

SOYFOODS IN THE DIETS OF WOMEN WITH BREAST CANCER



Interest in the protective effects of soyfoods against breast cancer focuses on their isoflavone content. Isoflavone-rich soyfoods such as tofu, soymilk and miso are thought to be one reason why breast cancer mortality rates have historically been low among women in Asia.^{1,2} Early research showing that **soybean isoflavones inhibit the development of chemically-induced mammary cancer** in rodents added strength to the hypothesis.³ However, both animal research and epidemiologic studies suggest that soyfoods offer protection against breast cancer only if they are consumed in adolescence or childhood.^{4,5} These findings are consistent with other evidence that events occurring during the first 20 years of life profoundly impact breast cancer risk later in life.⁶

Isoflavones are non-steroidal molecules classified as phytoestrogens, or plant estrogens. However, they are also classified as **selective estrogen receptor modulators (SERMs)**.⁷ This is because isoflavones vary in their effects in tissues that possess estrogen receptors. They may inhibit or stimulate estrogen-like activity, or they may have no effects.

The difference is thought to be due to the distribution of the two different types of estrogen receptors, estrogen receptor- α (ER α) and estrogen receptor- β (ER β). While estrogen activates both types of receptors equally, isoflavones preferentially activate ER β .⁸ For this reason, isoflavones are more likely to affect tissues with a preponderance of ER β receptors and less likely to have estrogen-like activity in tissues with a higher percentage of ER α receptors.

This may explain why clinical studies often find that the effects of isoflavones differ from those of estrogen. For example, estrogen has a proliferative effect on vaginal tissue whereas isoflavones don't.⁹ Importantly, in the breast, activation of ER β is thought to inhibit the proliferative effects of ER α activation.

Despite the proposed breast cancer-preventive effects, **there has been concern that soyfood consumption may worsen the prognosis of women with breast cancer** and increase the risk of developing breast cancer in women who are at risk for this disease. This concern is based almost entirely on in vitro and rodent studies.¹⁰ However, very recently, a short-term clinical trial by Shike et al.,¹¹ which received considerable media attention, led to cautionary statements by the authors about soyfoods in the diets of women with breast cancer, **a position that is inconsistent with those of the American Cancer Society¹² and the American Institute for Cancer Research.¹³**

CLINICAL DATA

The study in question involved women with early-stage breast cancer.¹¹ Prior to surgical removal of their tumors, one-half of the women were randomly assigned to consume 51.6 g of milk protein daily or a similar amount of soy protein that provided 103 mg of isoflavones, 62 mg of which were genistein. Of the three isoflavones in soybeans, genistein is the isoflavone that has been shown to stimulate the growth of existing estrogen-sensitive tumors in mice.^{14,15}





The amount of genistein consumed by the women in this study is provided by approximately **five or six servings of soyfoods per day**.¹⁶

Women consumed their assigned protein for an average of 14 to 15 days (range, 7 to 30 days). The primary endpoints of the study were **changes in breast cell proliferation and apoptosis** (programmed cell death). Increases in proliferation and/or decreases in apoptosis are viewed as adversely affecting breast cancer prognosis. Secondary endpoints were changes in the expression of genes that affect proliferation and apoptosis.

After the intervention, **breast cell proliferation and apoptosis, which were evaluated in tumors from 54 women in the soy group and 50 women in the control group, were unaffected**. Apoptosis significantly increased in the soy group in comparison to baseline, but not in comparison to the control group. However, in comparison to the control group (n=23), in a subset of women (11 of 54) with the highest blood genistein levels, there were subtle changes in the expression of genes that are involved in cell growth and proliferation.

The study authors¹¹ suggested that proliferation wasn't changed despite the changes in gene expression because the intervention was too short. However, as shown in the table, there were no changes in proliferation in response to isoflavone exposure in five other clinical studies,¹⁷⁻²¹ three of which ranged in duration from three months to one year.¹⁹⁻²¹ It is noteworthy that in the one-year pilot study by Palomares et al.,¹⁹ baseline cell proliferation in the women with breast cancer was increased relative to healthy controls, indicating that **this study was capable of detecting changes in cell proliferation**. Also, in a six-month study by Khan et al.,²¹ proliferation was unaltered even though women in the isoflavone group consumed 150 mg of genistein per day, an amount provided by **as many as 15 servings of soyfoods**. Importantly, the study by Shike et al.¹¹ is now the sixth to show that isoflavone exposure is without effect on breast cell proliferation in vivo.

Although the cell protein used to assess proliferation (Ki67) in the above discussed clinical studies is not used in routine clinical assessment, it has been shown to be associated with an aggressive phenotype.²² A recent international workshop concluded that measures of proliferation could be important both in standard clinical practice and, particularly, within clinical trials. According to this workshop, of the various measures of proliferation, immunohistochemical assessment of Ki67 with monoclonal antibody MIB1, has the largest body of literature support.²³ Agents that increase breast cancer risk, such as combined hormone therapy (HT, estrogen plus progestin) markedly increase proliferation^{24,25} whereas agents that decrease breast cancer risk, such as tamoxifen, decrease proliferation.²⁶⁻²⁸ **Therefore, the lack of effect of even high-dose isoflavone exposure provides considerable assurance about the safety of soyfoods**. Furthermore, there is a large body of supporting clinical data from studies that evaluated mammographic density. Unlike HT,²⁹ **isoflavones have no effect on this breast cancer risk marker**^{30,31} in postmenopausal women.²²

Interestingly, the study by Shike et al.¹¹ is not the first to suggest that isoflavone exposure affects gene expression in breast tissue. The study by Hargreaves et al.¹⁷ (see table) found that nipple aspirate levels of apolipoprotein D were significantly lowered and pS2 levels raised in response to soy supplementation. Because estrogen exerts similar effects on these proteins, the authors concluded that soy exerts a mild estrogenic effect on breast tissue but without affecting the critical markers of breast cell proliferation and apoptosis. Also, in the study by Khan et al.²¹ (see table), when compared to baseline there were changes in response to isoflavones in the expression of genes sampled from breast epithelium suggestive of a mild estrogenic effect although **gene expression did not differ between the isoflavone and placebo groups** nor was there a difference in proliferation between groups.

EPIDEMIOLOGIC DATA

In addition to the clinical data, extensive prospective epidemiologic research has evaluated the impact of post-diagnosis soy intake on the prognosis of women with breast cancer. Most relevant is a pooled analysis of three studies,³² two from the United States^{33,34} and one from China.³⁵ The 9,514 women with breast cancer participating in these studies were followed for an average of 7.4 years during which time there were 1,171 deaths from all causes, 881 breast cancer specific deaths, and 1,348 recurrences. When controlling for a wide range of potentially confounding variables, soy intake was found to markedly improve prognosis. More specifically, when comparing women in the third isoflavone intake tertile with those in the first, **risk of overall mortality, breast cancer-specific mortality and tumor recurrence were reduced by 13%, 17% and 25%**, respectively, with the latter finding being statistically significant. The results were similar in Chinese and U.S. women. A meta-analysis involving over 11,000 participants comprised of the three studies in the pooled analysis plus two additional Chinese prospective studies, reported similar benefits.³⁶ **The authors of that meta-analysis recommended that women with breast cancer consume soyfoods.**

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Since the **clinical studies show that isoflavone exposure has no effect on cell proliferation and apoptosis**, there isn't an obvious mechanistic explanation for the beneficial effects of post-diagnosis soy intake reported in the prospective studies. It may be that protective effects occur via mechanisms that are not detected by changes in cell proliferation or breast tissue density, such as angiogenesis inhibition. (Angiogenesis is the formation and differentiation of blood vessels.) Noteworthy in this regard, is the ability of genistein to inhibit metastases in an animal model.³⁷ Also, in three-year clinical trial involving postmenopausal women with osteopenia, BRCA1 and BRCA2 mRNA levels were unchanged in the group consuming 54 mg genistein daily whereas levels were decreased in the placebo group.³⁸ Since these genes are responsible for repairing damaged DNA, these findings provide a possible means by which **soyfoods can improve breast cancer prognosis**.

CONCLUSIONS

The clinical data overwhelmingly show that isoflavone exposure does not adversely affect breast tissue and markers of breast cancer risk in both healthy women and in women with breast cancer.

The prospective epidemiologic data show that post-diagnosis soyfood intake reduces breast cancer mortality and recurrence. Therefore, the human data are directly in line with the positions of the American Institute for Cancer Research and the American Cancer Society that women who have been diagnosed with breast cancer can safely consume soyfoods.

Women who have been diagnosed with breast cancer can safely consume soyfoods.



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CLINICAL STUDIES EVALUATING THE EFFECTS OF SOY ISOFLAVONE EXPOSURE AND BREAST CELL PROLIFERATION AND APOPTOSIS

AUTHOR/YEAR/ (REFERENCE)	MENOPAUSAL STATUS	BREAST CANCER STATUS	PERCENT ER+ PATIENTS	(N) ¹	STUDY DURATION, MEAN (RANGE)	INTERVENTION PRODUCT	TOTAL ISOFLAVONE EXPOSURE (MG/D) ²	PROLIFERATION	APOPTOSIS
Hargreaves/ 1999/(17)	Premenopausal	Mixed ³	Not indicated	28 Soy 53 Control	~14 days (8-14)	Textured vegetable protein	45	No change	No change
Sartippour/ 2004/(18)	Postmenopausal	Yes	84	17 Soy 26 Control	23 days (13-45)	Tablets	120	No change	No change
Palomares/ 2004/(19)	Postmenopausal	Yes	74	9 Soy 9 Control	11.7 months	Tablets	100	No change ⁴	Not evaluated
Cheng/ 2007/(20)	Postmenopausal	No	No applicable	26 Soy 25 Control	12 weeks	Tablets	36	No change	Not evaluated
Khan/ 2012/(21)	Pre- and post- menopausal ⁵	High risk ⁶	Not applicable	49 Soy 49 Control	6 months	Tablets	235 (150 genistein)	No change	No change
Shike/ 2014/(11)	Postmenopausal	Yes	85	54 Soy 50 Control	14 days (7-30)	Isolated soy protein	103 (62 genistein)	No change	No change

¹Based on the number evaluated for proliferation ²Expressed as aglycone equivalent weight ³Fibroadenoma (38), invasive ductal breast cancer (13), fibrocystic masses (9), duct ectasia (6), sclerosing adenosis (3), ductal carcinoma in situ (3), lipoma (1), assessor breast removal (1) ⁴Samples were normal tissue from contralateral breast ⁵n=45 postmenopausal, 53 premenopausal ⁶Women with a history of unilateral minimal risk breast cancer or with a 5-year Gail or Claus model risk estimate $\geq 1.66\%$ for women older than 40 years, $\geq 1.0\%$ for those aged between 30 and 39, and $\geq 0.1\%$ for women aged between 20 and 29.

KEY TAKEAWAYS FOR PATIENT CARE

- ✓ Soyfoods are uniquely-rich sources of isoflavones.
- ✓ Isoflavones are classified as phytoestrogens but differ from the hormone estrogen at both the molecular and clinical level.
- ✓ The estrogen-like activity of isoflavones has raised concern that soyfoods may adversely affect the prognosis of women with breast cancer.
- ✓ Limited clinical data show that exposure to high-doses of isoflavones may affect the expression of genes in breast tissue involved in controlling cell proliferation.
- ✓ Extensive clinical data show that exposure to high-dose isoflavones does not affect the rate at which breast cells replicate in healthy women and in women who have been diagnosed with breast cancer.
- ✓ Extensive prospective epidemiologic data from China and the United States show that the consumption of soyfoods after a diagnosis of breast cancer reduces breast cancer-specific mortality and tumor recurrence.
- ✓ The clinical and epidemiologic data are consistent with the positions of the American Cancer Society and the American Institute for Cancer Research which are that women with breast cancer can safely consume soyfoods.