**Soy Isoflavones and Breast Cancer**

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**OVERVIEW**

The soybean and its products have been a staple in the Asian diet for centuries. Although intake of soy remains low in most Western populations, the use of soy isoflavone supplements has become commonplace, and an increasing number of food products contain soy ingredients. This review will present an updated summary of the observational results on soy isoflavones and risk of breast cancer development and outcome in patients with breast cancer. Results from soy intervention studies that have specifically examined the effects of soy on breast cell proliferation in breast tissues will be discussed. We will conclude by highlighting gaps in our knowledge on soy and breast cancer and issues that need to be addressed in future studies.

Soybeans and their products have been a staple in the Asian diet for centuries. Soybeans are the predominant source of isoflavones, one of the three main classes of phytoestrogens or plant estrogens. Genistein and daidzein are the two major isoflavones; glycitein is a minor component. Soy isoflavones are structurally similar to 17-beta estradiol and bind to estrogen receptors (ER) and may have antiestrogenic or estrogen-like effects depending on factors such as endogenous estrogen levels. Interest in the potential effects of soy on breast cancer risk began in 1991 with the publication of a paper that highlighted several putative chemopreventive agents in soybeans.1

However, early enthusiasm for soy as having beneficial effects against breast cancer was replaced with fears and concerns that soy foods may have harmful effects among women with a history of breast cancer or among those at high risk of developing breast cancer. Concerns that soy may increase breast cancer risk were suggested in a 2-week intervention study of premenopausal women with benign and malignant breast conditions who were supplemented between time of diagnosis and surgery. Women randomized to the soy arm (19 patients) (45 mg per day isoflavones) exhibited nonsignificantly higher indices of increased DNA synthesis in the breast (based on Ki67) compared with women in the control arm not given soy (29 patients).2 Daily intake of soy protein (38 mg genistein) for 5 months was associated with increases in the yield and the appearance of hyperplastic epithelial cells in the nipple aspirate fluid in premenopausal women but not in postmenopausal women.3 In addition, a series of studies conducted by Helferich and colleagues found that isoflavones and isoflavone-containing soy products stimulate the growth of mammary tumors and inhibited the efficacy of tamoxifen and the aromatase inhibitor letrozole in athymic ovariectomised mice implanted with MCF7 cells.4 The American Cancer Society and other organizations cautioned the use of soy foods, particularly among women with breast cancer or at high risk for breast cancer.5

What is the current evidence on soy isoflavones and breast cancer? This manuscript will present an updated summary of the observational results on soy isoflavones and risk of breast cancer development and describe results on intake of soy in relation to the risk of mortality and recurrence in women with breast cancer. It will also review intervention studies that have specifically examined the effects of soy on various biomarkers (e.g., cell proliferation) in breast tissues. We will discuss current gaps in our knowledge on soy and breast cancer and issues to be addressed in future studies.

**SOY AND RISK OF BREAST CANCER**

Nearly 40 case-control and cohort studies on soy and risk of breast cancer development have been published since 1991. Approximately two-thirds of these were case-control studies that were conducted in Asian populations. In a meta-analysis of primarily case-control studies conducted in Asian populations, compared with the lowest level of soy food intake (≤5 mg isoflavones per day), risk was intermediate (summary odds ratio [OR] = 0.88, 95% CI, 0.78–0.98) among those with modest (approximately 10 mg isoflavones per day) intake, and further reduced (summary OR = 0.71, 95% CI, 0.60–0.85) among those with high intake (≥20 mg isoflavones per day).6 This inverse association was confirmed in a subsequent meta-analysis of prospective studies; relative to no/low soy intake, the summary OR for high intake was 0.76.
(95% CI, 0.65–0.86) in Asian populations and it was 0.97 (95% CI, 0.87–1.06) in Western populations. The lack of association in Western populations may be related, in part, to the much lower soy intake (1 to 2 mg isoflavones per day) and that most of the soy isoflavones in the Western diet are from soy components added to Western foods (instead of whole soy foods).

The meta-analyses results by menopausal status obtained from case-control studies and prospective studies were not entirely consistent. A significant inverse association between soy isoflavone intake and risk was observed in both premenopausal (summary OR = 0.65, 95% CI, 0.50–0.85) and postmenopausal women (summary OR = 0.63, 95% CI, 0.46–0.85) in case-control studies conducted in Asian populations. In contrast, Dong and colleagues reported an inverse association in postmenopausal women (summary OR = 0.78, 95% CI, 0.63–0.93) but not in premenopausal women (summary OR = 0.90, 95% CI, 0.64–1.15) in prospective studies. However, this may be related to the inclusion of Western studies in this analysis. When we updated the meta-analysis of prospective studies restricting to those conducted in Asian populations, an inverse association was also found in both premenopausal (summary OR = 0.82, 95% CI, 0.64–1.04) and postmenopausal (summary OR = 0.83, 95% CI, 0.72–0.96) women.

Analysis of the soy-breast cancer association by hormone receptor status may provide further clues regarding the mechanism of soy, because some of the breast cancer risk factors that are believed to mediate risk via a hormonal mechanism (e.g., parity, age at first birth, body size) appear to have clearer effects on hormone receptor-positive breast tumors. To date, the soy-breast cancer association by hormone receptor status has been investigated in a subset of studies conducted in Asian and Western populations. The meta-analysis results we obtained from these studies show a consistent inverse association in estrogen receptor (ER)-positive/progesterone receptor (PR)-positive tumors (summary OR = 0.66, 95% CI, 0.59–0.74) and ER/PR-negative tumors (summary OR = 0.61, 95% CI, 0.52–0.73). The results are essentially identical when we restricted the analysis to the studies conducted in Asian populations (summary ORs = 0.65 [95% CI, 0.57–0.74] for ER-positive/PR-positive tumors and 0.56 [95% CI, 0.46–0.68] for ER/PR-negative tumors). Soy genistein has been reported to downregulate HER2 in human breast cancer cells. However, it is unclear whether the effects of soy are specific to HER2-negative tumors. Soy intake was associated with a decreased risk of HER2-negative breast cancer in one case-control study, but HER2 status has not been considered in subsequent studies.

### Key Points

- Results from observational epidemiologic studies conducted in Asian populations showed decreased risk of breast cancer development in association with high intake of soy (approximately > 10 mg isoflavones per day).
- Results from observational epidemiologic studies conducted in Asian and western populations show decrease risk of breast cancer mortality/recurrence in association with high intake of soy.
- Results from clinical/intervention studies on the short-term effects of soy products on intermediate biomarkers of breast cancer risk have not shown clear beneficial or deleterious effects.
- Additional studies are needed to further investigate the relationships (e.g., timing, dose-response) between intake of soy (Asian soy foods, other soy products, soy supplements) and risk of breast cancer development and outcome in Western and Asian populations.

### Soy and Risk of Breast Cancer Recurrence/Mortality

As noted previously, the safety of soy food consumption among women with breast cancer or at high risk for breast cancer has been a concern. Since 2005, three studies from the United States, one study from Korea, and four from China have investigated the effect of soy consumption on the prognosis of patients with breast cancer. Of these, three studies specifically assessed intake of soy after diagnosis. In other studies, the assessment was primarily on intake of soy before diagnosis or around the time of interview.

When we combine these results in a meta-analysis, high soy intake was significantly inversely associated with overall mortality (summary hazard ratio [HR] = 0.70, 95% CI, 0.58–0.85) and recurrence (summary HR = 0.77, 95% CI, 0.63–0.95); results were significant in postmenopausal women (respectively, summary HRs were 0.76 and 0.71) but not in premenopausal women (respective summary HRs were 0.94 and 0.86). Results by tamoxifen use were presented in six studies. Soy intake was associated with reduced risk of total mortality among both tamoxifen users (summary HR = 0.65, 95% CI, 0.38–1.09) and nonusers (summary HR = 0.72, 95% CI, 0.41–1.27), but its effect on recurrence was found only among tamoxifen users (summary HR = 0.84, 95% CI, 0.63–1.10) but not among nonusers (summary HR = 1.01, 95% CI, 0.66–1.55).

Three of the above mentioned studies where soy intake after breast cancer diagnosis was assessed—Shanghai Breast Cancer Survival Study (SBCSS), Women’s Healthy Eating Living (WHEL) study, and Life After Cancer Epidemiology (LACE) study—were included in a pooling project, the After Breast Cancer Pooling Project (ABCP). This pooling approach is particularly noteworthy. First, all three studies used validated food frequency questionnaires so that the assessment of soy intake was comprehensive and specifically related to intake after breast cancer diagnosis. Second, the pooled analysis included additional years of follow up and events compared with the previously published results. More importantly, Netchuta and coworkers had access to individual data from all three cohorts and were able to adjust for clinical covariates.
factors, sociodemographic characteristics, and lifestyle-related factors; to investigate the potential effect modification by menopausal status, ER status, and tamoxifen use; and to use common soy isoflavone intake cutoffs (<4, 4 to 9.99, ≥10 mg) in the United States (LACE and WHEL) and Shanghai cohorts. In the U.S. cohorts, consumption of 10 mg or more per day compared with less than 4 mg per day was associated with reduced risk of total mortality (HR = 0.93, 95% CI, 0.69–1.24), breast cancer mortality (HR = 0.84, 95% CI, 0.59–1.19), and breast cancer recurrence (HR = 0.76, 95% CI, 0.58–0.99); the corresponding HRs in Shanghai, China, were 0.84 (95% CI, 0.54–1.33), 0.75 (95% CI, 0.47–1.20), and 0.69 (95% CI, 0.47–1.01). There were no clear differences in the effects of soy by menopausal status, ER status, and tamoxifen use.

**SOY AND BREAST TISSUE CHANGES IN CLINICAL INTERVENTION STUDIES**

Because the possibility of residual confounding associated with healthier lifestyle of soy consumers and selection bias cannot be ruled out in observational studies, a large number of clinical intervention studies on soy have also been conducted to evaluate potential mechanistic effects of soy on circulating hormone levels, mammographic density, and cell proliferation, established biomarkers of breast cancer risk. These clinical studies were typically short-term and rarely used whole soy foods (as in the observational studies conducted in Asian populations) but used a diverse group of soy products that varied in soy composition and in the amount of soy. Positive and negative results on hormone levels have been reported in a few individual studies, but the overall evidence showed little support of hormonal effects of soy. In a comprehensive review and meta-analysis of 47 controlled intervention studies, Hooper and colleagues concluded there were no effects of soy or isoflavones on circulating estrogen levels in healthy premenopausal and postmenopausal women. A similar conclusion was reached in a meta-analysis of eight randomized trials on mammographic density. Results on breast tissue cell proliferation changes in association with soy intervention are also inconclusive. In addition to using soy products of different composition and amounts of soy, these studies were usually conducted among women with a history of different benign and malignant breast diseases. In the only study that was conducted among 60 healthy premenopausal women who received 60 mg isoflavone or placebo daily for 3 months, the proliferation marker, Ki67, was seen in a very small percentage of samples (<3%) but showed no apparent changes by soy isoflavones. Investigators at Manchester, United Kingdom, conducted two studies among premenopausal women with breast cancer or benign breast conditions (e.g., fibroadenoma, fibrocystic masses, duct ectasia). Participants were supplemented with soy (45 mg isoflavones in the form of ground textured vegetable protein in bread rolls) or consumed a normal diet for 14 days before surgery. Cell proliferation rate increased after soy supplementation (19 patients) in the first study but not in the second study (28 patients in the soy arm, 56 in the control arm). A study of mostly postmenopausal patients with breast cancer (stages I to III) (15 of 17 were postmenopausal) who were supplemented with 200 mg of soy isoflavones for an average of 23 days (until their surgery) showed no change in mitotic index compared with a historic control group of patients with breast cancer. Interestingly, an increase in apoptotic index and the ratio of apoptosis/mitosis was found in the soy compared with the control group. A fifth study included 18 postmenopausal patients with breast cancer (stage 0 to II) who were disease-free after completing cancer therapy and were randomly assigned to receive 100 mg isoflavone (9 participants) or placebo tablets (9 participants) for 12 months. In this longer-term study, Ki67 levels reduced in association with soy supplementation, but these results were reported only in an abstract.

New results from a placebo-controlled randomized study were published in 2012. In this study, premenopausal women with no cancer (23 received soy, 21 in control arm), postmenopausal women with no cancer (14 receiving soy, 16 in control arm) and women with breast cancer (15 receiving soy, 10 in control arm) received high soy (150 mg genistein, 74 mg daidzein, 11 mg glycitein) or placebo supplementation for 6 months (note: The numbers presented under “soy stratification” are inconsistent with the number of participation in the “soy group and control group” [Table 1 of Khan et al.]). This high dose of soy had no benefit in this study; the overall results show no significant changes in Ki-67 levels in all subjects and separately in premenopausal and postmenopausal women.

**CONCLUSION**

The evidence to date from observational epidemiologic studies, suggests that soy food intake, in the amount consumed in Asian populations about 10 to 20 mg isoflavones per day), may be associated with a reduction of risk of breast cancer development as well as mortality and recurrence among women with breast cancer. As the intake of soy (both traditional Asian soy foods and other soy products) and use of soy supplements are becoming more common place in Western populations, additional investigations of the relationship between soy and breast cancer risk in non-Asian populations should be encouraged, as they may provide insights regarding the effects of timing of soy intake as well as dose-response relationships. This would require the assessment of traditional soy foods and other soy products and supplements and collecting information on the duration as well as reasons for eating/using soy foods and products. Continued follow-up of cohorts of patients with breast cancer with information on soy intake at baseline and the inclusion of relevant biomarkers will further inform the potential benefits of soy among patients with breast cancer. Investigation of the effect of soy in relation to overall mortality, breast cancer-specific mortality, and recurrence by hormone receptor status (ER/PR, HER2) of breast tumor, by tamoxifen use, and by
menopausal status will be needed as the results to date are still based on relatively small numbers.

The large number of clinical intervention studies on soy that have investigated intermediate biomarkers of breast cancer risk including circulating estrogen levels, mammographic density, and breast tissue changes (cell proliferation) have not shown clear beneficial or deleterious effects. A 2009 National Institutes of Health-sponsored scientific workshop highlighted many of the challenges in the design, implementation, and evaluation of soy intervention studies and advocated careful consideration of a number of study design issues in the next generation of soy intervention studies. In addition to the many issues related to study design (e.g., study population, menopausal status, duration of study, sample size), the heterogeneous soy agents (product composition, type, and amount of soy), and variability of response to soy (e.g., depending on equol status) represent important challenges in intervention studies and should be carefully considered in future studies.

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Disclosures of Potential Conflicts of Interest

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References


