



This monograph was prepared by The Ottawa Integrative Cancer Centre (OICC), in collaboration with the Complementary Medicine Education and Outcomes (CAMEO) Research Program. It is part of a series of monographs being developed to share results of a review of the research evidence related to common therapies and products used within cancer patient care.

The following monograph is designed to summarize evidence-based research and does not advocate for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published.

Please note that this monograph does not include an exhaustive list of all potential adverse events; individuals may experience unique side effects. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a licensed health care provider. Prior to using a new therapy or product, always consult a licensed health care provider.

For the safe use of natural health products, please consider the following:

- Consult a licensed health care provider prior to using a natural health product and make a plan to monitor its effectiveness and any side effects. This is particularly important for pregnant or breast-feeding women and people with serious medical conditions.
 - To help prevent interactions with your prescribed medication, ensure your health care provider is aware of any drugs or natural health products you may be using. Make sure to note all natural health ingredients listed in compound products.
 - Read and follow all instructions on the product label.
- If purchasing natural health products in Canada, look for Health Canada approved products. Look for Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label to identify licensed products. Avoid internet pharmacies, as the quality of products cannot be guaranteed and products might not be licensed for sale through Health Canada. For more information, visit <http://www.hc-sc.gc.ca/dhp-mps/prodnatur/about-appropos/cons-eng.php>

Please note: While the aim was to draw from the most extensive research, in some circumstances the information used was limited by the selection and caliber of available research studies. Full references are available in the corresponding full-length monographs found on the OICC website.

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SOY AND SOY ISOFLAVONES

Proper Name

Glycine max

Common Name

Soy, soybean, soy isoflavones

Active Ingredients

Soy isoflavones: genistein, daidzein (converted to equol by gut flora), glycitein, formononitein. Soy exists as soyfoods and as soy isoflavone- based supplements.

Common Uses in Cancer Care

Management of hot flashes

Prevention of breast cancer

Prevention of breast cancer recurrence

Route of Administration

Oral.

Mechanism of Action

The mechanism of action of soy is not well defined, however it is thought to be related to selective estrogen receptor modulating (SERM) activity. This means that soy isoflavones may be able to activate the estrogen receptor (ER) present in some types of tissues such as bone, however not in other tissue types (1).

In addition, soy is thought to be a weak, or partial ER agonist, such that it binds and activates the receptor when stronger agents such as endogenous estradiol are in low concentration; in this situation soy may act as an ER agonist(2). In the presence of stronger agents such as estradiol, soy isoflavones may compete for some of the receptor binding sites and block some of the effects of estradiol; in this situation, soy may act as an ER antagonist.

In addition, soy has been shown to possess preferential ER-beta agonist activity in vitro (3). The ER-beta subtype has been shown to balance the effects of the ER-alpha type receptor and possess anti-cancer effects in breast cancer models(4), which may also help explain soy's anticancer effects observed in human studies.

Clinical Evidence related to Hot Flashes

Based on five RCTs assessing hot flashes or menopausal symptom scores in breast cancer survivors, soy may have a modest effect on hot flashes. All five of the RCTs found symptom reductions in both soy and control groups of between 15-50% compared to baseline(5-9). However when comparing the soy and the control groups, there were no significant differences between them.

Clinical Evidence related to Breast Cancer Prevention

The majority of observational studies showed that higher soy consumption reduced risk of developing breast cancer. Of 39 case control studies(10-48), 26 found protective effects from higher soy consumption. Eight found no effect, and none of the studies showed an increased risk. Of 12 cohort studies(49-60), 3 showed protective effects from higher soy consumption, while 9 showed no significant effects. None suggested increased risk.

Clinical Evidence related to Breast Cancer Recurrence

Four observational studies assessed the effect of soy on breast cancer recurrence(61-64). Two studies found no effect on recurrence overall (61, 62), while two studies found protective effects at dosages of >15g soy protein per day and >62mg soy isoflavones per day (63, 64): one study found a 34% reduction in risk of recurrence, HR 0.66 (95% CI 0.52-0.84), while the other found a 26% reduced risk, HR 0.74 (0.59-0.95). One study found a trend toward lower risk of recurrence among women on tamoxifen who were consuming a median 26mg isoflavones per day (61), and another study reported a trend toward similar benefit among post-menopausal women on anastrozole(63). Importantly, no studies found an increased risk of recurrence from consumption of soy.

Of six observational studies assessing the effect of soy on survival, one study found reduced risk of breast cancer related death by 33% (64), and one study found reduced risk of all cause mortality by 48% (65). One study found a trend toward reduced risk of death among tamoxifen users with an intake of isoflavones >6mg per day (median 26mg), as well as among ER+ or PR+ patients, though these results did not reach statistical significance (61). The remaining studies found no significant effects on survival.

Based on 33 RCTs and nine uncontrolled trials assessing the impact of soy/ soy isoflavones on estrogen responsive tissues among breast cancer patients or healthy women, there was no detectable pattern of impact on the following endpoints: circulating estradiol, endometrial thickness, mammographic density or mammographic breast changes, menstrual cycle length, nipple aspirate volume, uterine fibroid growth, or vaginal cytology(5-9, 30, 66-101). With respect to urinary estrogen metabolites, 3 of 6 studies found no changes, while 3 studies found increases in the purportedly protective metabolite 2-hydroxyestrone (67, 72, 84). This suggests that soy is not likely to have estrogen-like effects on these hormonally responsive tissues.

Clinical Evidence related to Estrogenic Effects

Based on 33 RCTs and nine uncontrolled trials assessing the impact of soy/ soy isoflavones on estrogen responsive tissues among breast cancer patients or healthy women, there was no detectable pattern of impact on the following endpoints: circulating estradiol, endometrial thickness, mammographic density

or mammographic breast changes, menstrual cycle length, nipple aspirate volume, uterine fibroid growth, or vaginal cytology (5-9, 30, 66-101) . With respect to urinary estrogen metabolites, 3 of 6 studies found no changes, while 3 studies found increases in the purportedly protective metabolite 2-hydroxyestrone (67, 72, 84). This suggests that soy is not likely to have estrogen-like effects on these hormonally responsive tissues.

Adverse Events and Side Effects

The most common side effects reported in human trials of soy were mild gastrointestinal side effects, however this was generally equally reported in both soy and control groups.

Interactions with other Therapies, including Drugs and Natural Health Products

The main concern around use of soy in the context of breast cancer is potential for interactions with hormonal therapies such as selective estrogen receptor modulators (eg. tamoxifen) or aromatase inhibitors (eg. anastrozole). Randomized human trials prospectively examining the effect of soy plus tamoxifen on risk of breast cancer recurrence are lacking; however data exists from large prospective observational studies. Four of these suggest that soyisoflavones 40-60mg/d is not likely to interfere with the activity of these drugs (61-64);on the other hand there is an indication that soy may help augment the anticancer effects of tamoxifen and aromatase inhibitors (61, 63). Nonetheless, until more data is available, caution is warranted, especially in relation to concentrated isoflavone isolates.

Cautions and Contraindications

Soy should be avoided by individuals with a known or suspected soy allergy.

According to the American Cancer Society, soy is safe for women with breast cancer when consumed in dietary dosages (2-3 servings per day), however soy isolates or concentrated isoflavones should be avoided due to lack of data regarding long term use (102). Therefore caution should be used by women who are on hormonal therapy in relation to concentrated isoflavone isolates.

Dosing, frequency and length of treatment

2-3 servings of soy foods per day as part of a healthy dietary pattern.

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Funding for this project was provided by the Canadian College of Naturopathic Medicine



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