

POSITION STATEMENT

SELENIUM

Key Messages

- 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.
- Selenium helps to prevent tissue damage caused by free radicals.
- The Cancer Council Australia supports the National Health and Medical Research Council recommended dietary intake of 65µg/day for men and 55µg/day for women with an upper intake limit of 400µg/day (six times the recommended dietary intake). (*Note these values are under review*). Selenium is safe if taken in moderation. However selenium supplements are toxic if taken in high doses.
- Some studies suggest that selenium may be inversely associated with prostate cancer and colorectal cancer, but most of this evidence comes from trials designed to answer questions about other types of cancer. 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.
- The Cancer Council Australia 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 The Cancer Council Australia to have a clear position on the protective effects of selenium against cancer.

Background

Selenium is found in cereals, meat, poultry, seafood, and eggs (1). 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 (1).

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 (1). The current Recommended Dietary Intake (RDI) for men is 85µg/day and 70µg/day for women, but the update of the nutrient reference values by the National Health and Medical Research Council (NHMRC) has proposed a reduction in the recommendations for selenium to 65µg/day for men and 55µg/day for women (*Note these values are under review*) (1). The upper dietary intake limit for adults has been proposed at 400µg/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 (1).

Selenium supplements sold in Australia warn that selenium is toxic in high doses and a daily dose of 100µg/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.

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 (1). Selenium deficiency has also been reported to increase the risk of cretinism in conjunction with iodine-deficiency (1).

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 (2). 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 (3).

Selenium and Cancer Prevention

Evidence from Randomised Controlled Trials

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.

The Nutritional Prevention of Cancer Trial, a randomised controlled trial with 1312 subjects, was conducted to test whether selenium supplements (200µg/day) would reduce basal and squamous cell carcinomas in the USA (4). 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 (5) 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) (6).

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 (7;8). 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 (9). 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) (10).

The Nutritional Prevention of Cancer Trial did not support an earlier finding of a protective effect against lung cancer incidence (11).

Two lower quality trials, with unclear and inadequate methodology, were conducted in China that showed a reduced incidence of liver (12) and stomach cancers (13).

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 (14). 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 2-4years of follow-up, however the dosage of the supplement varied in the different trials but did not exceed 200µg/day (15).

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 (16). 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 (17).

Evidence from Observational Studies

Some but not all observational studies have suggested that selenium is inversely associated with cancer risk (18).

Observational studies have suggested an inverse association between selenium and both breast and prostate cancers (19). The Health Professionals Follow-Up Study showed a strongly inverse association of toenail selenium content and prostate cancer incidence (20). 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 (21).

Views on Selenium in the Major Cancer Prevention Reports

1. The World Health Organisation in the *Diet, Nutrition and the Prevention of Chronic Diseases Report* (2003) concluded that (22):
 - The strength of evidence for the role of selenium in decreasing the risk of cancer is possible/insufficient.
 - The evidence from randomised controlled trials has suggested that selenium might have a protective role in prostate cancer development.
2. The Committee on Medical Aspects of Food and Nutrition Policy in the *Nutritional Aspects of the Development of Cancer* report (1998) concluded that (23):
 - There is not enough evidence to reach conclusions for any specific links between selenium in the causation or prevention of some cancers.
 - Evidence from intervention studies suggests that reduced risk of gastric cancer with a multisupplement of vitamins A and D and selenium may be limited to those with low intakes of these nutrients.
 - Evidence is insufficient to draw conclusions on selenium and reduced risk of lung cancer.
3. The World Cancer Research Fund in *Food, Nutrition and the Prevention of Cancer: a Global Perspective* (1997) concluded that (24):
 - There is some evidence that diets high in selenium might protect against lung cancer i.e. it is possible that a high selenium intake decreases the risk of lung cancer.

- Data for other cancer sites are limited and inconclusive. Insufficient evidence exists to support the role of selenium in decreasing the risk of stomach, liver and thyroid cancers.
- There is also some evidence that selenium protects against the overall risk of cancer, but it is not strong, and it does not all point in the direction of protection.

New Research Directions on the Role of Selenium in Primary Cancer Prevention

It is important to note that most of the evidence of a protective effect of selenium on prostate and colorectal cancer comes from randomised controlled trials which were designed to answer questions about other types of cancer. Therefore the next step in definitively answering the question of whether antioxidants, such as selenium, are effective in the primary prevention of prostate cancer will be conducting the *Selenium and Vitamin E Cancer Prevention Trial* (SELECT). The SELECT trial, sponsored by the National Cancer Institute, began in July 2001, and will determine if these two dietary supplements can protect against prostate cancer. The 32,400 participants have been randomised to receive daily supplements of either: selenium and vitamin E (alpha-tocopherol); selenium and placebo; vitamin E and placebo; or two placebos. The results of the SELECT trial will not be available until 2012.

<http://cancer.gov/clinicaltrials/digestpage/SELECT/allpages>

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 (25-28).

Health Claims

The effects of selenium are related to the specific compounds and breakdown products of selenium present in the food (29). 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” (30). 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.

Research Needs for Learning More about Selenium

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 (31). 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.

The Functional Foods Centre based at Wollongong University is investing in research on the role of selenium as a potential functional food component¹, which may also contribute to the substantiation required to make health claims for selenium as a protective factor for cancer (<http://www.nceff.com.au/substantiation/projects03-2.htm>).

Related Cancer Council policies or documents:

National Cancer Prevention Policy 2004-06

TCCN Position Statement on Chemoprevention

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¹ 'Functional foods' are defined as foods that support human health and wellbeing, providing health benefits beyond basic nutrition.

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