Cancer-Protective Properties of High-Selenium Broccoli

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Selenium (Se) from high-Se garlic reduces the incidence of chemically induced mammary tumors, and Se from high-Se broccoli reduces colon cancer. However, the ability of Se from high-Se broccoli to protect against mammary cancer has not been tested. Also, the sprout form of broccoli contains many secondary plant compounds that are known to reduce cancer risk, but the anticarcinogenic activity of broccoli sprouts has not been investigated. The present studies examined the ability of high-Se broccoli or high-Se broccoli sprouts to protect against chemically induced mammary or colon cancer. In one experiment, Sprague−Dawley rats that consumed diets containing 3.0 μg of Se/g supplied as high-Se broccoli had significantly fewer mammary tumors than rats fed 0.1 μg of Se as selenite with or without the addition of regular broccoli. In the second experiment, Fisher F-344 rats fed 2.0 μg of Se/g of diet supplied as either high-Se broccoli florets or high-Se broccoli sprouts had significantly fewer aberrant colon crypts than rats fed 0.1 or 2 μg of Se/g of diet supplied as selenite with or without the addition of low-Se broccoli. These data demonstrate that the cancer-protective effect of Se in high-Se broccoli extends to mammary cancer and the protective forms of broccoli against colon cancer include high-Se broccoli sprouts.

Keywords: *Selenium; cancer; broccoli; rat; mammary cancer; colon cancer; broccoli sprouts*

INTRODUCTION

Supplemental selenium (Se) in the form of Se-enriched yeast has been found to reduce the incidence and mortality of several important cancers in humans (*1*, *2*). This is consistent with a wealth of animal studies showing cancer-preventative properties of Se (*3*−*8*). However, different chemical forms of Se offer varying degrees of cancer protection (*9*). The primary dietary or supplemental forms of Se are the amino acids, selenocysteine (SeCys) and selenomethionine (SeMet), amino acid derivatives such as Se-methylselenocysteine (SeMSC), and Se salts such as selenite and selenate. Each of these forms enters the Se metabolic pathway at a different point and thus will have different metabolic fates (*5*, *10*, *11*). Although various forms of Se offer different degrees of protection, those that can be easily converted to methylselenol apparently offer superior protection against carcinogenesis (*9*, *12*). Because SeMSC can be converted in vivo directly to methylselenol, it is receiving much scientific attention as a chemopreventive agent (*12*).

Se-methylselenocysteine (and derivatives) is a primary form of Se found in Se-enriched vegetables including high-Se garlic and broccoli (*13*). Numerous studies of Ip and co-workers show that Se from high-Se garlic effectively prevents chemically induced mammary tumors in rats (*3*, *14*−*17*). Finley and co-workers (*17*) reported that the Se in high-Se broccoli florets effectively reduces 3,2-dimethyl-4-aminobiphenyl (DMABP) and dimethylhydrazine (DMH) induced aberrant colonic crypts (AC) and aberrant crypt foci (ACF). (Aberrant colonic crypts and aberrant crypt foci are preneoplastic lesions in the colon that are statistically associated with the number of tumors that ultimately develop. As such, they are excellent markers for determining colon cancer risk without going through a lengthy tumor study.) However, the ability of high-Se broccoli florets to prevent mammary tumors has not been evaluated.

High-Se garlic does not contain sulforaphane, indole carbinol, and chlorophyll; however, these compounds are present in broccoli florets. Sulforaphane reduces mammary tumors in rats (*18*), indole carbinol reduces colonic tumors in rats (*19*), and chlorophyllin is a potent inhibitor of aflatoxin hepatocarcinogenesis in rainbow trout (*20*). The antitumorigenic activity of these compounds may serve to further enhance the cancer protective benefits of Se in broccoli. Broccoli sprouts are reported to contain 8−10 times the concentration of sulforaphane found in florets (*21*), and thus they could be more effective than florets in tumor reduction, but the anticarcinogenic potential of high-Se broccoli sprouts has not been studied.

The present study addresses two questions: Is high-Se broccoli effective in protecting against mammary tumors, and do the additional phytochemicals in broccoli

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sprouts increase the anticarcinogenic potential of high-Se broccoli? The effect of high-Se broccoli on mammary cancer was studied in rats with methylnitrosourea-induced mammary tumors, and the protective benefits of high-Se broccoli sprouts on colon cancer were studied in rats with dimethylhydrazine-induced aberrant crypts of the colon.

MATERIALS AND METHODS

Broccoli Sprout Production. Broccoli seeds (International Speciality Supply, Cookeville, TN) were soaked for 4 h in a solution of distilled water containing Se as sodium selenate (25 mg/L). After the solution was decanted, the seeds were spread over a sheet of plywood (1.2 × 2.4 m) with retaining walls that had been lined with a plastic sheet. The seeds were sprayed with an aqueous solution of Se (same concentration as soaking solution) and then covered with a plastic sheet in order to retain the moisture. The seeds were allowed to sprout in a dark room at 30 °C for 2 days, after which time the lights were turned on for all of the remaining 6 days of sprouting. The sprouts were harvested, washed once with distilled water, and dried at 70 °C in a circulating air dryer. The dried sprouts were ground in a desingerator (Robber Industries, Belding Division, Belding, MI) with a coarse screen (2.5 cm squares), followed by a 0.079 cm screen. These ground sprouts were incorporated into the rat diets for the experiment. Regular broccoli sprouts were produced according to this same procedure except that the seeds were soaked in distilled water and the sprouts were likewise sprayed with distilled water. The high-Se sprouts were analyzed as containing 62.3 ± 0.6 μg of Se/g of dry weight, and the low-Se sprouts averaged 2.28 ± 0.08 μg Se/g of dry weight.

Broccoli Production. Germinating broccoli seeds (Waltham 29 cultivar from Lethermans, Inc., Canton, OH) were planted in an equal mix (v/v) of sphagnum peat moss and vermiculite. They were grown outdoors in 1.54 × 9.24 m wooden frames with a polyethylene lining. Selenium fertilization started a month later with the application of 3.8 L of a water solution (containing 1.5 g each of sodium selenate and sodium selenite) to each frame with a hand-operated pressure sprayer. This procedure was repeated four times at weekly intervals. Control broccoli received no selenium fertilization but was sprayed with distilled water. The edible broccoli florets were harvested, minced in a mechanical chopper, and freeze-dried. Lyophilized material was milled to a powdery consistency, thoroughly mixed by tumbling, and subsampled for analysis of total Se. The control and Se-fertilized broccoli samples contained 0.13 and 278 μg of Se/g of dry weight, respectively.

Mammary Tumor Experiments. The mammary tumor study was conducted as described previously (*3*) except that methylnitrosourea (MNU) was used as the carcinogen. Briefly, 90 pathogen-free female Sprague−Dawley rats were purchased from Charles River Breeding Laboratories (Wilmington, MA) at 45 days of age. All animals were fed AIN-76A basal diet. Each rat was injected with MNU intraperitoneally at a dose of 50 mg/kg of body weight at age 50 days; 1 day afterward the rats were randomized into three groups. The first group was fed the basal diet containing 0.1 mg of selenium (as sodium selenite)/kg. The second group of rats was fed the basal diet containing 11 g of low-Se broccoli powder/kg of diet. The low-Se broccoli contributed such a negligible amount of selenium to this diet that the final concentration of selenium in the diet remained essentially at 0.1 mg/kg, that is, the same as the first group. The third group was fed the basal diet containing 11 g of high-Se broccoli/kg of diet, thus raising the final concentration to 3 mg of Se/kg of diet. These diets were fed continuously for 22 weeks until the experiment was terminated. All animals were palpated for mammary gland tumors once per week. At necropsy, all tumors were excised and fixed for histological evaluation. Only confirmed adenocarcinomas are reported in the results. Samples of liver, kidney, mammary gland, and plasma were saved for selenium analysis by the fluorometric method of Olson et al. (*22*).

Table 1. Effect of Amount and Dietary Form of Se on the Incidence and Total Number of Mammary Tumors in Rats 22 Weeks after Injection with Methylnitrosourea

group	treatment	Se in diet	tumor incidence[a]	total no. of tumors[a]	% with tumors[a]
A	none	0.1	27/30[a]	76[a]	90[a]
B	low-Se broccoli	0.1	17/30[b]	48[b]	57[b]
C	high-Se broccoli	3	11/30[c]	21[c]	37[c]

[a] Values compared by chi square analysis; $n = 30$/treatment. Values with different superscripts are significantly different.

Aberrant Colon Crypts. Aberrant colon crypt experiments were conducted as previously described (*7*). Briefly, 120 Fisher F-344 weanling, male rats (Charles River Laboratories) were randomly assigned to one of six dietary treatments. The basal diet was a commercially prepared Se-deficient torula yeast-based diet (Tek-Lad, Madison, WI) to which was added Se in the following amounts and chemical forms: A, 0.1 μg of Se/g of diet as selenite; B, 0.1 μg of Se/g of diet as selenite plus low-Se broccoli sprouts; C, 2 μg of Se/g of diet as high-Se broccoli; D, 2 μg of Se/g of diet as selenite; E, 2 μg of Se/g of diet as selenite plus low-Se broccoli sprouts; F, 2 μg of Se/g of diet as high-Se broccoli sprouts. Rats were individually housed in hanging wire cages in a room controlled for temperature, humidity, and light cycle and were given free access to food and deionized water.

Animals were fed for three weeks and then injected subcutaneously with dimethylhydrazine (25 mg/kg of body weight in phosphate-buffered saline with 1 mmol/L EDTA (Sigma Chemical Co., St. Louis, MO) once per week for two consecutive weeks. Eighteen rats per treatment were injected with the carcinogen, and two rats per treatment were injected with vehicle control (phosphate-buffered saline with 1 mmol/L EDTA). Following injections, animals were returned to their cages for 8 additional weeks. Rats were killed by cardiac puncture following ketamine/xylazine anesthesia. Tissues and organs (except lower bowel) were removed, flash frozen in liquid nitrogen, and stored at −70 °C. The lower bowel was removed, washed with saline, split open, laid flat, and stored in ethanol. Aberrant crypts in the entire colon were counted by a trained microscopist following staining with methylene blue. Tissue selenium concentrations were determiend by hydride generation atomic absorption spectrometry (HG-AAS) as previously described (*23*).

Statistics. Tumor incidences at the final time point were compared by chi-squared analysis, and the total tumor yield was compared by frequency distribution analysis as described previously (*24*). Concentrations of selenium in tissues of rats fed regular or high-Se broccoli and injected with NMU were analyzed by one-way analysis of variance (ANOVA). Because the number of AC and ACF in the colon cancer studies did not follow a normal distribution, all data were transformed to their natural log before statistical analysis. All studies were analyzed by ANOVA, and contrasts between treatment means were computed when appropriate. For presentation of data, log values were back-transformed to actual values and a confidence interval was generated by back-transforming ($\log_x \pm \log_{SDx}$).

RESULTS

Experiment 1. When fed at a concentration of 3 μg of Se/g of diet, high-Se broccoli significantly reduced the incidence and total number of mammary tumors as compared to rats fed 0.1 μg of Se/g of diet as either selenite alone or 0.1 μg of Se/g of diet in combination with low-Se broccoli (Table 1). Some of the reduction in tumor numbers was a result of substances other than Se in broccoli, because the addition of low-Se broccoli (at the same percentage in the diet as the high-Se broccoli) decreased the number and incidence of tumors (57%) intermediate between that of the group fed 0.1

Table 2. Effect of Amount and Dietary Form of Se on Tissue Se Concentration in Rats 22 Weeks after Injection with Methylnitrosourea

group	treatment	Se in diet	Se concentration[a] (μg/g or mL)			
			liver	kidney	mammary	plasma
A	none	0.1	3.5 ± 0.1^{b}	4.4 ± 0.2^{b}	0.09 ± 0.01^{b}	0.46 ± 0.02^{b}
B	low-Se broccoli	0.1	3.6 ± 0.1^{b}	4.4 ± 0.2^{b}	0.08 ± 0.02^{b}	0.48 ± 0.03^{b}
C	high-Se broccoli	3	11.8 ± 0.8^{a}	14.1 ± 1.2^{a}	0.18 ± 0.02^{a}	0.77 ± 0.05^{a}

[a] Values are means ± standard error; $n = 30$/treatment; means with different superscripts are significantly different.

Table 3. Effect of Amount and Dietary Form of Se on the Total Number of Aberrant Crypt Foci in Rats 8 Weeks after Injection with Dimethylhydrazine

group	treatment	Se in diet	Se source	total ACF	*n*
A	selenite	0.1	selenite	137 (120−156)[a]	18
B	selenite + low-Se sprouts	0.1	selenite	103 (95−112)[a]	18
C	high-Se broccoli	2	broccoli	68 (59−78)[b]	18
D	high selenite	2	selenite	115 (100−133)[a]	18
E	selenite + low-Se sprouts	2	selenite	115 (100−133)[a]	18
F	high-Se sprouts	2	sprouts	71 (58−86)[b]	18

[a] Values are means and (±1 SD confidence interval). Statistics were computed on natural log-transformed data. Confidence interval was generated by back-transformation of ($\log_x \pm \log_{SDx}$). Numbers within a column with different superscripts are significantly different ($P < 0.05$). Overall effect of diet $P = 0.0006$.

μg of Se/g of diet as selenite (81%) and the group fed 3 μg of Se/g of diet as high-Se broccoli (36%).

Plasma, liver, kidney, and mammary tissue Se concentrations were greatest in animals fed 3.0 μg of Se/g of diet (Table 2); Se concentrations in liver and kidney were ~3-fold those in animals fed 0.1 μg of Se/g of diet. In animals fed 0.1 μg of Se/g of diet, Se from selenite and Se from high-Se broccoli were equally effective in accumulating in tissues. There were no differences in growth of the rats among the three treatment groups (data not shown).

Experiment 2. Compared to other treatments, high-Se broccoli and high-Se broccoli sprouts that supplied 2 μg of Se/g of diet numerically decreased the incidence of ACF (Table 3). The number of ACF in colons of rats fed these diets was significantly less than in animals fed 0.1 or 2.0 μg of Se as selenite/g of diet with or without low-Se broccoli sprouts.

Rat weights were statistically similar for all diets (Table 4) but glutathione peroxidase (GSH-Px) activity in the erythrocytes and liver cytosol were significantly ($P < 0.0001$) affected by diet. GSH-Px activities in liver from rats fed diets with high-Se broccoli or high Se as selenite were significantly higher than in rats fed diets with 0.1 μg of Se/kg as selenite or as selenite combined with low Se-sprouts. However, GSH-Px activity in the liver of rats fed the high-Se sprouts was higher than in any other treatment. In erythrocytes, diets with either 0.l or 2.0 μg of Se as selenite/kg with low-selenium broccoli sprouts resulted in significantly lower erythrocyte GSH-Px activities than for any other diets.

The chemical forms of selenium in the broccoli sprouts were determined to include 20% selenate, 45% SeMSC, 12% selenomethionine, and 3% adenosylselenohomocysteine [analysis by ICP-mass spectrometry similar to that used by Ip et al. (*25*)].

DISCUSSION

The data in this paper are consistent with a wealth of evidence showing that dietary Se consumed in excess of the Recommended Dietary Allowance lowers the risk of several important cancers (*2*, *14*, *26*, *27*). Previous research has established a strong association between the dietary form of Se and the cancer-preventive properties of this element (*5*, *28*). This paper extends the evidence that Se in chemical forms known to accumulate in garlic and some *Brassica* species are especially effective in the prevention of chemically induced carcinogenesis (*14*, *17*).

Similar to regular garlic, regular broccoli florets reduced the incidence of mammary tumors (Table 1) (*3*); this indicates that there are components in addition to Se in each of these plants which have anticarcinogenic activity. Se-enriched broccoli was not more effective (Table l) than enriched garlic (*3*) in reducing the number of tumors; this suggests that the combination of sulforaphane, indole carbinol, and chlorophyll with Se did not provide additional protection against mammary tumors. However, firm conclusions cannot be made because the concentrations of these compounds were not determined in the broccoli used in this experiment and because a direct comparison of high-Se garlic and high-Se broccoli was not made.

Results of the second experiment (Table 3) show that Se-enriched broccoli sprouts have properties similar to enriched broccoli florets that contain SeMSC as the predominant form of Se (*13*). Consumption of Se from high-Se broccoli sprouts, as compared to Se from selenite, resulted in a significant decrease in the number of

Table 4. Effect of Amount and Dietary Form of Se on Rat Weight and Measures of Se Status in Rats 8 Weeks after Injection with Dimethylhydrazine[a]

group	treatment	Se in diet[b]	Se source	wt (g)	GSH-Px[c] (liv cyt)	GSH-Px[c] (RBC)
A	selenite	0.1	selenite	339 ± 11	1403 ± 48^{b}	2.7 ± 0.07^{a}
B	selenite + low-Se sprouts	0.1	selenite	342 ± 12	1355 ± 40^{b}	1.7 ± 0.02^{b}
C	high-Se broccoli	2	broccoli	320 ± 13	1429 ± 49^{ab}	2.4 ± 0.03^{a}
D	high selenite	2	selenite	332 ± 11	1454 ± 51^{ab}	2.5 ± 0.04^{a}
E	selenite + low-Se sprouts	2	selenite	315 ± 9.3	1135 ± 40^{a}	1.7 ± 0.03^{b}
F	high-Se sprouts	2	sprouts	332 ± 10	1602 ± 59^{c}	2.4 ± 0.03^{a}

[a] Values are means ± SEM; $n = 20$/treatment except GSH-Px (liv cyt) (RBC), treatment A, GSH-Px (liv cyt) treatment C and E, $n = 19$; and GSH-Px (liv cyt) treattment D, $n = 18$. Significant effect of diet for GSH-Px (liv cyt) and GSH-Px (RBC); $P = 0.0001$; no significant effect of diet for weight ($P > 0.05$). [b] Selenium concentrations in mg/kg. [c] Glutathione peroxidase values given as enzyme units (EU = nanomoles of NADPH oxidized per minute)/milligram of protein.

aberrant crypts. Additional experimentation is needed to determine whether the decrease in carcinogenesis is a result primarily of the presence of SeMSC, and if there is a correlation between SeMSC content in enriched plants and the reduction of carcinogenesis. If such a correlation is established, then the SeMSC content of various enriched plants could be used to screen for the greatest efficacy in tumor reduction. Se-enriched broccoli appears to be similar to enriched broccoli florets, for which the predominant form of selenium was also shown to be SeMSC (*13*).

High-Se broccoli sprouts were not more effective than high-Se broccoli florets for the prevention of DMH-induced aberrant colon crypts (Table 3). This result, in conjunction with the finding that low-Se broccoli was not more effective than regular garlic for prevention of MNU-induced mammary tumors (experiment 1, Table 1), provides strong evidence that the cancer-preventive qualities of secondary plant compounds found in broccoli but not garlic, such as sulforaphane, indole carbinol, and chlorophyll, are masked by a much stronger protective effect of Se in broccoli.

The present results also point to differences between the mammary tumor model and the ACF model for evaluating the potential cancer protective effects of Se in broccoli. A previous study (*17*) showed that high-Se broccoli florets decreased the number of DMH-induced ACF. Similarly, in the present study high-Se broccoli sprouts decreased DMH-induced ACF, but low-Se broccoli sprouts alone did not have any effect (Table 3). In the mammary tumor model, however, broccoli alone, similar to garlic alone (*3*), reduced the number of tumors (Table 1). This contrasting effect could be the result of a difference between tumor and preneoplastic lesion models, a difference between carcinogens, or a difference between mammary and colonic tissues.

In response to the findings of the Se-responsive reduction of cancer risk in humans, many nutritionists and other health professionals have begun to suggest supplemental intakes of as much as 200 μg of Se/day. However, the present results provide evidence that the total Se intake is not the only factor to consider for the reduction of carcinogenesis. Similar to our previous findings concerning the ability of high-Se broccoli to reduce the incidence of colon cancer (*17*), an equal amount of Se supplied as selenite did not significantly reduce the incidence of ACF. This means that in addition to total Se intake, the form of Se in a particular food or supplement must be taken into consideration. Grains and meat supply a major portion of dietary Se (*29*), and the Se in grains and meat is very effective for increasing tissue Se concentrations and GSH-Px activities (*30*−*32*). However, the form of Se in meat and grain is greatly different from the form in broccoli and garlic (*13*), foods that seem to provide superior anticarcinogenic properties. Consequently, more work needs to be conducted before concrete recommendations of the optimum forms of supplemental Se can be made.

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