produced high-Se broccoli could certainly be used as a nutritional advantage of broccoli in marketing strategies, and perhaps high-Se broccoli could be sold as a specialty crop. It also may be possible to up-regulate the methyl-transferase gene in broccoli that allows accumulation of Se as SeMSC; such a genetic modification might allow increased Se content of broccoli grown on soils that are only moderately high in Se.

INTERACTION BETWEEN SELENIUM AND OTHER BIOACTIVE COMPONENTS OF BROCCOLI

In addition to cancer protection, Se also is essential for the activity of numerous proteins, including thioredoxin reductase (TR), the primary enzyme that reduces thioredoxin. It is unclear whether any of the anticancer properties of Se are mediated through TR, but thioredoxin controls many reactions that regulate cell growth. It is well known that Se intake affects TR activity in the body, but recent reports suggest that glucosinolates in broccoli also may upregulate TR. TR activity is stimulated by high oxygen tension.⁴⁶ Hintze et al.⁴⁷ used a reporter gene construct to demonstrate that electrophilic substances, such as sulforaphane (a glucosinolate hydrolysis product), upregulate TR through interaction with a promoter sequence.⁴⁷ Glucosinolates and Se in broccoli may interact synergistically to provide greater health benefits.

CONCLUSION

Selenium (Se) is an essential nutrient that has been proven to reduce the risk of many cancers. Broccoli is a popular vegetable, and consumption of broccoli also reduces cancer risk. Broccoli is able to accumulate Se and to convert it into a form that is especially chemoprotective against cancer. There is also evidence that other substances in broccoli may turn on selenoproteins that may regulate cell growth. Development of agricultural methods or broccoli varieties that accumulate Se under natural agricultural conditions may further enhance

the health-promoting properties of this already beneficial vegetable.

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