

# POSITION STATEMENT

## Selenium



### Key messages

Selenium helps to prevent tissue damage caused by free radicals. Selenium is found in cereals, meat and fish. Cereals provide about 50% of dietary selenium. The selenium content of plant foods varies with the selenium content of the soil.

Cancer Council supports the National Health and Medical Research Council recommended dietary intake of 70 µg/day for men and 60 µg/day for women with an upper intake limit of 400 µg/day (six times the recommended dietary intake). Selenium is safe if taken in moderation. However selenium supplements are toxic if taken in high doses.

Studies suggest that selenium probably reduces the risk of prostate cancer and may be inversely associated with cancer of the colorectum, lung and stomach. The evidence of a protective role of selenium in other types of cancers is weak and inconsistent. The true effects of selenium require confirmation in an independent trial(s) before new public health recommendations regarding selenium (either from dietary sources or as supplements) can be made.

Cancer Council does not support the use of health claims on food labels that suggest selenium protects against the development of cancer.

### Rationale

As the food industry has proposed health claims be permitted on food labels about selenium and cancer, it is important for Cancer Council to have a clear position on the protective effects of selenium against cancer.

### Background

Selenium is found in cereals, meat, poultry, seafood, and eggs.<sup>1</sup> Cereals may provide about 50% of dietary selenium, however data on the selenium content of Australian foods is limited. The selenium content of plant foods varies with the selenium content of the soil.<sup>1</sup>

Selenium acts as an antioxidant and helps protect the body against the damaging effects of free radicals. Selenium is essential for the activity of glutathione peroxidase, an enzyme that protects against reactive oxygen species and subsequent cell membrane damage.<sup>1</sup>

### Views on selenium in cancer prevention reports

The World Cancer Research Fund found in 2007 that there was *probable* evidence that selenium and selenium supplements reduced the risk of prostate cancer, and *limited suggestive* evidence that they reduced the risk of lung and colorectal cancer.<sup>2</sup> Selenium was also linked to a *limited suggestive* lower risk of stomach cancer, and selenium supplements to a *limited suggestive* increased risk of skin cancer.<sup>2</sup>

In 2003, the World Health Organization concluded that the strength of evidence for the role of selenium in decreasing the risk of cancer was *possible/insufficient*, and the evidence from randomised controlled trials suggested that selenium might have a protective role in prostate cancer development.<sup>3</sup>

## Epidemiological evidence

The evidence for the protective effects of selenium has come from the following sources: randomised controlled trials, and corroborative evidence from observational and in vitro studies.

### Randomised controlled trials

The *Selenium and Vitamin E Cancer Prevention Trial* (SELECT), sponsored by the National Cancer Institute, began in August 2001.<sup>4</sup> The trial aims to determine if these two dietary supplements can protect against prostate cancer.

Over 35,500 participants were randomised to receive daily supplements of either: selenium (200 µg/day) and placebo; vitamin E (400 IU/d alpha-tocopherol) and placebo; selenium and vitamin E; or two placebos. Participants stopped taking the study supplements in October 2008 and are being followed for another three years.

Preliminary analysis suggests that selenium does not prevent prostate cancer (hazard ratio (HR)= 1.04, 95% confidence interval (CI)= 0.87-1.24 for selenium; HR= 1.05, 95% CI= 0.88-1.25 for selenium + vitamin E).<sup>4</sup> In fact a small increased risk of diabetes mellitus was seen in the selenium group, but not the selenium + vitamin E group.<sup>4</sup> However final results of the SELECT trial will not be available until 2012 (<http://www.cancer.gov/clinicaltrials/digestpage/SELECT/allpages>).

The Nutritional Prevention of Cancer Trial, a randomised controlled trial with 1312 subjects, was conducted to test whether selenium supplements (200 µg/day) would reduce basal and squamous cell carcinomas in the USA.<sup>5</sup> It is interesting to note that the trial showed that selenium treatment did not protect against the development of basal or squamous cell carcinomas of the skin,<sup>5</sup> and subsequent analysis of the Nutritional Prevention of Cancer Trial actually found that selenium supplementation increased the risk of squamous cell carcinoma and total non-melanoma skin cancer (result was statistically significant).<sup>6</sup>

However the results of secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of cancers at other sites, including prostate and colon-rectum.<sup>6,7</sup> This trial showed a significant protective effect of selenium supplementation on the incidence of prostate cancer, although the effect was restricted to those with lower baseline prostate specific antigen (PSA) and plasma selenium concentrations.<sup>7</sup> The protective effects of selenium were not apparent for all groups of subjects. In the case of total cancer incidence, selenium treatment produced significant reductions only in males (males represented 75% of the total sample).<sup>8</sup>

The Nutritional Prevention of Cancer Trial did not support an earlier finding of a protective effect against lung cancer incidence.<sup>8</sup>

Two lower quality trials, with unclear and inadequate methodology, were conducted in China that showed a reduced incidence of liver<sup>9</sup> and stomach cancers.<sup>10</sup>

A Cochrane review found that in four trials, selenium showed a beneficial effect on the incidence of gastrointestinal cancer but this finding may have been biased because of low methodological quality in three of the four trials.<sup>11</sup> The only study that was of high methodological quality was the Nutritional Prevention of Cancer Trial. The reviewers recommended that the potential preventive effect of selenium should be studied in appropriately designed randomised controlled trials.

The trial results showed an effect of selenium after only two to four years of follow-up, however the dosage of the supplement varied in the different trials but did not exceed 200 µg/day.<sup>11</sup>

A pooled analysis of three other randomised controlled trials, the Wheat Bran Fiber Trial, the Polyp Prevention Trial, and the Polyp Prevention Study, showed an inverse relationship between higher blood selenium concentration and adenoma risk.<sup>12</sup> It is important to note that none of these three trials was specifically testing selenium as an intervention for adenoma protection. However these results suggest that selenium may have a protective effect on the development of colorectal cancer, which warrants further investigation.<sup>12</sup>

## Observational studies

Some but not all observational studies have suggested that selenium is inversely associated with cancer risk.<sup>13</sup>

Observational studies have suggested an inverse association between selenium and both breast and prostate cancers.<sup>14</sup> The Health Professionals Follow-Up Study showed a strongly inverse association of toenail selenium content and prostate cancer incidence.<sup>15</sup> For colorectal cancer, observational studies have been mixed with some showing a statistically significant or suggestive protective association and some showing a null or harmful association between selenium and colorectal adenomas or cancer.<sup>16</sup>

## Potential mechanisms of action

Animal studies have consistently shown that selenium treatment can reduce tumour yields, inhibit cell growth and angiogenesis, stimulate apoptosis, protect against oxidative damage, and increase immune function.<sup>13, 17-19</sup>

## Toxicity and recommended dietary intake

The Recommended Dietary Intake (RDI) of selenium for men is 70 µg/day and 60 µg/day for women.<sup>1</sup> The upper dietary intake limit for adults has been proposed at 400 µg/day, based on no adverse effect levels seen in some of the Chinese randomised controlled trials. There is limited data about selenium toxicity in humans but the most common side effects include: hair and nail brittleness and loss, gastrointestinal disturbances, skin rash, fatigue, irritability and nervous system disturbances.<sup>1</sup>

Selenium supplements sold in Australia warn that selenium is toxic in high doses and a daily dose of 100 µg/day from all sources other than food should not be exceeded. Selenium containing supplements are not recommended for children under the age of 15 years.

## Current level of intake in Australia

There is limited data on the selenium status of Australians, with a recent study showing that the mean plasma selenium concentration of a group of 834 South Australians was relatively high by European standards.<sup>20</sup> The study questioned if Australians are getting enough selenium to achieve optimal enzymatic activity of glutathione peroxidase, even though plasma selenium concentrations were above those reported for most other countries.<sup>20</sup>

Selenium deficiency is rare in Australia. In areas of China with low soil selenium, deficiency is manifested as Keshan Disease, a form of fatal cardiomyopathy.<sup>1</sup> Selenium deficiency has also been reported to increase the risk of cretinism in conjunction with iodine-deficiency.<sup>1</sup>

## Health claims

The effects of selenium are related to the specific compounds and breakdown products of selenium present in the food.<sup>13</sup> Therefore considerations of health claims must be related to the presence of these specific selenium compounds in the food.

The Food and Drug Administration (FDA) in the USA has permitted a qualified health claim for selenium and cancer. A qualified health claim is when there is less scientific evidence for a substance-disease relationship and the claim therefore requires qualifying language such as “FDA has determined that the evidence is limited and not conclusive”.<sup>14</sup> It is noteworthy that foods and natural products are regulated under different rules to pharmaceutical compounds, not having to meet the stringent criteria for demonstrated efficacy and safety.

## Future research

Because of the metabolic complexity of selenium, research studies are required on what selenium dose and biologic form are the most effective for chemoprevention. Methods are needed to characterise the specific forms of selenium present in food. A better understanding is required of the selenium dose (chemical form and amount) that would be both safe and effective in reducing cancer risk.<sup>13</sup> The effects of selenium require confirmation in an independent randomised controlled trial of appropriate design before new public health recommendations regarding selenium supplementation can be made.

## Further information

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