

# Effect of Dietary Soy on Breast Cancer Recurrence and Mortality: A Review

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## Abstract

As the number of breast cancer survivors rises, interest in lifestyle modifications that can improve survival increases. The role of soy in breast cancer prevention has been studied and debated for years, and the role of soy's bioactive compounds known as isoflavones continues to be a focus of research. This review summarizes the existing epidemiologic data evaluating the effect of dietary soy intake on breast cancer recurrence and mortality. While some concern exists regarding the pro-estrogenic effect of soy as a risk factor for disease relapse, the vast majority of data shows no increase in breast cancer recurrence and mortality with dietary soy intake.

**Keywords:** Breast cancer; Mortality; Dietary soy; Biomarker

## Introduction

More than 3 million women were living in the USA following a diagnosis of breast cancer in 2014 [1]. About 61% were diagnosed with early stage disease [2]. As a result of early detection with mammography and improved treatment, more and more women are living many years after a diagnosis of breast cancer. Yet, breast cancer recurrence for many, looms as a possibility with profound implications regarding morbidity and mortality. Lifestyle modifications, including dietary intervention, have the potential to reduce risk of recurrence, but recommendations regarding lifestyle changes often lack clarity and specificity [3]. One particular area of contention is whether soy products can positively or negatively impact breast cancer outcomes. While mentioning ideal dietary constituents for breast cancer survivors, the most recent Breast Cancer Survivorship care guidelines published by the American Cancer Society/American Society of Clinical Oncology did not mention soy [4].

Soy foods are a major, and essentially the only, dietary source of isoflavones, a subclass of flavonoids [5]. Traditional soy foods, including tofu, miso and natto, consist of 0.2–0.4 mg of isoflavones per gram of fresh weight product [5]. The predominant isoflavones are the glycosides genistin and daidzin and aglycones genistein and daidzein (Figure 1). Isoflavones' presumed ability to selectively modulate the ER $\beta$  receptor more than  $\alpha$  initially prompted the terms selective estrogen receptor modulator (SERM) and phytoestrogen, raising questions of a potential relationship to hormone receptor positive breast cancers [5]. While traditionally considered weakly estrogenic, isoflavones are dependent on a variety of factors, including coactivators and corepressors present in the tissue milieu, in order to bind receptors, preventing a definitive descriptor as anti- or pro-estrogenic [6]. The term phytoestrogen fails to encompass soy's ability to serve as an antioxidant, boost the immune response, and inhibit DNA topoisomerase I and II, proteases tyrosine kinases, inositol phosphate and angiogenesis [7,8]. Both *in vitro* and *in vivo* studies in mammals have demonstrated varying effects of soy, including both tumor promotion and inhibition [5]. While the bioactive properties of soy continue to be a complicated and active area of research, epidemiologic data on the population of breast cancer survivors in whom dietary soy affects recurrence can provide some insight regarding clinically relevant mechanisms of this potential dietary intervention.

While the scientific evidence of soy's bioactive properties has resulted in recommendations of caution regarding consumption of soy supplements in the literature [9], to our knowledge, no previous

reviews have been published recommending avoidance of dietary soy intake for patients with a history of breast cancer. In 2014, the World Cancer Research Fund International stated that limited evidence suggests increased consumption of foods containing soy 12 months or more after a diagnosis of primary breast cancer reduces risk of all-cause mortality [10]. In 2009, a report by the American Academy of Family Physicians published that "there is no clear evidence to recommend for or against changes in soy intake for women who have a history of breast cancer," giving soy intake in patients with a history of breast cancer a rating of C [11]. In 2006, the American Cancer Society (ACS) published in a guide for breast cancer survivors that recommended moderation of soy foods [12]. In 2003, the ACS expert committee gave a grading of B for increasing soy intake in patients with breast cancer due to insufficient evidence to conclude benefit or risk in cancer survivors [13]. In 2001, an ACS workgroup gave a C rating for breast cancer patients' consumption of soy containing foods, indicating that both harm and benefit had been shown in this population [14].

Studies show that some breast cancer survivors modify their soy intake after diagnosis. A study on women recently diagnosed with breast cancer in Ontario, Canada showed that since diagnosis, 17% of women started or stopped soy foods, with most stopping [15]. A study on dietary changes in Malaysian women diagnosed with breast cancer showed that post-diagnosis roughly 15% increased their consumption of soy milk, and that physician and dietitian advice and desire to cure cancer were the reasons for diet alterations [16]. A retrospective cross-sectional study of female breast cancer survivors in Oklahoma found that while only about 16% of women on tamoxifen ate more soy foods after compared to before diagnosis, only 30% of women received any specific dietary advice from their physician with over half the survivors preferring more information [17].

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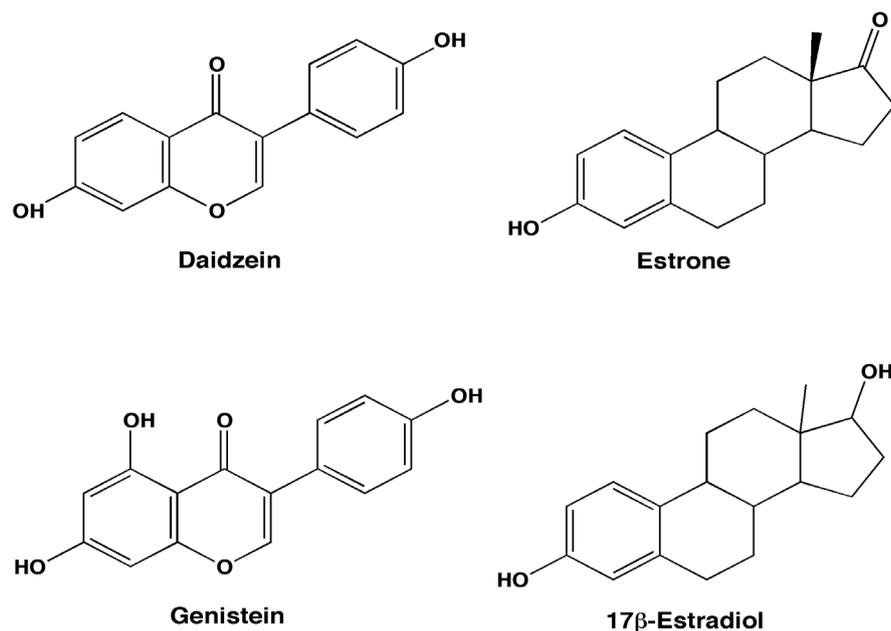


Figure 1: Chemical structures of estrone, estradiol, and bioactive compounds (isoflavones) found in soy.

In order to ascertain evidence-based recommendations for breast cancer survivors regarding dietary soy intake, the association between dietary soy, including soy protein, isoflavones, and legumes and total soy, and breast cancer recurrence and mortality in breast cancer survivors was investigated. This narrative review is unique in that it focuses entirely on the relationship between dietary soy and breast cancer recurrence and mortality in patients following a diagnosis of breast cancer.

## Literature Search

In order to identify epidemiological studies investigating the relationship between soy intake and breast cancer recurrence and mortality in breast cancer survivors, PubMed and Web of Science databases were searched using the following terms for articles published within the past twenty years: (neoplasm recurrence OR mortality OR survival OR survivor) AND (soy OR soy foods OR soy milk) AND (breast neoplasms). The PubMed search yielded 91 total studies and Web of Science yielded 136 citations. Additional studies were identified using bibliography cross-referencing.

Our focus was on primary epidemiological studies. Animal studies, *in vitro* experiments, studies focusing on changes in breast tissue in terms of physiological properties and tumor markers, studies conducted in people without a diagnosis of breast cancer, and epidemiological studies focusing on pre-diagnosis soy intake were excluded.

## Breast Cancer Recurrence as a Function of Soy Consumption

Among the five individual prospective studies on the post-diagnostic effect of soy on breast cancer recurrence [18-22], three studies identified a statistically significant reduction in risk in the overall cohort when comparing highest to lowest soy intake (Table 1). In the largest individual cohort of the articles included in this review, which followed 5,042 Chinese women, Shu et al. found that the significant relationship between isoflavone intake and cancer recurrence/metastasis or death related to breast cancer was no longer significant

when stratified by positive or negative estrogen receptor status of breast cancer or by nonuser and users of tamoxifen [18]. These investigators also found a significant reduction in breast cancer recurrence when comparing highest soy protein to lowest soy protein intake, and this relationship was significant among women with ER+ (HR: 0.69; 95% CI: 0.50-0.98) but not ER- (HR: 0.77; 95% CI: 0.54-1.09) breast cancer. No relationship was found among users or nonusers of tamoxifen [18]. In a smaller cohort of 524 Chinese women, Kang et al. found a significant reduction in risk of recurrence when comparing highest to lowest isoflavone intake, supported by a statistically significant linear trend, in postmenopausal women (P for trend=0.02) but not in premenopausal women (P for trend=0.46); pooled analysis of all subgroups was not included [19]. In a pooled analysis of 339 Korean women, Woo et al. did not find a significant reduction in breast cancer recurrence with soy intake [20]. However, in their adjusted analysis stratified by HER2 status, the investigators found a significant inverse relationship between isoflavone (HR: 0.23, 0.06-0.89; P for trend= 0.01) and legume (HR: 0.27, 0.13-0.57; P for trend <0.01) intake and breast cancer recurrence in the sub-group of women with HER2 negative breast cancer. They also found a significant positive trend for legume intake and breast cancer recurrence (P for trend=0.02) [20]. Eight HER2+ recurrences were part of this analysis, and this positive association was not supported by a significant hazard ratio when comparing highest to lowest legume intake (10.61, 0.90-124.68) [20]. While a study by Guha et al. did not find a significant reduction in breast cancer recurrence when pooling all subgroups, these investigators identified a decreased risk of recurrence in non-tamoxifen users who consumed 3.62-8.16 mg glycerin/day (0.32, 0.13-0.78) and 8.17-14.99 mg glycerin/day (0.26, 0.10-0.73), and post-menopausal women consuming 1.45-9.60 mg glycerin/day (0.48, 0.24-0.93), when comparing to the lowest dose of glycerin [21]. The dosages in which these statistically significant recurrence reductions occurred were not the highest dose out of all doses studies, unlike other studies included in this review (Table 1).

All three meta-analyses/pooled analyses that investigated the relationship between soy intake and breast cancer recurrence found a

Author & year	Cohort	Type of study	Sample size	Follow-up (years)	Highest to lowest dietary intake measured	HR, 95%CI	P-Trend
Shu et al. 2009 [18]	The Shanghai Breast Cancer Survival Study (SBCSS), China	Prospective Cohort	5,042	Median: 3.9 Range: 0.5-6.2	>15.31 vs. ≤5.31 g protein/day ----- >62.68 vs. ≤20.00 mg isoflavones /day	0.68, 0.54-0.87 ----- 0.77, 0.60-0.98	
Kang et al. 2010 [19]	Cancer Hospital of Harbin Medical University in Harbin, China	Prospective Cohort	524	Median: 5.1	>42.3 vs. <15.2 mg isoflavones/ day	Premenopausal: 0.88, 0.61-1.23 Postmenopausal 0.67, 0.54-0.85	Premenopausal: 0.46 Postmenopausal: 0.02
Woo et al. 2012 [20]	Center for Breast Cancer in National Cancer Center Hospital, Korea	Prospective cohort	339	Median: 2.7 Range: 0.108-4.37	65.7 vs. <36.2 g total soy products/day  ≥ 4.2 vs. <1.0 g legumes/day  ≥15.2 vs. <7.4 mg isoflavones/day	0.71, 0.28-1.80  0.40, 0.13-1.21  0.56, 0.20-1.53	0.26  0.06  0.08
Guha et al. 2009 [21]	Life after Cancer Epidemiology Study (LACE), California and Utah	Prospective cohort	1,954	Mean: 6.31 Range: 0.11-8.65	≥9.60 vs. 0 mg daidzein /day ----- >0.795 vs. 0 mg glycerin/day ----- ≥13.03 vs. 0 mg genistein/day	0.96, 0.52-1.76 ----- 0.80, 0.42-1.50 ----- 0.95, 0.52-1.75	----- 0.10 ----- 0.24
Caan et al. 2011 [22]	Women's Healthy Eating and Living Study (WHEL), US	Prospective cohort	3,088	Median: 7.3 Range: 0.17-4	16.33-86.9 vs. 0-0.07 mg isoflavones /day	0.78, 0.46-1.31	0.47
Dong and Qin 2011 [23]		Meta-analysis of cohort studies	9,656		Isoflavones	RR: 0.84, 0.70-0.99	
Nechuta al. 2012 [24]	After Breast Cancer Pooling Project (SBCSS, LACE and WHEL), US and China	Pooled analysis of prospective cohort studies	9,514	Mean: 7.4	≥10.0 vs. <4.0 mg isoflavones/ day	0.75, 0.61-0.92	0.0759
Chi et al. 2013 [25]		Meta-analysis of cohort studies	11,206		Highest vs. lowest soy food intake	0.74, 0.64-0.85	

**Table 1:** Summary of epidemiological studies evaluating effect of dietary soy on breast cancer recurrence.

significant risk reduction when comparing highest to lowest soy intake (Table 1) [23-25]; however, two out of the four studies included in the meta-analysis by Dong & Qin examined pre-diagnostic soy isoflavone intake rather than post-diagnostic soy isoflavone intake [23]. In their stratified analysis, Dong & Qin found that this relationship held in post-menopausal women (0.78, 0.63-0.93), but not in pre-menopausal women (0.90, 0.64-1.15) [23]. After stratifying their pooled analysis, Nechuta et al. found that the reduction in breast cancer recurrence when comparing highest to lowest isoflavone intake was statistically significant in all US women (0.76, 0.58-0.99) and non-Asian US Women (0.74, 0.56-0.97), but not the Chinese cohort (0.69, 0.57-1.01), although an inverse association was still observed [24]. When comparing highest to lowest isoflavone intake (>10 vs. <4 mg/d), a statistically significant reduction in breast cancer recurrence was observed among women with ER negative tumors (0.64, 0.44-0.94), post-menopausal women (0.64, 0.48-0.87), and tamoxifen users (0.63, 0.46-0.87) [24]. In the largest meta-analysis on this topic, including data from 11,206 women, Chi et al. found that the significant reduction in recurrence seen with all doses of soy held among postmenopausal women, ER- and ER+/PR+ tumors [25]. Subgroup analysis showed an association of highest vs. lowest soy food intake with reduced recurrence in ER negative (0.64, 0.44-0.94), ER+/PR+ (0.65, 0.49-0.86), and postmenopausal patients (0.67, 0.56-0.80) [25] (Table 1).

## Breast Cancer Mortality as a Function of Soy Consumption

While not an epidemiological study, Nagata found, in an ecological study surveying different regions in Japan, that the total amount of soy products consumed had no relationship to the breast cancer mortality rate, although consumption of soy products was associated with decreased death from stomach cancer and heart disease [26].

Among the five individual prospective studies investigating soy intake and mortality, three found a significant reduction in mortality when comparing highest to lowest soy food intake (Table 1) [18,19,22,27,28]. In their stratified analysis of the largest cohort of a prospective study, consisting of 5,042 Chinese breast cancer survivors, comparing highest to lowest soy protein intake and mortality, Shu et al. found that soy protein's clinically significant reduction of mortality no longer held among women with positive or negative estrogen receptor status and nonusers or users of tamoxifen [18]. Kang et al. conducted no stratified analysis [27]. In a cohort of breast cancer patients admitted to the Affiliated Hospital of Inner Mongolia Medical College of China, Zhang et al. found that soy protein's significant reduction in cancer related deaths held among women with ER+ breast cancer (0.66, 0.44-0.93) and that soy isoflavone's significant reduction in cancer related

deaths held among both women with ER+ (0.78, 0.47-0.98) and ER-breast cancer (0.59, 0.40-0.93) [28] (Table 2).

Among the pooled-analysis and meta-analysis that investigated soy's effect on mortality, the meta-analysis by Chi et al. identified a statistically significant reduction in mortality when comparing highest to lowest soy food intake among women with ER+ (0.74, 0.60-0.91) and ER- (0.70, 0.58-0.84) tumors, and premenopausal (0.78, 0.69-0.88) and postmenopausal (0.81, 0.73-0.91) women, but not tamoxifen users [25] (Table 2).

No epidemiological studies identified showed increased breast cancer recurrence or mortality.

## Discussion

### Summary of findings

5 out of 8 studies showed a statistically significant reduction in breast cancer recurrence, and 4 out of 7 studies showed a statistically significant reduction in mortality with increasing amounts of dietary soy intake in breast cancer survivors. The only evidence of an association between dietary soy intake and increased breast cancer recurrence or mortality was observed in a study following 339 women by Woo et al. that showed a statistically significant positive trend in legume intake and breast cancer recurrence in women with HER2 positive tumors [20]. However, this was the case for only one specific subgroup out of eleven studies including multiple subpopulations of women based on tamoxifen use, differing tumor types, and menopausal status. Thus, the overwhelming body of evidence indicates that dietary soy has no harmful impact on breast cancer survivorship. While soy's benefit to post-menopausal women arose as a common theme, stratified analyses from the various studies showed that neither tumor type nor use of

tamoxifen had an impact on soy's efficacy in preventing breast cancer recurrence. This suggests that soy's properties are more complex than its role solely at the level of the estrogen receptor.

Various hypotheses exist for how soy might decrease breast cancer recurrence. Both antagonistic and agonistic effect at the ER receptor, which could result in increased sex hormone binding globulin (SHBG) and clearance of estrogen, could decrease the effect of estrogens. Given the lack of a trend in populations affected by soy, and the fact that change was observed in ER-patients as well, it makes sense that more general mechanisms, such as anti-inflammatory, anti-proliferative, and anti-oxidant effects, are at play [25]. Interestingly, isoflavones can exert hormonal effects even without direct interaction at the receptor, for example through inhibition of conversion of weak estrone into potent estradiol, further suggesting a lack of soy's dependence on the estrogen receptor to have beneficial effects [5]. The one trend of more of an effect in post-menopausal women suggests that while estrogen receptors may not be directly at play, hormones and their location of production certainly are, given the increased levels of estrogen in the periphery and decreased levels in the ovary [25]. Isoflavone metabolism has also been shown to vary based on intestinal flora and genetic polymorphisms; thus, individual variability is important to keep in mind if future efforts at prevention fail in certain subpopulations of patients [6]. The existing epidemiologic data coming largely from East Asia and the U.S. limits generalizability to women of different backgrounds, in whom different genetic and environmental factors may affect isoflavone metabolism.

### Strengths and limitations

While some studies included in this review used food frequency questionnaires that have been shown to be good estimates of

Author, year (ref.)	Name or Location of cohort	Type of study	Sample size	Follow-up (years)	Dietary intake	Mortality HR/RR, 95%CI	P for trend mortality
Shu et al. 2009 [18]	The Shanghai Breast Cancer Survival Study (SBCSS), China	Prospective Cohort	5,042	Median: 3.9 Range: 0.5-6.2	>15.31 to ≤5.31 g protein/day ----- >62.68 vs. ≤20.00 mg isoflavones /day	0.71, 0.54-0.92 ----- 0.79, 0.61-1.03	
Kang et al. 2010 [19]	Cancer Hospital of Harbin Medical University in Harbin, China	Prospective Cohort	524	Median: 5.1	>42.3 vs. <15.2 mg isoflavones/ day	Premenopausal: 1.05, 0.78-1.71  Postmenopausal: 0.88, 0.56-1.24	Premenopausal: 0.87  Postmenopausal: 0.76
Caan et al. 2011 [22]	Women's Healthy Eating and Living Study (WHEL), US	Prospective Cohort	3,088	Median: 7.3 Range: 0.17-4	16.33-86.9 vs. 0-0.07 mg isoflavones /day	0.46, 0.2-1.05	0.02
Nechuta al. 2012 [24]	After Breast Cancer Pooling Project (SBCSS, LACE and WHEL), US and China	Pooled analysis of prospective cohort studies	9,514	Mean: 7.4	≥10.0 vs. <4.0 mg isoflavones/day	All-cause: 0.87, 0.70-1.10 ----- Breast cancer specific: 0.83, 0.64- 1.07	All-cause: 0.6354  ----- Breast cancer specific: 0.4974
Chi et al. 2013 [25]		Meta-analysis of cohort studies	11,206		Highest vs. lowest soy food intake	0.84, 0.71-0.99	
Kang et al. 2012 [27]	First Affiliated Hospital of Inner Mongolia Medical College, China	Prospective cohort	256	Range: 5-7	>35.30 vs. <8.45 mg isoflavone/day  >15.78 vs. <4.55 g protein/day	0.25, 0.09-0.54  0.38, 0.17-0.86	
Zhang et al. 2012 [28]	Affiliated Hospital of Inner Mongolia Medical College of China in Hohhot, China	Prospective cohort	616	Median: 4.34 Range: 0.75-5	>28.3 vs. < 7.56 mg isoflavone /day ----- >13.03 vs. <2.12 g protein/day	0.62, 0.42-0.90  ----- 0.71, 0.52-0.98	

Table 2: Summary of epidemiological studies evaluating effect of dietary soy on breast cancer mortality.

true consumption, conducting nutritional studies is challenging given variability in documentation and susceptibility to recall bias. Furthermore, determining the level of processing through a questionnaire is impossible. Hexane, lectins, saponins and oxalates found in processed soy are thought to inhibit vitamin and mineral absorption, resulting in a misbalance in nutrients that could have negative health outcomes [29]. Pure or highly enriched isoflavones have been shown to increase estrogen dependent tumor growth, whereas minimally processed soy foods such as flour have not, a phenomenon that has been attributed to the presence of other bioactive compounds besides isoflavones in soy foods [30].

Given that different studies were stratified for different variables, it is difficult to ascertain in which subpopulations that varies by hormone receptor status, menopausal status, and tamoxifen use post-diagnostic soy intake might be more beneficial. In addition to differences in doses studied, there was variability in whether isoflavone intake, protein intake, legume intake or total soy intake was measured. The difference in populations limits our ability to directly compare the different studies and magnitude of effects.

Nonetheless, our review clearly shows that the evidence does not support an increase in breast cancer recurrence or mortality with post-diagnostic dietary soy intake. There may be a decrease in recurrence and mortality, as shown in Chinese and Korean cohorts and meta-analyses that include American cohorts. The majority of existing data comes from prospective cohort studies.

While the specific nature of our question allowed us to provide a comprehensive review of the evidence, it resulted in the exclusion of many valuable studies investigating pre-diagnostic soy intake and breast cancer risk, preventing exploration of the temporal relationship of nutrition in breast cancer risk and mortality. The literature suggests that pre-diagnostic soy intake does not increase risk of breast cancer, and is likely protective [31,32] although the data is mixed. A systematic review and meta-analysis of RCTs found an association in pre-menopausal women between dietary soy and increased breast density, a biomarker for breast cancer risk [33].

**Implications to practice and research:** In conclusion, our review demonstrates that there is no scientific evidence to support advising breast cancer survivors not to consume dietary soy. Our review does not address the role of soy supplements in breast cancer survivorship. There is a moderate level of evidence to suggest that dietary soy intake could improve breast cancer outcomes, although the magnitude of this effect and population of relevance remain unclear. It is possible that post-menopausal women might gain more benefit than pre-menopausal women and the receptor status of the initial tumor may also play a role. Future studies are required to make a formal recommendation to reduce recurrence and mortality in breast cancer survivors.

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