SELENIUM FROM BROCCOLI: A UNIQUE ANTI-CANCER AGENT?

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A recent placebo-controlled study has demonstrated that supplemental intakes of selenium (Se), an essential nutrient, may reduce the incidence and mortality of several important cancers. Selenium is found as a component of many molecules, including amino acids, methylated compounds and inorganic salts. The chemical form of Se determines the metabolic route of the molecule, and consequently, the potential health benefits. The chemical form of Se, as well as the total Se content of a food, varies. Broccoli, which contains Se in a unique organic form, has the ability to accumulate high concentrations of Se. Selenium from high-Se broccoli does not accumulate in the tissues and organs of humans and rats as well as other forms of Se. However, animal studies have demonstrated that Se from high-Se broccoli is more effective than other forms of Se for the prevention of chemically induced colon and mammary cancers.

Introduction

Selenium (Se) was demonstrated in the 1950s to be an essential nutrient. Subsequently, many biological functions of Se have been discovered, including its function in enzymes such as glutathione peroxidase and thioredoxin reductase (1), the immune system (2), neuropsychological function (3), as an antioxidant (4) and as a regulator of metabolism (4-6).

However, the most publicised health benefit of Se is protection against several important cancers. Clark et al. (7) fed subjects with a prior history of skin cancer for 10 years a placebo or 200 μg of Se/day, and found that Se decreased prostate cancer by 70%, lung and colorectal cancer by 50%, and total cancer incidence and morphology by 50%. 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,” stated that the available evidence is sufficient to recommend increased Se intakes in Great Britain (8).

Anti-cancer Benefits of Selenium

The evidence for the anti-cancer benefits of Se is strong, but Se occurs as part of many different molecules, and the form that provides optimal cancer protection is not defined. Selenium in food is found as inorganic salts (e.g. selenite and selenate), Se-substituted forms of sulfur amino acids (e.g. selenomethionine (SeMet), selenocysteine), amino acid derivatives (e.g. selenohomocysteine, selenocystathione) and methylated Se (e.g. methyl selenol, dimethyl selenide, Se methyl selenocysteine (SeMSC)), and perhaps compounds yet to be identified. 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 consequently its health benefits (9-11). For example, selenomethionine may be substituted for methionine (1) and thus accumulates in proteins that need methionine, whereas selenite is incorporated only into proteins that specifically require Se (12). Cancer-preventive benefits of Se, however, are not related to the amount of Se in a tissue or in a specific protein, but are probably related to the production of methyl-selenol, a form of Se that is ultimately changed to a form found in urine (9). Consequently, forms of Se easily converted to methyl selenol may be the most effective for cancer prevention (13) and SeMSC is such a form.
TABLE I
Concentration of selenium in similar foods of different brands purchased from a local grocery store (14)

<table>
<thead>
<tr>
<th>Food/brand</th>
<th>Se concentration (pg/g)</th>
<th>% Daily recommended intake in a 100-g serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tortilla, corn, Brand A</td>
<td>0.03±0.002</td>
<td>5</td>
</tr>
<tr>
<td>Tortilla, corn, Brand B</td>
<td>0.35±0.03</td>
<td>64</td>
</tr>
<tr>
<td>Corn masa mix, Brand A</td>
<td>0.047±0.006</td>
<td>8</td>
</tr>
<tr>
<td>Corn Masa mix, Brand B</td>
<td>0.50±0.008</td>
<td>91</td>
</tr>
<tr>
<td>Ground beef, SW Missouri</td>
<td>0.06±0.001</td>
<td>11</td>
</tr>
<tr>
<td>Ground Beef, N. Dakota</td>
<td>0.37±0.009</td>
<td>67</td>
</tr>
</tbody>
</table>

Selenium in Plants

Some plants (e.g. wheat) accumulate Se in direct proportion to the amount of Se available in the soil. The concentration of Se in wheat may vary from an average of 0.2 µg Se/g to 50 µg Se/g for wheat grown in high-Se soils (15). Se-accumulator plants, however, actively accumulate Se to concentrations many orders of magnitude beyond the Se content of soil (16). Some astragalus species (a weed that grows in the western US) are Se-accumulators, and we have found Se concentrations in astragalus that were in excess of 2,000 pg Se/g, although wheat growing in close proximity contained only 8 µg Se/g (Table II) (17).

Selenium-accumulating plants produce special forms of Se, such as Se-methyl selenocysteine (18). These forms of Se can safely be stored within the plant cell, presumably as a defence against grazing animals. Very little Se is found in proteins of such plants (generally less than 10% of the total plant Se, as compared with greater than 50% of total Se in other plants) (16). Plants that produce Se-methyl selenocysteine are able to do so because they contain a specific enzyme that forms Se-methyl selenocysteine. Formation of this molecule makes the Se atom less toxic to the plant and allows it to be stored within the plant. Insertion of the gene for this enzyme into a plant species that does not usually accumulate Se allows the new plant to accumulate Se (19,20).
TABLE II
Selenium content of plant and animal material from a high-selenium area in South Dakota (14)

<table>
<thead>
<tr>
<th>Item</th>
<th>Se concentration (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>9.2±1.0</td>
</tr>
<tr>
<td>Alfalfa hay</td>
<td>15.9±2.0</td>
</tr>
<tr>
<td>Ground beef (raw)</td>
<td>0.64±0.5</td>
</tr>
<tr>
<td>Princess plume</td>
<td>2843±170</td>
</tr>
<tr>
<td>Astragalus plant</td>
<td>1658±122</td>
</tr>
<tr>
<td>Astragalus flower</td>
<td>3178±500</td>
</tr>
</tbody>
</table>

Selenium Metabolism

The metabolism of Se from different food sources is also shown in Fig. 1. Because the predominant form of Se in wheat is selenomethionine, Se from wheat easily accumulates in the body and is quite effective for increasing markers of Se status such as blood Se or glutathione peroxidase enzyme activity (21). Many Se supplements use salts such as selenate and selenite, which may either form selenoproteins or be excreted (12). In broccoli, however, the primary form of Se is Se-methyl selenocysteine (SeMSC), which can be easily converted to a form that is excreted in urine (22). This prevents Se from broccoli from accumulating in the body to the same extent as other forms of Se (23) and should make Se from broccoli more effective (than other food forms of Se) against carcinogenesis (24). High-Se garlic also contains Se-methyl selenocysteine (22) and Se from high-Se garlic is especially protective against breast cancer (25,26).

Selenium from Broccoli

Selenium from high-selenium broccoli is metabolised in a unique manner. Broccoli is an important vegetable in the western diet and consumption of broccoli in the USA has increased many-fold in the last 30 years. Numerous studies have shown an inverse correlation between the incidence of many cancers and consumption of cruciferous vegetables, especially broccoli. Broccoli also accumulates Se when grown in an Se-rich environment, and broccoli has been used as a phytoremediation tool to remove toxic amounts of Se from high-Se soils (27).

We have developed a method to grow broccoli with very high amounts of Se (>500 µg Se/g) (23). When Se from high-Se broccoli was fed to Se-deficient rats, it did not accumulate or increase glutathione peroxidase enzyme activity in liver, kidney or blood as well as Se from salts or from SeMet (23). Likewise, selenium from high-Se broccoli was not used to make proteins as efficiently as other forms of Se (unpublished data).

The utilisation of Se from broccoli by humans was studied by growing broccoli hydroponically, adding a stable isotope of Se to the growth medium and feeding the labelled broccoli to healthy young men (28). Measurement of the Se isotope in blood showed that Se from high-Se broccoli did not accumulate in blood as well as Se from selenate (Fig. 2). The sum of all human and animal studies indicates that Se from broccoli is utilised in a way that allows less accumulation of Se in tissues than Se salts or amino acid forms, suggesting that it is less toxic than other forms of Se.

Cancer-protective Effect of Selenium from Broccoli

Selenium from broccoli is efficacious in the prevention of colon cancer. The protective benefits of Se from broccoli against colon cancer were studied in rats using a pre-tumour abnormality, aberrant colonic crypts (AC), as an indication of cancer risk. The number of aberrant crypts in the colon is highly correlated with the eventual number of tumours in the colon. An initial study determined that Se decreased the risk of AC in a manner that was affected by the total dose of Se as well as the chemical form of the Se (29). High-Se broccoli grown in the manner described above was added to an Se-deficient diet in amounts that supplied 0.1 or 2.0 µg Se/g diet. In our model, diets containing 0.1 µg Se/g diet are representative of human diets that are adequate in Se for normal health, whereas 2.0 µg Se/g diets are representative of the supplemental levels of Se shown to protect against...
cancer. Because broccoli itself prevents cancer, all diets contained the same amount of broccoli, but low-Se diets utilised broccoli grown without added Se.

Fig. 2. Per cent of a dose of a stable isotope of selenium administered as selenate (salt) or high-Se broccoli that was retained in the plasma of humans. Stable 74Se was incorporated into hydroponically grown broccoli or was synthesised into selenate; Equal amounts of 74Se were fed to human subjects consuming a low-selenium diet or a high-selenium diet. Plasma was obtained at timed intervals and 74Se was determined by ICP-mass spectrometry. Less total 74Se accumulated from broccoli than from selenate (28).

Rats were assigned to dietary treatments for 3 weeks and cancerous lesions were induced by injecting with a carcinogen (either 2,3-dimethyl-4-amino biphenyl or dimethyl hydrazine). Rats consumed diets for 8 additional weeks before they were killed and their colons prepared for microscopic evaluation. Compared with selenate or selenite (considered effective anti-cancer sources of Se), high-Se broccoli reduced the number of ACF almost 60% (Fig. 3) (29,30). Subsequent studies demonstrated that high-Se broccoli sprouts were as effective as broccoli florets for reduction of AC and ACF (31). Also, Se from high-Se broccoli has been proved effective against DMBA-induced mammary cancer (31) and against spontaneous tumours in multiple intestinal neoplasia (Min) mice (32).

Fig. 3. Se from high-selenium broccoli is more effective that 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 tumours (30). * = significantly different from deficient diet.

Although our cancer studies have used broccoli with unnaturally high concentrations of Se (more than 500 µg Se/g dry broccoli, compared with
0.01-0.2 μg/g found normally in broccoli), broccoli can also accumulate Se naturally. The aquifers in many vegetable-farming areas of California pass through Se-rich rock layers, and broccoli irrigated with this water may accumulate high (1-5 μg Se/g) concentrations of Se (Banuelos, personal communication). Broccoli has been used as a phyto-remediation method to remove Se from seleniferous soils in these areas of California (27). Broccoli that has accumulated Se grown in this manner has not been tested for an anti-carcinogenic effect. 

The lower tissue accumulation of Se (and hence its lower toxicity), the greater the effectiveness of the Se against cancer, and the general acceptability of broccoli by the general public make this vegetable a potentially excellent source of supplemental Se. However, the practical benefits to humans of consumption of high-Se broccoli are not known. There have been no long-term human studies that have fed either laboratory-produced high-Se broccoli or broccoli that naturally accumulated Se under real agricultural conditions. Laboratory-produced high-Se broccoli (500-1,000 mg Se/kg) could be used as a selenium supplement, and a check of the World-Wide Web found several manufacturers claiming to sell such a product. The Se content of naturally produced high-Se broccoli could certainly be used as a nutritional advantage of broccoli in marketing strategies, and high-Se broccoli could perhaps be sold as a specialty crop. It may also be possible to up-regulate the methyl-transferase gene in broccoli that allows accumulation of Se as SeMSC, and perhaps such a genetic modification would allow increased Se content of broccoli grown on soils moderately high in Se. Ongoing studies are addressing these questions.

References


