

POSITION STATEMENT

Soy, phyto-oestrogens and cancer prevention



Key messages

- Phyto-oestrogens are bioactive substances found in plant foods, with naturally occurring oestrogenic activity. Soy beans and other foods containing soy, such as tofu, tempeh and soy milk, are rich sources of phyto-oestrogens.
- There is *limited suggestive* evidence that soy foods may lower the risk of prostate and stomach cancer. The evidence for soy foods and cancer of the pharynx, oesophagus, pancreas, breast and endometrium is *limited* with *no conclusion* possible. There is no association between soy foods and the risk of other cancers, including bowel cancer.
- While they may have a protective effect, there is also some evidence that phyto-oestrogens might stimulate the growth of existing hormone dependent cancers.
- Cancer Council supports the consumption of soy foods in the diet. This is consistent with Cancer Council recommendations and national dietary guidelines to eat a diet high in plant based foods.
- Cancer Council does not recommend or support the use of supplements such as soy protein isolates or isoflavone capsules for healthy men and women to prevent cancer.
- Cancer Council does not recommend or support the use of supplements for breast cancer survivors. There is evidence to suggest that women with existing breast cancer or past breast cancer should be cautious in consuming large quantities of soy foods or phyto-oestrogen supplements.

Rationale

The purpose of this position statement is to evaluate and summarise the evidence linking soy foods and phyto-oestrogens with cancer. There is increasing interest in soy foods and phyto-oestrogens regarding their possible health benefits for a number of conditions, including cardiovascular disease, menopausal symptoms, osteoporosis and cancer. It is important that Cancer Council evaluate the associations between soy and cancer risk in order to develop its messages and recommendations, especially for women who already have breast cancer.

Background

Phyto-oestrogens are phytochemicals (bioactive substances that occur in plant foods) with naturally occurring oestrogenic activity. Particularly high concentrations of phyto-oestrogens are found in soy beans and other foods containing soy.

Phyto-oestrogens achieved notoriety in the 1940s in Western Australia when sheep fed large quantities of clover fodder developed a reproductive abnormality known as clover disease, which resulted in fertility problems and loss of productivity. The phyto-oestrogens in the clover were subsequently identified as the bioactive substance responsible for the reproductive abnormality.¹

The lower breast and prostate cancer mortality rates in Asian countries and the potential anti-oestrogenic effects of phyto-oestrogens have led to speculation that soy foods reduce cancer risk.

Types of phyto-oestrogens

There are three important classes of phyto-oestrogens:

- Isoflavonoids/isoflavones - found in legumes, with soy beans being the richest source.
- Lignans - a constituent of dietary fibre and found mainly in nuts, seeds, legumes, cereals, vegetables and fruits.
- Coumestans - found in sprouted beans, alfalfa and clover.

Soy beans and soy products provide the main sources of phyto-oestrogens in the human diet. Soy phyto-oestrogens (isoflavones) comprise mainly genistein (60%) and daidzein (30%), with smaller quantities of glycitein (10%).² Isoflavonoids are stable to heating and some processing techniques.² Genistein and daidzein have a similar structure to oestradiol, and are able to bind to oestrogen receptors, albeit with a lower affinity than oestradiol.²

Food sources

Foods containing soy include tofu, tempeh and soy milk, which are rich sources of phyto-oestrogens. A list of different soy foods and their relevant phyto-oestrogen content is shown in table 1. Although fermentation of soy can reduce the amount of isoflavones present, the bioavailability of isoflavones is higher in fermented products.³ Generally, it is thought that 30-50mg of isoflavones is enough to offer health benefits.

Table 1. The phyto-oestrogen content of different soy foods^{3,4}

Food	Total Isoflavone (mg/100g)
Soy beans	2-221
Tofu	4-67
Tempeh	103
Soy milk	1-21

Dietary intake of phyto-oestrogens

In communities consuming traditional soy foods, estimates of average isoflavone intakes range between 11 and 54mg/day.^{5,6} This is equivalent to one or two serves of soy foods on a daily basis.

Tofu contributes the largest amount of soy to most Asian diets.⁷ In Western diets, the majority of the isoflavone/phyto-oestrogen intake comes from non-soy foods, such as soy additives in baked goods, tuna or coffee.⁸ A high dietary intake of phyto-oestrogens in most studies in Western populations corresponds to a low intake in most studies of Asian populations.⁹

Epidemiological evidence

The results from experimental studies have been conflicting, with soy foods and phyto-oestrogens showing both risk enhancing and risk reducing effects. Caution is required in interpreting the results of epidemiologic studies relating to phyto-oestrogens due to potential exposure misclassification, confounding and lack of a dose response.

Breast cancer

A meta-analysis found that soy intake is associated with a modest reduction in breast cancer risk (odds ratio (OR)=0.86, 95% confidence interval (CI)=0.75-0.99).⁹ This meta-analysis included results from 12 case-control and six cohort studies. However, the heterogeneity across studies limited the ability to interpret the findings and the authors advised against making any recommendations for using soy as a cancer prevention agent.

The inverse association between soy exposure and breast cancer risk was slightly stronger in premenopausal women (OR=0.70, 95% CI=0.58-0.85) than in post menopausal women (OR=0.77, 95% CI=0.60-0.98).⁹

An earlier meta-analysis found that consumption of soy foods was associated with a lower risk of breast cancer (OR=0.78, 95% CI=0.68-0.91).¹⁰ This study was funded by the soy food industry. This meta-analysis included results from 11 case-control and three cohort studies.

Prostate cancer

A meta-analysis showed that soy consumption was related to a lower risk of prostate cancer in men (OR=0.70, 95% CI=0.59-0.83).¹¹ It should be noted that this study was funded by the soy food industry. This meta-analysis included results from six case-control and two cohort studies.

Another review,¹² although not a systematic review, identified different case-control and cohort studies to the meta-analysis¹¹ described above. It concluded that there was inconsistency with few studies showing a statistically significant protective effect.¹²

Some trials (although not randomised) suggest that phyto-oestrogen supplements may benefit some patients with prostate cancer, by decreasing or stabilising PSA values but the evidence is too limited to recommend supplementation.^{13,14}

Colorectal cancer

There does not appear to be an association between soy consumption and colorectal cancer.¹⁵ Although most case-control and cohort studies show weak inverse associations between higher soy consumption and colorectal cancer, the results have not been statistically significant, with most of the confidence intervals crossing one.¹⁵

Other cancers

There is no association between soy foods and the risk of other cancers. There is some limited evidence to suggest that phyto-oestrogens have enough oestrogenic activity to stimulate cell growth in the endometrium of post menopausal women, although the evidence overall is inadequate to draw conclusions on whether phyto-oestrogens taken by perimenopausal or post menopausal women eventually would cause endometrial cancer.¹⁶

Views on soy and phyto-oestrogens in cancer prevention reports

The World Cancer Research Fund found in 2007 that there was *limited suggestive* evidence that pulses (legumes), including soy and soy products, lowered the risk of prostate and stomach cancer. WCRF also found that the evidence for soy and soy products was *limited* with *no conclusion* possible for cancer of the pharynx, oesophagus, pancreas, breast and endometrium.¹⁷

The World Health Organization concluded in 2003 that there was *insufficient evidence* that soy foods or phyto-oestrogens reduce the risk of breast cancer.¹⁸

Potential mechanisms of action

Breast cancer

As phyto-oestrogens are strikingly similar in chemical structure to oestradiol, a potential mechanism of action for phyto-oestrogens is their ability to bind to oestrogen receptors. However phyto-oestrogens also have effects that are unrelated to oestrogen activity. They act as antioxidants to inhibit free radical damage, and have anti-proliferative properties to inhibit tumour growth.

Most of these actions of phyto-oestrogens occur only at pharmacologic concentrations (30-185µM) in experimental studies, rather than at the lower concentrations achievable from a dietary intake. However, at concentrations within the range achievable from dietary soy exposures (<4µM in the blood), genistein (a type of phyto-oestrogen) exhibits oestrogenic properties, some of which could theoretically enhance breast cancer risk.¹⁹

In contrast, daidzein, the other key phyto-oestrogen in soy, enhances tamoxifen efficacy at physiologic levels in a rat model.²⁰

Timing of exposure

Early life may be a critical period for soy exposure. Animal studies have shown that pre-pubertal exposure to phyto-oestrogens reduces carcinogen-induced breast cancer in rats.²¹⁻²⁴ Some human epidemiologic studies have also shown that there is an inverse association between childhood soy exposure and reduced breast cancer risk.^{25,26} As Asian women are likely to have been exposed to soy during early life, this may explain the stronger protective association seen in studies of Asian populations.

Prostate cancer

The exact mechanism of action by which soy consumption is associated with a lower risk of prostate cancer remains to be elucidated. Short intervention studies show that serum sex hormone-binding globulin concentrations increase in men consuming tofu.^{27,28} Intake of phyto-oestrogens may lead to a reduction in cell proliferation and angiogenesis and an increase in apoptosis.²⁹⁻³²

Issues for women with existing breast cancer

It is not clear whether it is safe for women with existing breast cancer to consume soy supplements or even large quantities of soy foods. The results of scientific studies are contradictory, with cell culture studies reporting both the oestrogenic stimulation of oestrogen receptor positive breast cancer cell lines and the antagonism of tamoxifen activity at physiological phyto-oestrogen concentrations.^{33,34}

Thus phyto-oestrogens (genistein and daidzein) may stimulate existing tumour growth and antagonize the effects of tamoxifen.^{33,35} Women with current or past breast cancer should be aware of the risks of potential tumour growth when taking soy products.

There are no clinical trials available to definitively answer this question.

Menopause

Soy phyto-oestrogens are seen by some as an alternative to oestrogen therapy to treat post-menopausal symptoms. However the oestrogenic effect of soy in potentially promoting tumour recurrence raises concern for its use by breast cancer survivors.³⁶

A systematic review found that phyto-oestrogens available as soy foods, soy extracts and red clover extracts do not significantly improve hot flushes or other menopausal symptoms.³⁷ Most of the trials lasted only three to four months, so the long term effects remain unclear.³⁷

Recommendations

Although the evidence is not conclusive for soy foods to protect against cancer, soy foods can be encouraged as part of a varied and nutritious diet. This is consistent with Cancer Council recommendations and national dietary guidelines to eat a diet rich in plant foods.

Safe and efficacious levels of phyto-oestrogens have yet to be established for cancer prevention. As the results of some experimental studies suggest adverse effects from phyto-oestrogens, high dose phyto-oestrogen supplementation is not recommended or justified at this stage, especially for women with existing breast cancer.

Health claims about soy

In 2004, the American Soybean Association petitioned the Food and Drug Authority in the USA for permission to use a health claim for the association between soy protein intake and lower risk of certain cancers, including breast cancer. The industry has since withdrawn their petition. The inconsistency of the evidence appears to have been the driving force in the withdrawal of this petition for a health claim.

In the USA, health claims on soy protein and lowered risk of heart disease are permissible.

Cancer Council does not support the use of health claims on food labels that suggest soy foods or phyto-oestrogens protect against the development of cancer.

Future research

It would be useful for future studies to report associations for both soy foods and specific phyto-oestrogens. Studies vary as to whether they report on the following exposures:

- Fermented vs non-fermented soy.
- Total soy vs soy protein.
- Dietary soy consumption vs urinary isoflavones.

As with many other nutritional factors, there is a need for better quality, well-reported, larger and longer duration studies. Studies need to be performed in populations with sufficient variation in intake of soy and phyto-oestrogens. A better understanding of the factors that affect the bioavailability of ingested phyto-oestrogens, such as absorption rate, incorporation rate into the bloodstream, and metabolism of the intestinal bacterial environment, are required.

The issue of when soy foods are eaten during the lifetime needs to be resolved, with early life exposure to soy foods appearing to be of most benefit.

Clinical trials to assess the efficacy and safety of soy foods and supplements for women with existing breast cancer are also needed.

Further Information

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