Current Nutrition Reports (2025) 14:50
https://doi.org/10.1007/s13668-025-00640-5

REVIEW

A Review of the Clinical and Epidemiologic Evidence Relevant to the Impact of Postdiagnosis Isoflavone Intake on Breast Cancer Outcomes

Mark Messina[1] · **Sarah Nechuta**[2]

Accepted: 10 March 2025

Abstract

Purpose of Review This narrative review aims to determine the impact of postdiagnosis isoflavone intake, via supplements and foods, on breast cancer outcomes. Foods derived from soybeans are uniquely rich sources of isoflavones, naturally occurring compounds that can bind to estrogen receptors although the extent to which they exert estrogen-like effects in humans is unclear. Isoflavones have been rigorously investigated for a wide range of health benefits including breast cancer prevention. However, their classification as phytoestrogens has led to concern that isoflavones and hence, soy food consumption, could worsen the prognosis of women with breast cancer and interfere with the efficacy of endocrine therapy for this disease.

Recent Findings Research in athymic ovariectomized mice shows isoflavones stimulate the growth of existing estrogen-sensitive mammary tumors. However, extensive clinical research indicates that neither soy foods nor isolated isoflavones affect markers of breast cancer risk including mammographic density and breast cell proliferation. No effects are observed even when isoflavone exposure greatly exceeds typical intake in Asian countries. Furthermore, the results from epidemiologic studies indicate postdiagnosis isoflavone intake from soy foods reduces recurrence and possibly mortality from breast cancer. Additionally, the limited observational data do not show that isoflavones interfere with the efficacy of tamoxifen or aromatase inhibitors.

Summary Regardless of their treatment status, evidence indicates that women with breast cancer can safely consume soy foods. Limiting intake to no more than two servings of traditional Asian soy foods daily, an amount that provides approximately 50 mg isoflavones, is recommended, not because data indicate exceeding this amount is harmful, but because few population-based studies involved participants consuming more than this intake recommendation.

Keywords Breast cancer · Isoflavones · Soy · Clinical research · Epidemiology · Tamoxifen

Introduction

In 2022, there were an estimated 2.3 million women diagnosed with breast cancer and 665,000 deaths globally from this disease [1]. There are also nearly 8 million women alive who were diagnosed with breast cancer within the past 5 years [1]. Evidence indicates diet impacts risk of developing this disease and possibly breast cancer recurrence and survival [2, 3]. Foods made from soybeans have been rigorously investigated for their impact on both breast cancer prevention and prognosis.

The findings of a 1990 workshop sponsored by the National Cancer Institute in the United States (US) led this institute to fund research examining the soy and breast cancer relationship [4]. Fueling interest was the historically low breast cancer incidence rate in Japan [5] and research demonstrating that isoflavone-rich soy protein, but not soy protein devoid of isoflavones, inhibited the development of chemically-induced mammary tumors in rats [6]. Subsequently published migration data showing that the variation in breast cancer mortality rates between East Asian countries and the US are due to differences in lifestyle and environmental exposures, not to genetic differences, added to the focus on soy [7].

✉ Mark Messina
mark.messina@sniglobal.org

1 Soy Nutrition Institute Global, Jefferson, MO, USA

2 Grand Valley State University, Allendale, MI, USA

Published online: 25 March 2025

Isoflavones are naturally occurring plant compounds found in uniquely high amounts in soybeans [8]. Although isoflavones are commonly classified as phytoestrogens, they may also exert effects independent of their interaction with estrogen receptors (ERs) [9]. A recent systematic review and meta-analysis of 24 observational studies found that isoflavone intake was associated with a statistically significant decreased risk of developing breast cancer [odds ratio (OR) (95% confidence interval (CI)); 0.71 (0.72, 0.81)] [10]. However, it may be that the proposed chemopreventive effects of isoflavones stem primarily from intake early in life, a hypothesis first proposed in 1995 [11, 12] and for which there is considerable epidemiologic support [13–16].

The proposed breast cancer chemopreventive effects of isoflavones continue to be rigorously investigated although much of the discussion surrounding these soybean constituents involves the potential impact of postdiagnosis intake on breast cancer recurrence and survival. Concerns that isoflavone-containing soy foods are contraindicated for women with breast cancer, henceforth referred to as the soy and breast cancer controversy (SBCC), arose in earnest in the late 1990s. Concerns were due to research showing that in athymic ovariectomized mice implanted with MCF-7 cells (a human estrogen sensitive breast cancer cell line), isoflavones stimulate the growth of existing mammary tumors [17]. Over the past 25 years, much clinical and observational research relevant to the SBCC has been published. Although no long term randomized controlled trial (RCT) has examined the effect of postdiagnosis soy intake on breast cancer recurrence or survival, several cancer and health organizations have concluded that soy foods can be safely consumed by, and may even benefit, breast cancer survivors (Table 1).

However, in most instances, these position statements were based primarily on epidemiologic research, which in many cases, was somewhat limited when they were issued. Also, few agencies have specifically commented on soy consumption during endocrine therapy. This omission is problematic because women with ER-positive (ER+) breast cancer, which accounts for about 70% of all breast cancers [18–20] may be treated with tamoxifen and/or aromatase inhibitors (AIs) for up to 10 years [21]. Further, among high-risk women, tamoxifen [22–24] and AIs [25, 26] have been shown to reduce the risk of developing breast cancer. Thus, many women will be using medications that could potentially interact with isoflavones [27, 28].

An interaction between isoflavones and tamoxifen would not be unusual as there are a host of well-established food and drug, and dietary supplement and drug, interactions [29]. A cross-sectional study involving 380 Asian American breast cancer patients revealed that neither soy intake nor circulating isoflavone levels were associated with circulating levels of tamoxifen or its metabolites [30]. However, isoflavones may affect efficacy independent of effects on tamoxifen metabolism. Isoflavones could interfere with the efficacy of tamoxifen by inhibiting its binding to ERs and/or simply by exerting an estrogenic effect that overwhelms the anti-estrogenic effect of the drug [31]. In fact, Deng et al. [32] concluded that soy foods might weaken the efficacy of tamoxifen based on changes in gene expression found in 14 premenopausal women with luminal A breast cancer. These results align with the inhibitory effect of isoflavones on the efficacy of both tamoxifen [33, 34] and the AI, letrozole [35], in athymic ovariectomized mice.

Finally, since the median age of breast cancer diagnosis in the US is 62 (60 and 64 for black and white women, respectively) [36] and the 15-year overall US survival rate is 80% [36], most women with breast cancer will transition to long-term survivorship. Therefore, breast cancer survivors may adhere to dietary recommendations aimed at improving overall health [37]. In developed countries, these recommendations typically call for increasing plant protein intake [38, 39]. Soy protein is commonly viewed as the prototypical plant protein, and research shows that soy foods can make important contributions to plant-forward diets [40, 41]. Furthermore, isoflavones may exert a range of health benefits in postmenopausal women [42–44]. Given that women with breast cancer have an increased risk of developing cardiovascular disease [45, 46], the hypocholesterolemic effects of soy protein [47, 48] and the possible vascular effects of isoflavones [49], may be especially relevant. Thus, it is particularly important for breast cancer survivors, and health care providers who counsel survivors, to fully understand the health impact of soy food consumption.

Therefore, the purpose of this review is to provide health professionals with 1) background information on isoflavones 2) an historical perspective on the origins of the SBCC and 3) an evaluation of the clinical and epidemiologic evidence related to the impact of postdiagnosis soy intake on the prognosis of breast cancer in women overall and by endocrine therapy use. Additional topics discussed are the relevance of the isoflavone delivery vehicle (supplements vs soy foods) and the acceptable postdiagnosis intake range for isoflavones.

Isoflavones—Background

The three soybean isoflavones (aglycone form) genistein, daidzein and glycitein and their respective glycosides, represent approximately 50%, 40% and 10% of total isoflavone content, respectively [50]. Isoflavones bind to both ERs. The original ER, now known as ER-alpha (ERα), was first described in 1958 [51]. Not until 1996 was ERβ identified, the second ER [52]. Two years later it was shown that unlike estrogen, which binds with equal affinity to both ERs, isoflavones preferentially bind to ERβ [53]. These receptors have

Table 1 Position statements about soy food intake by women with breast cancer

Organization	Recommendation	Reference
Cancer Council (Australia) Accessed, 4/30/24	The available evidence does not suggest that soy foods need to be avoided by breast cancer survivors	https://www.cancer.org.au/about-us/policy-and-advocacy/prevention/obesity/related-resources/information-sheet-soy-isoflavones
Dana Faber Cancer Institute Accessed, 9/25/23	Moderate amounts of soy foods (1–2 servings/d) can be included in the diet of cancer survivors including those with ER+ breast cancer even when being treated	https://www.dana-farber.org/for-patients-and-families/care-and-treatment/support-services-and-amenities/nutrition-services/faqs/soy-and-cancer/
MD Anderson Cancer Center Accessed 9/25/23	Soy foods may reduce risk of cancer recurrence – even in patients with ER+ breast cancer	https://www.mdanderson.org/cancerwise/is-soy-safe-for-patients-with-breast-cancer.h00-159538167.html
Canadian Cancer Society Accessed 9/25/23	Soy consumed as part of a healthy, well-balanced diet is unlikely to harm breast cancer survivors and may improve breast cancer survival, especially in postmenopausal women. Up to 3 servings of soy foods daily is acceptable	https://cancer.ca/en/cancer-information/cancer-types/breast/supportive-care/eating-well-after-breast-cancer
Irish Cancer Society	Soy should not be taken if you have hormone-sensitive breast cancer and are taking tamoxifen. Soy may also interfere with aromatase inhibitors used in breast cancer treatment	https://www.cancer.ie/sites/default/files/2019-11/diet_and_cancer_2017.pdf
Irish Nutrition & Dietetic Institute (INDI), The National Cancer Control Programme and the Irish Society of Medical Oncology Accessed 9/25/23	Healthy eating during cancer treatment. Include 2–3 portions of dairy in your diet each day. If you dislike dairy then use dairy alternatives, such as soya or almond milk	https://www.breakthroughcancerresearch.ie/wp-content/uploads/2022/04/TRUTH-ABOUT-FOOD-CANCER-LR.pdf?fbclid=IwAR1JuKzRmJeG_RmW2UinWx-Em64CQJBDmtDrm3Hnr60b9RbyC6XwnmwTW5U
Oncology Nutrition Dietetic Practice Group Accessed 9/25/23	Breast cancer survivors can safely eat soy foods. Soy foods may decrease breast cancer recurrence	https://www.oncologynutrition.org/erfc/healthy-nutrition-now/foods/soy-and-breast-cancer
American Cancer Society	Soy intake, whether prediagnosis or postdiagnosis, or postdiagnosis soy isoflavone intake is associated with a lower risk of recurrence. Soy isoflavones may increase breast cancer survival through the modulation of ERβ, which has anticarcinogenic and antiproliferative effects	https://www.ncbi.nlm.nih.gov/pubmed/32515498
American Institute for Cancer Research	Limited evidence shows potential for greater overall survival, and perhaps decreased recurrence, among women a year or more after diagnosis who consume moderate amounts of soy	https://www.aicr.org/cancer-prevention/food-facts/soy/
Japanese Cancer Society	Patients with breast cancer can be recommended to consume soy because this may decrease the risk of recurrence	https://www.ncbi.nlm.nih.gov/pubmed/38147174

different tissue distributions and when bound by ligands result in different and sometimes opposite physiological effects [54]. In general, activation of ERα and ERβ is seen as exerting proliferative and anti-proliferative effects, respectively [54]. Isoflavones bind more weakly to ERs than estrogen. However, their weaker relative binding affinity does not rule out these soybean components from exerting effects similar to those associated with the hormone estrogen, since in response to the consumption of 1–2 servings/d of traditional Asian soy foods, which provide approximately 50 mg isoflavones, circulating isoflavone concentrations can be 1,000-fold higher than estrogen concentrations [55, 56]. In other words, the higher circulating isoflavone concentrations theoretically compensate for their weaker relative binding activity thereby potentially resulting in transactivation of ERs and turning on the expression of target genes within cells.

The preferential binding to ERβ provides a molecular basis for classifying isoflavones as selective estrogen receptor modulators (SERMs) [57–59], a classification they have in common with tamoxifen [57]. It is notable that three decades before the discovery in 1996 of ERβ, Folman and Pope [60] opined that the importance of genistein "… may lie as much in their ability to antagonize the natural steroid oestrogens as in their own oestrogenic activity." In other words, Folman and Pope [60] are suggesting the possible anti-estrogenic effect of genistein, that is, functioning as an ER antagonist, may be a more significant attribute of this isoflavone than its estrogenic effect, that is, functioning as an ER agonist. However, despite their classification as phytoestrogens and SERMs, the extent to which isoflavones exert anti-estrogen or estrogen-like effects in women has not been established. To this point, a recently published meta-analysis of RCTs found that isoflavones did not affect the four endpoints affected by the hormone estrogen that were examined (endometrial thickness, vaginal maturation index, follicle-stimulating hormone, and circulating estradiol levels) [61].

Furthermore, isoflavones, and especially genistein, may exert cellular effects independent of their interaction with ERs; in fact, the ER-independent actions accounted for much of the initial interest in the proposed chemopreventive effects of isoflavones. In vitro, genistein inhibits the activity of tyrosine protein kinase [62] and DNA topoisomerases [63, 64]. Tyrosine kinases are overexpressed in cancer cells and are implicated in several steps of neoplastic development and progression [65]. DNA topoisomerases catalyze changes in the topological state of DNA [66]. However, these in vitro effects occur at concentrations beyond that which could likely be achieved in vivo. This point warrants emphasis because, although the consumption of high amounts of isoflavones (> 100 mg/d) produce low micromolar isoflavone concentrations – concentrations at which a range of effects are observed in vitro – in the circulation, ≥ 98% of the isoflavones are conjugated with glucuronic acid or sulfate, forms of isoflavones which are mostly biologically inactive [55].

There are approximately 3–4 mg of isoflavones per gram of protein in traditional Asian soy foods such as tofu, tempeh, and miso [67, 68]. Note that in this manuscript, isoflavone amounts refer to the aglycone equivalent weight. Isoflavones occur in soybeans and unfermented soy foods almost exclusively as glycosides with the biologically inactive sugar molecule accounting for approximately 40% of the glycoside weight. As a rough guide, one serving of a traditional soy food, such as one cup of soymilk made from whole soybeans, contains approximately 25 mg of isoflavones [69]. However, as a result of processing losses, concentrated sources of soy protein such as soy protein isolate and soy protein concentrate, which are approximately 90% and 65% protein respectively [70], typically have a lower (≤ 2 mg/g protein) and more variable isoflavone content than traditional Asian soy foods [50, 71, 72].

In Japan, older adults consume approximately 30 to 50 mg/d isoflavones [67, 68, 73, 74] whereas in China, soy intake varies considerably among geographical regions [75, 76]. For example, mean isoflavone intake in rural Chinese women was found to be only ~ 18 mg/d [75] whereas among Shanghainese men [77] and women [78] it is closer to 40 mg/d. A small percentage of individuals in Japan or China consume more than 100 mg/d [77–79]. In comparison, US [80], Canadian [81] and European [82] per capita isoflavone intake is typically < 3 mg/d. Most soy consumed throughout the world is in unfermented form, as ethnic Chinese consume relatively little fermented soy whereas in Japan, about half of all soy consumed is fermented, and in Korea, about 20–30% is [67, 83].

Although estimates vary somewhat, the elimination half-life for isoflavones is approximately eight hours [84–91]. Therefore, steady state plasma concentrations would be more readily maintained by repeated ingestion of isoflavones throughout the day than by ingestion just once daily [84]. Also, the bioavailability of isoflavones is nonlinear at higher intakes, suggesting that uptake is rate-limiting and saturable [85]. Work in postmenopausal women showed that doubling isoflavone intake increased plasma concentrations by slightly more than 50% [92]. Therefore, taking a bolus of isoflavones will lead to lower sustained circulating concentrations compared to dividing intake into separate doses. This pattern of intake mimics intake in Asian populations wherein soy foods may be consumed throughout the day.

Finally, because of the differences in the way rodents and humans metabolize isoflavones, the former are not a particularly good model for evaluating the health effects of these diphenolic compounds. Rodents poorly conjugate phenolic compounds (e.g., flavonoids) such that the percentage of the total circulating concentration of the biologically active form of isoflavones, i.e., the form not conjugated with glucuronic acid or sulfate [93–95], will be much higher in rodents than in humans [55]. Also, rodents very efficiently convert the isoflavone daidzein into the isoflavonoid equol, whereas only about 25% of Europeans and North Americans and about 50% of Japanese [96] and Chinese [97] host the intestinal microbiota that can make this conversion. Equol binds with much greater affinity to ERs than its parent isoflavone daidzein [98]. It was proposed in 2002, that those who possess equol-synthesizing microbiota are more likely to benefit from soy food consumption than those who not [99]. Interestingly, unlike genistein, equol does not stimulate the growth of existing ER+ mammary tumors in athymic ovariectomized mice [100].

Origins of the SBCC

High in vitro concentrations (> 10^{-5} M) of genistein via ER-independent mechanisms [62, 63], inhibit the growth of ER+ and ER- breast cancer cells. However, at lower and more physiologic concentrations (10^{-8} – 10^{-6} M) as a result of ERα activation [101], the growth of ER+, but not ER- breast cancer cells, is stimulated [17, 28, 102–104]. The latter finding received relatively little attention until studies utilizing athymic ovariectomized mice largely supported the in vitro work. However, whether growth is stimulated likely depends upon the relative proportion of ERα and ERβ, and how the ER-ligand complex interacts with co-activators and co-repressors in the cell [105]. In addition to this in vitro research, in 1996 and 1998, pilot intervention studies involving premenopausal women provided support for the preclinical findings. One study examined nipple aspirate fluid volume [106] and the other, in vivo breast cell proliferation [107], although in the latter case, the results were based on a preliminary analysis of the data, which were not confirmed when the complete analysis was published one year later [108]. Parenthetically, because of their lower circulating estrogen levels, it is postmenopausal women who are thought to be most sensitive to any estrogen-like effects of isoflavones.

Work in athymic ovariectomized mice is primarily responsible for the SBCC. In these mice, T cells are not produced because they lack a thymus, which allows foreign cells to be implanted without rejection. To mimic the postmenopausal state, the ovaries are surgically removed at about three weeks of age to eliminate estrogen production. When studying mammary cancer, at about the same time as ovariectomy, MCF-7 cells are implanted subcutaneously into the fat pads (not orthotopically implanted into the mammary gland) to initiate tumors. An estrogen pellet is initially implanted in all groups to stimulate tumor growth. Once tumors reach a designated size, typically around 35 mm^2, the animals are randomized into dietary groups and the pellet is removed from all groups except the positive control. As highlighted below, the results from this model published between 1998 and 2012 come mostly from one laboratory and represent the primary evidence upon which concerns about soy consumption by women with breast cancer are based [109].

Dietary genistein in concentrations ranging from 250 to 1000 ppm stimulate tumor growth in mice implanted with MCF-7 cells in a dose dependent manner [110].

Dietary daidzein has only a very modest stimulatory effect on tumor growth [99] and its bacterially-derived metabolite, equol, is without effect [100].

Genistein does not affect the growth of tumors in mice implanted with ER- breast cancer cells [111].

Genistein stimulates tumor growth in athymic ovariectomized mice implanted with MCF-7 cells and an estrogen pellet designed to produce circulating estrogen levels that mimic concentrations in postmenopausal women [112].

Genistein inhibits the tumor growth-inhibitory effect of both tamoxifen [33, 34] and letrozole [35].

Soy protein isolate containing varying amounts of genistein increases estrogen-dependent mammary tumor growth in a dose-dependent manner [113].

Tumor stimulation increases in a stepwise fashion in response to genistein-containing

products the more they are refined or processed [114].

Translating results from rodents to humans should be done with caution [115, 116] and not all studies utilizing the athymic ovariectomized mouse model show genistein stimulates tumor growth [117]. Nevertheless, the research stemming from this model provided a basis for concerns, especially because not until 2009, was epidemiologic research published that directly refuted this work [118]. Much of the concern about isoflavones focused specifically on isoflavone supplements rather than traditional soy foods [119], although as discussed later, the evidence justifying differentiating supplements from soy foods is limited.

Positions of Cancer Organizations

Table 1 lists ten health/cancer agencies/organizations that have opined on soy consumption by breast cancer survivors. Of those, eight concluded women can safely consume soy and five mention that soy food consumption may improve prognosis. Because of their recency, it is especially notable that in 2022, the American Cancer Society concluded that postdiagnosis soy intake may reduce recurrence and improve survival [120] and in 2023, the World Cancer Research Fund International (Global Cancer Update Programme) identified soy intake as one of five factors that *may* improve the survival of breast cancer patients, the other four being healthy body mass index, fiber intake, physical activity and overall healthy eating pattern [3]. However, only two of the ten position statements specifically address the issue of soy consumption during endocrine therapy. The Irish Cancer Society advises against it whereas the Dana Faber Cancer Institute states that soy is not contraindicated.

Randomized Controlled Trials

As noted previously, no RCT has evaluated the impact of postdiagnosis soy consumption on breast cancer recurrence or survival. However, many RCTs have evaluated the impact of isoflavones on markers of breast cancer risk, notably breast tissue density and breast cell proliferation. Mammographic breast density is a well-established risk factor for breast cancer [121, 122]. Although breast density decreases with age [123], prospective data show that a slower rate of decrease is associated with an increased breast cancer risk [124]. A recently published meta-analysis of prospective cohort and case–control studies found that increased breast tissue density over time was associated with a more than 50% to almost 100% increased breast cancer risk whereas a decrease in density was associated with a decreased risk [125]. Both tamoxifen and AIs reduce breast tissue density [126]. Estrogen only hormone replacement therapy very slightly increases density whereas combined hormone therapy (CHT, estrogen plus progestin) has a much more pronounced effect, indicating it is the progestin component of CHT that has an adverse effect on breast tissue [127, 128]. The effect of CHT on breast tissue density aligns with its effect on breast cancer risk [129]. According to the North American Menopause Society, systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists {The Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel, 2022 #27620} [130].

The other marker examined, although to a lesser extent, is breast cell proliferation. In vivo breast cell proliferation is a better predictor of breast cancer risk than mammographic density [130]. A fundamental hallmark of cancer cells involves their ability to sustain chronic proliferation [130]. The most widely practiced measurement of proliferation involves immunohistochemical detection of the nuclear non-histone protein Ki67, which is thought to be involved in ribosomal RNA synthesis [131]. The observation that Ki67 is detected in proliferating cells but absent in quiescent cells led to its adoption as a measure of the proportion of cells proliferating in a tumor [132]. Because cells that proliferate more quickly have less time to repair DNA damage, they are more likely to be transformed into cancer cells [133]. CHT has been shown to increase proliferation four to tenfold within just twelve weeks [134–136], whereas tamoxifen [137] and letrozole [138], decrease proliferation.

Randomized Controlled Trials: Mammographic Density

Fourteen RCTs were identified that evaluated the effects of isoflavone exposure on mammographic density (Table 2). None of the trials found a significant increase relative to baseline or to the change in the placebo group. Four of the RCTs involved premenopausal women [139–142], seven involved entirely or nearly all postmenopausal women [143–149], and three involved women of varying menopausal status [150–152]. All trials except one were at least one year in duration [141]. Isoflavone intake ranged from 40 [151] to 120 mg/d [146] and total (placebo and isoflavone) sample size from 30 [139] to 401 [151], although most trials included at least 75 women. Note that one RCT was informally published [141], but the pertinent details were reported in a meta-analysis by Hooper et al. [153].

The three RCTs that intervened with isoflavones derived from red clover [142, 150, 151] are considered here for the purposes of examining effects on breast tissue density because although it contains only small amounts of genistein and daidzein, the primary red clover isoflavones biochanin A and formononetin are metabolized in vivo to genistein and daidzein, respectively [154]. The isoflavone content of a tofu extract (Tofupill/Femarelle, Se-cure Pharmaceuticals, Dalton, Israel) that served as the intervention product in one study was not reported so its isoflavone content is unclear [143]. One study intervened with isoflavones derived from soy germ [146]. Genistein represents about 15% of the total isoflavone content of soy germ whereas in soybeans, soy foods and soy protein isolate, it accounts for about 50% [50]. In several studies, it was unclear if the isoflavone content of the food or supplement referred to the aglycone or glycoside weight. One study intervened with isolated genistein in aglycone form [145]. As noted previously, isoflavones are present in soybeans and unfermented foods primarily as glycosides.

It is also notable that in the two-year trial by Ferraris et al. [142], involving premenopausal ER+ breast cancer patients on tamoxifen with or without luteinizing hormone-releasing hormone analogues, that the decrease in breast tissue density in the placebo group was similar to the decrease in the group consuming 80 mg/d isoflavones derived from red clover (Table 2). These results indicate that at least with respect to this one marker, isoflavones do not interfere with the efficacy of tamoxifen. However, no clinical studies evaluating the impact of isoflavones on the effects of tamoxifen on breast cell proliferation were identified.

In 2010, Hooper et al. [153] conducted a meta-analysis of eight RCTs (N = 1287) that evaluated the impact of isoflavones on mammographic density. They found no significant mean difference for all women or postmenopausal women in response to isoflavones but a modest increase for premenopausal women that was lost in one of three sensitivity analyses. More recently, after systematically reviewing the relevant RCTs, Finkeldey et al. [155] concluded that there is little evidence that isoflavone treatment modulates breast cancer risk factors, including mammographic density, in pre- and postmenopausal women. Finally, in a two-year RCT, Chilibeck et al. [156] reported

Table 2 Details and results of randomized controlled trials examining the effects of isoflavones (IF) on breast tissue density

Author/year/(reference)	Duration/Location	Isoflavone delivery vehicle	Dose (mg/d, aglycone equivalents)	Group/(n)/Age (years)	Percentage density	P-value for mean difference/Comments To
Premenopausal women						
Maskarinec/2003/[139]	1 y /USA	Supplement	76	Placebo/ (15)/ 43.1 ± 1.7 IF/(15)/ 41.1 ± 3.1	Initial Final Placebo 49.5 ± 12.6 49.9 ± 12.8 IF 34.6 ± 18.8 37.1 ± 16.5	0.37
Maskarinec/2004/[140]	2 y/ USA	Soy foods	58 ± 15.8	Control/(103)/ 42.8 ± 2.9 IF/(98)/ 43.2 ± 3.1	Initial Final Control 48.1 ± 25.2 43.2 ± 24.3 IF 45.6 ± 23.3 40.5 ± 23.7	0.37
Tice/2005/[141]	26 wk/ USA	SPI	50	Control/(24)/ 44.6 IF/(23)/44.8	Control: Pre vs Post, −2.8 IF Pre vs Post, −1.00	0.30. Abstract indicates – "2.7 vs −2.4%, p = 0.48"
Ferraris/2020/[142]	24 mo/ Italy	Supplement (red clover)	80	Placebo/(39)/44.6 IF/(42)/44.4 BCa patients	Initial Final Placebo 2.8 ± 0.9 2.5 ± 0.5 IF 2.8 ± 0.9 2.5 ± 0.9 85% of patients received tamoxifen + LHRH analogues, 15% received tamoxifen alone	P = 0.64 Surgical menopause, ER + BCa patients ER + on tamoxifen SS ↓, no difference between group
Postmenopausal						
Labos/2013/[143]	12 mo/ Greece	Tofu extract	Not indicated	Usual diet/(36)/ 50.6 ± 5.8 DT56a/(27)/48.7 ± 4.8 HT/(26)/51.5 ± 4.1	DT56a (644 mg/d) HT (1 mg 17B E2 + 0.5 mg norethisterone acetate)	DT56a use was not associated with changes in mammography
Verheus/2008/[144]	1 y/ Netherlands	36.5 g milk protein 36.5 g SPI	99	Control/(56)/65.3 ± 4.0 IF/(70)/66.3 ± 4.3	Initial Final Control 15.1 10.7 IF 10.3 7.9	0.78
Marini/2008/[145]	3 y/ Italy	Supplement	54 (genistein aglycone)	Placebo/(67) 53.5 ± 2.0 IF/(71)/ 53.8 ± 2.9	Image mean index calculated in arbitrary units. Data in graph in arbitrary units	Using Wolfe classification, a greater percentage of genistein recipients were rated as having improved breast density but not SS
Maskarinec/2009/[146]	2 y/ USA	Supplement (Soy germ)	80, 120	Placebo (123) 54.8 ± 3.6 IF-80 (115) 55.2 ± 4.0 IF-120 (120) 54.7 ± 3.8	Initial Final Placebo 32.0 ± 17.5 29.3 ± 18.0 IF-80 28.9 ± 17.4 25.8 ± 17.4 IF-120 32.3 ± 19.0 30.6 ± 19.2	0.17
Colacurci/2012/[147]	1 y/ Italy	Supplement	60	Placebo (62)/ 55.3 ± 7.6 IF (62)/5.7 ± 7.7	Initial Final Placebo 1.75 ± 0.85 1.58 ± 0.84 IF 1.89 ± 0.96 1.80 ± 0.95	Difference not SS
Delmanto/2013/[148]	10 mo/ Brazil	Supplement	100	Placebo (34)/56.2 ± 7.7 IF (32)/55.1 ± 6.0	Initial Final Placebo 2.0 2.0 (median) IF 1.5 1.0 (median)	0.393
Mixed menopausal status						

Table 2 (continued)

Author/year/(reference)	Duration/Location	Isoflavone delivery vehicle	Dose (mg/d, aglycone equivalents)	Group/(n)/Age (years)	Percentage density	P-value for mean difference/Comments To
Atkinson/2004/[150]	1 y/ UK	Supplement (Red clover)	43.5	Placebo (91)/55.2 ± 4.9 IF (86)/55.1 ± 4.7	Final change vs baseline Placebo −3.9 ± 11.7 IF −3.2 ± 11.7	0.73
Powles/2008/[151]	3 y/ UK	Supplement (Red clover)	40	Placebo (202)/45 (35–69) IF (199)/45 (35–69)	Final change vs baseline Premenopausal Postmenopausal n = 111 −6.60 n = 11 −8.0 n = 111 −3.03 n = 8 −6.9	Premenopausal, 0.2 Postmenopausal, 0.7
Wu/2015/[152]	1 y/ USA	Supplement	50 (unclear if aglycone equivalent weight)	Placebo (41)/55.0 ± 7.6 IF (44)/57.6 ± 8.1	Initial Final All patients Placebo 19.9 (14.6, 26.0) 18.3 (13.3, 24.1) IF 3.3 (9.4, 17.8) 12.7 (9.0, 17.0) Breast cancer patients (29 per group) Placebo 17.0 (12.1,22.7) 16.0 (11.2,21.7) IF 11.8 (7.4,17.3) 11.7 (7.4,17.1) Values are means (95% confidence intervals)	0.38 for all patients 0.44 for breast cancer patients
Rajaram/2023/[149]	12 mo/ Malaysia	Supplement Soy foods	50 100	Control (33)/56 ± 8.0 IF (28)/58 ± 5.0 Soy foods (30)/56 ± 5.8	% change in dense area from baseline Control n = 22 −2.5 ± 32.9 IF n = 19 −15.5 ± 35.4 Soy foods n = 21 −7.4 ± 34.7	P = 0.460

Values are means plus standard deviation unless otherwise indicated. Abbreviations: BCa (breast cancer), HT (hormonal therapy), LHRH (luteinizing hormone-releasing hormone), SPI (soy protein isolate), SS (statistically significant) no differences in abnormal mammograms between women consuming 105 mg/d isoflavones and the placebo group.

Randomized Controlled Trials: Breast Cell Proliferation

None of the six RCTs [108, 157–161] that evaluated in vivo breast cell proliferation found isoflavone exposure had an impact in comparison to the control or placebo group, even though intake greatly exceeded typical Japanese intake in several trials (Table 3). Three RCTs were approximately three or fewer weeks in duration [108, 157, 161], the other three were three [159], six [160], and 12 [158] months long. These studies involved healthy women [159], women with benign breast disease and breast cancer [108], women at increased risk for breast cancer or women with a history of unilateral minimal risk breast cancer [160], and breast cancer patients [157, 158, 161]. The isoflavone dose ranged from 36 [159] to 235 [160] mg/d. As an aside, a German cross-sectional study involving invasive breast cancer patients, found that genistein intake was inversely associated with Ki67 expression [162], but because of the extremely low isoflavone intake of this cohort, the association is unlikely to have a causal basis [163].

There are several aspects to the breast cell proliferation research that warrant mention. For example, the longest study was published only as an extended abstract and included only 18 breast cancer patients [158]. Nevertheless, this study did find that at baseline breast cell proliferation in the non-cancerous breast of women in both the isoflavone and placebo groups was increased relative to healthy women, which is consistent with the two-to-six-fold increased risk women have of developing contralateral breast cancer compared with the risk in the general population of women developing a first primary cancer [164]. The study by Hargreaves et al. [108] is the final analysis of a study involving 28, 23, and 33 women in the soy, control, and historical control groups, respectively. There were no statistically significant differences in proliferation as measured by thymidine labeling index (TLI) and Ki67 labeling index (Ki67LI), between the combined control groups and the soy group, nor were there differences in ER and progesterone receptor (PR) status, apoptosis, mitosis, or Bcl-2 expression [108]. As noted previously, a preliminary analysis of this research minus the historical controls, which has been erroneously cited in the literature as a separate study, did find an increase in proliferation as measured by TLI but not Ki67LI [107].

In the study by Khan et al. [160], after 6 months exposure to a daily supplement that provided 235 mg isoflavones, breast cell proliferation in high-risk premenopausal ($n=53$) ($p=0.31$) and postmenopausal ($n=45$) ($p=0.73$) women did not differ significantly from the placebo group. However, compared to baseline, there was a statistically significant increase [median Ki67 labelling index (interquartile range)] in premenopausal women in the isoflavone group [1.71 (1.12–2.35) vs. 2.18 (1.18–3.04), $p=0.04$). In addition to not being the primary comparison of interest, this ~27% increase is approximately 16 to 40-fold less than the increase in response to CHT [134, 165]. Furthermore, the increase occurred in response to a pharmacologic dose of isoflavones. Of the 235 mg provided by the supplement, 150 mg was comprised of genistein, the isoflavone shown to stimulate tumor growth in athymic ovariectomized mice [17, 100]. This amount of genistein, which is about 8 times typical Japanese intake, is provided by approximately 15 servings of traditional soyfoods [67]. In the study by Shike et al. [161], there were no effects of isoflavones on proliferation but the increase in a measure of apoptosis (Cas3) in response to isoflavones almost reached statistical significance (0.07).

Finally, despite cell proliferation not increasing, in three of the six RCTs gene expression was modified in a way suggestive of an increased breast cancer risk and similar to that which might be expected from exposure to estrogen [108, 160, 161]. Several other studies that examined gene expression produced mixed results. For example, after 5 d of soymilk (250 ml) consumption Coussement et al. [166] reported no major general epigenetic reprogramming in the breast of women undergoing aesthetic breast reduction surgery. In contrast, Qin et al. [167] found that in healthy premenopausal women there were changes in the expression of two genes but the effects of the two isoflavone doses (40 and 140 mg/d for one menstrual cycle) were inconsistent and the authors questioned the biological significance of the observed changes. In this study, there was no change in nipple aspirate fluid C3 levels in response to isoflavone intake, indicating the lack of an estrogenic effect based on this one marker, but that finding contrasts with the change Petrakis et al. [106] observed in nipple aspirate fluid in response to isoflavone-rich soy protein.

Epidemiology: Postdiagnosis Soy Intake and Breast Cancer Prognosis

Nine prospective observational studies and one pooling study were identified that examined the impact of postdiagnosis soy intake on breast cancer recurrence and/or survival. Table 4 displays key characteristics of the studies. For completeness, studies that collected dietary soy food or isoflavone intake after diagnosis, using a measure that included both pre- and post-diagnosis intake (as most assessments included the last year of usual intake) are considered.

One study was conducted in Hong Kong [168], three in China [118, 169, 170], two in the US [171, 172], and three in Korea [173–175]. The pooling study included a pooled analysis of individual data from one of the Chinese studies [118] and the two US studies with additional follow-up time and consideration of both recurrence and mortality outcomes [176]. Two US studies that found postdiagnosis isoflavone intake reduced mortality [177, 178] are not included in Table 4 because the low isoflavone intake in these cohorts suggests the findings are

Table 3 Effect of isoflavone (IF) intake on in vivo breast cell proliferation (Ki67 labeling index)

Author/year/(reference)	Duration/ Location	Isoflavone delivery vehicle	Isoflavone dose (mg/day)	Group/(n)/age	Results	P value/comments
Hargreaves/1998/[108]	14 days/ UK	Textured vegetable (soy) protein	45	Premenopausal women Control (53)/34.9 ± 8.8 IF (28)/31.6 ± 7.6	Weeks 1–2 Weeks 3–4 Control 3.16 ± 3.08 6.03 ± 4.27 IF 4.76 ± 6.16 6.17 ± 7.00	P = 0.38 between groups
Sartippou/2004/[157]	22 days/ USA	Supplement	120	Breast cancer patients Placebo (26)/ 59 (37–81) Soy/(17)/ 62 (45–79)	Apoptotic to mitotic ratio Initial Final Placebo 6.5 ± 7.0 5.5 ± 4.7 IF 3.3 ± 3.4 5.8 ± 8.3	P = 0.376 between groups
Palomares/2004/[158]	12 months /USA	Supplement	100	Breast cancer patients Placebo (12)/ 57.3 ± 2.0 IF(11)/56.5 ± 2.1	6 mo 12 mo Placebo 7.4 ± 7.8 I5.9 ± 5.2 IF 6.1 ± 5.0 5.4 ± 6.5	At 6 mo and 12 mo Ki67 index ↓ 3.1% ± 9.5% and ↓ 4.9% ± 11.5% in the IF group, respectively. These figures were 0.9% ± 8.1% and 4.1% ± 9.0%, respectively in the placebo group. Differences between groups not statistically significant
Cheng/2007/[159]	3 months/ Sweden	Supplement	36	Postmenopausal women Placebo(25)/56.9 ± 4.2 Soy (26)/58.4 ± 5.0	No changes in Ki67-positive expression were found in either group after treatment (P < 0.05)	Proliferation rate in both groups was very low
Khan/2012/[160]	6 months/ USA	Supplement	235	Placebo/49)/50 (46–55) IF/(50)/48 (43–53)	All participants (n = 98) Initial Final Placebo 0.97 (0.70,1.90) 0.92 (0.59, 1.96) IF 1.17 (0.66, 1.93) 1.09 (0.75, 2.33) Premenopausal (n = 53) Placebo 1.90 (0.88, 2.33) 1.94 (0.92,2.55) If 1.71 (1.12, 2.35) 2.18 (1.18,3.04) Postmenopausal (n = 45) Placebo 0.70 (0.57,1.07) 0.63 (0.42, 0.98) If 0.63 (0.52,1.08) 0.77 (0.35, 0.94)	Women at increased risk for breast cancer or women with a history of unilateral minimal risk breast cancer. Statistically significant ↑ in IF premenopausal women vs baseline but no difference between groups. No significant changes in postmenopausal women
Shike/2014/[161]	14–15 days/ USA	Soy protein isolate	103	Milk/(50)/ 56.1 ± 12.6 Soy/(54)/56.3 ± 11.3	Invasive breast cancer patients Initial Final Placebo 16.5 (0–80) 20.0 (1–72) If 15.5 (1.8–80) 21.0 (4.0–80) Cas3 (apoptosis) Placebo 1.0 (0–10) 1.25 (0–31) IF 1.0 (0–25) 1.55 (0–31)	P = 0.21 between groups. Placebo: ER + , 84%; ER-, 16%; premenopausal, 44%; postmenopausal, 56%. IF: ER + , 80%; ER-, 20%; Premenopausal 35.2%, postmenopausal,, 64.8%. Cas3 (apoptosis) Placebo 1.0 → 1.25; IF 1.0 → 1.55 (p = 0.07)

Values were means or medians plus standard deviation or 95% confidence interval

Table 4 Characteristics of prospective cohort studies of postdiagnosis[a] dietary soy intake and breast cancer prognosis

Author/year/reference	Study characteristics	Sample size (follow-up)	Post-diagnosis soy measurement and timing of measurement	Outcomes	Stratified by endocrine therapy or tumor subtypes
Pooling Study					
Nechuta/2012/[176]	US Shanghai, China Age range: 20–75 AJCC Stage: Stage I, II, III Recruitment years: 1995–2002 (US), 2002–2006 (China)	9514 (7.4 years, mean)	FFQ implemented at 6 months post-diagnosis in Chinese cohort and an average of 22–23 months post-diagnosis in the US Cohorts Soy isoflavones (mg/d)	Recurrence, n = 1348 Breast cancer deaths, n = 881 Total deaths, n = 1171	Tamoxifen ER status
Individual Cohort Studies					
Guha/2009/[171]	U.S Age range: 29–75 AJCC Stage: I, II, III Recruitment years: 2000–2002	1954 (6.31 years, mean)	FFQ, implemented on average, 23 months after diagnosis Daidzein (μg/d) Genistein (μg/d) Glycitein (μg/d)	Recurrences, n = 282	Tamoxifen ER/PR status
Shu/2009/[118]	Shanghai, China Age range: 20–75 AJCC Stage: 0-IV Recruitment years: 2002–2006	5042 (3.9 years, median)	FFQ implemented at multiple post-diagnosis time points (6 months, 18 months, and 36 months) to assess post-diagnosis, usual dietary intake Time-dependent intake of soy was used to incorporate all post-diagnosis measures Soy protein (g/day) Soy isoflavones (mg/day)	Recurrence, n = 534 Total deaths, n = 444	Tamoxifen ER status
Kang/ 2010/[170]	Harbin, China Age range: 29–72 AJCC Stage: I, II, III Recruitment years: 2002–2003	524 (5 years, median)	FFQ for the previous five years (includes some post-diagnosis time). Median time between diagnosis and survey was 120 days. Women were asked if their intake of soy foods changed after diagnosis Soy isoflavones (mg/d)	Recurrence, n = 185 Total deaths, n = 154	Among women receiving either tamoxifen or aromatase inhibitors for breast cancer treatment
Caan/2011/[172]	US Age range: 26–70 AJCC Stage: I, II, III Recruitment years: 1995–2000	2736 (7.3 years, median)	FFQ, implemented on average two years after diagnosis Total isoflavones (mg/d)	Recurrence, n = 448 Total deaths, n = 271	Tamoxifen ER/PR status
Zhang/2012/[169]	Hohhot, China Age range: < 40 to ≥ 60 AJCC Stage: 0-IV Recruitment years: 2004–2006	616 (52.1 months, median)	FFQ, collected close to diagnosis (dietary intake in the past year)[b] Soy protein (g/day) Soy isoflavones (mg/day)	Breast cancer deaths, n = 79	ER status

Table 4 (continued)

Author/year/reference	Study characteristics	Sample size (follow-up)	Post-diagnosis soy measurement and timing of measurement	Outcomes	Stratified by endocrine therapy or tumor subtypes
Woo/ 2012/[173]	Korea Age range: 25–77 AJCC Stage: I, II, III Recruitment years: 2007–2008	339 (32.6 months, median)	FFQ, implemented close to diagnosis (dietary intake in the past year)[b] Total soy products (g/day) Isoflavones (mg/day)	Recurrences, n = 25	HER2 status
Ho/2021/[168]	Hong Kong, China Age range: 25–79 AJCC Stage: 0-III Recruitment years: 2011–2014	1460 (72.3 months, median)	Two FFQs to assess usual intake in the past year (one at about 3 months and the second at 18 months post-diagnosis) Post-diagnosis intake was the mean of intake from the two FFQs Soy isoflavone intake (mg/1000 kcal)	Recurrences, n = 210 Breast cancer deaths, n = 115 Total deaths, n = 130	ER status, TNBC status, Tamoxifen
Yang/2023/[174]	Seoul, Korea Age range: Not available AJCC Stage: 0-III Recruitment years: 2011–2021	606 (89 months, mean)	24-h dietary recall on a weekday (collected within 3 years of diagnosis) Fermented soy products (g/day)	Recurrences, n = 61 Total deaths, n = 35	HR, ER, and PR status
Song/2024/[175]	Korea Age range: 29–75 AJCC Stage: 0-III Recruitment years: 2012–2017	592 (4.3 years, median)	3-day dietary record for most (96.4%) participants, on average 3.32 years after diagnosis Soy protein (g/day) Isoflavones (mg/day) Soy food (g/day)	Recurrences, n = 47	ER status

Abbreviations: AJCC (American Joint Committee on Cancer), FFQ (Food frequency questionnaires), TNBC (Triple Negative Breast Cancer), HER2 (human epidermal growth factor receptor 2), HR (hormone receptor), ER (estrogen receptor), NA (Not available), PR (progesterone receptor). [a]For completeness, we included studies that collected soy food dietary intake after diagnosis using a measure that included a mixture of pre- and post-diagnosis intake (as most assessments included the last year of usual intake). [b]Mixture of pre- and post-diagnosis intake as timing close to diagnosis and in the past year.

biologically implausible [163]. The two individual US studies that were included in this review [171, 172] created a 95th percentile isoflavone intake category to mimic an isoflavone intake similar to some Asian populations.

Table 5 summarizes overall findings from the ten previously cited studies on postdiagnosis dietary soy intake and breast cancer prognosis. In 2012, Nechuta et al. [176] analyzed the pooled results (N = 9514) from three of these studies, including the largest Chinese study (Shanghai Breast Cancer Survival Study, SBCSS) [118] and the two US studies, the Life After Cancer Epidemiology (LACE) study [171] and the Women's Healthy Eating and Living (WHEL) study [172]. Mean (SD) isoflavone intake (mg/d) in the SBCSS (n = 4856), LACE study (n = 1929) and WHEL study (n = 2729) was 45.9 ± 38.3, 4.1 ± 11.9 and 2.6 ± 7.9, respectively. The three isoflavone intake categories (mg/d) for this pooled analysis were < 4, 4.0–9.99, and ≥ 10.0. As shown in Table 5, inverse associations were observed for isoflavone intake of ≥ 10 mg/d vs < 4 mg/d for recurrence, breast cancer-specific mortality, and all-cause mortality, however the association was only statistically significant for recurrence. When only Chinese women (n = 4856) were included in the analysis, the hazard ratios (HRs) (95% CI) comparing the highest isoflavone intake group with the lowest for all-cause mortality, breast cancer-specific mortality and recurrence were 0.84 (0.54, 1.33), 0.75 (0.47, 1.20) and 0.69 (0.47, 1.01), respectively (Table 5). Similar results were reported for non-Asian US women (n = 4458), the HRs (95% CIs) comparing the highest isoflavone intake with the lowest intake group were 0.89 (0.66, 1.20), 0.80 (0.55, 1.15) and 0.74 (0.56, 0.97) for all-cause mortality, breast cancer-specific mortality and recurrence, respectively. This pooled analysis included the largest sample size to date, with 1348 recurrences and 881 breast cancer deaths. But it should be recognized that although the two US studies combined included more patients with recurrences than the SBCSS, only 5% of women in the US studies consumed isoflavones in amounts likely to have a physiological effect.

In the other study involving Chinese women (n = 616), the HRs (95% CI) for breast cancer-specific mortality when comparing quartile (Q) 4 with Q1 isoflavone and soy protein intakes were 0.62 (0,42, 0.90) and 0.71 (0.52, 0.98), respectively (Table 5) [169]. This study included only 79 total deaths during the median follow-up period of 52.1 months and only examined all-cause mortality. Woo et al. [173] found that isoflavone intake was non-significantly inversely associated with breast cancer recurrence among 339 Korean breast cancer patients for isoflavone intakes of ≥ 15.2 mg/d (compared with the lowest intake tertile) (Table 5). When examined by human epidermal growth factor receptor 2 (HER2) status, a statistically significant inverse association was found for the highest vs. the lowest isoflavone intake levels and recurrence [HR: 0.23, 95% CI (0.06–0.89)] among women with HER2- breast cancer. Among HER2 + patients, a non-significant positive association between isoflavone intake and recurrence was found [HR: 3.85, 95% CI (0.43, 34.67)]. However, there were only 17 and 8 recurrences among HER2- and HER2 + patients, respectively. In a second Korean study involving 606 women, intake of fermented soy foods (neither intake of unfermented soy foods nor isoflavones was reported) was inversely associated with recurrence [HR: 0.336, 95% CI (0.14, 0.78)] and all-cause mortality [HR: 0.173, 95% CI (0.03, 0.76)] comparing Q4 with Q1 intake (Table 5) [174]. The utility of this finding is unclear since only approximately 20-30% of isoflavone intake in Korea comes from fermented soy foods [175]. The most recent Korean study which involved 592 breast cancer survivors found no association between the intake of isoflavones, soy protein, or soy food and recurrence (Table 5). Overall, all these studies were of small sample size and varied in timing of assessment of postdiagnosis soy intake (Table 4).

In the largest individual non-US study, except for the SBCSS, which was conducted in Hong Kong (n = 1460), isoflavone intake when comparing Q4 with Q1 was not associated with all-cause mortality, breast cancer-specific mortality and breast cancer recurrence (Table 5) [168]. However, the authors noted that in the fully adjusted model when comparing Q3 vs Q1, risk (HR; 95% CI) for breast cancer-specific mortality was reduced (0.49; 0.23, 1.01), which might imply that a more moderate isoflavone intake is protective. But as discussed later, this was not observed by Shu et al. [118] in their much larger study. A final study of isoflavone intake and recurrence and all-cause mortality conducted in China (n = 524) among women who were receiving endocrine therapy (tamoxifen or AIs) is described below with studies considering outcomes according to endocrine therapy [170].

Outcomes According to ER Status

In the pooled analysis by Nechuta et al. [176], when comparing the highest isoflavone intake with the lowest, the HRs (95% CI) for breast cancer-specific mortality and recurrence for ER + patients were 0.93 (0.67, 1.28) and 0.81 (0.63, 1.04), respectively, and for ER- patients, they were 0.67 (0.43, 1.05) and 0.64 (0.44, 0.94), respectively. Thus, isoflavones appeared to be more protective against ER- breast cancer. However, in the study by Zhang et al. [169], when comparing Q4 with Q1 isoflavone intakes, the HR (95% CI) was lower for ER + patients 0.59 (0.40–0.93) than ER- patients 0.78 (0.47–0.98). In the study by Ho et al. [168], isoflavone intake was not associated with a decreased risk of breast cancer-specific mortality or recurrence, although for recurrence, the HR effect size was lower for ER + patients and closer to the null (1.05 vs 1.52) comparing the highest and lowest isoflavone intake groups. Finally, in the study by Yang et al. [174], the HRs (95% CI) for fermented soy intake when comparing Q4 with Q1 were similar for ER + 0.328 (0.11, 0.92) and ER- 0.257 (0.03, 2.19) breast cancer, although only for ER + breast cancer was the reduced risk statistically significant. Sample sizes were small for this

Table 5 Overall findings of prospective cohort studies of postdiagnosis[a] dietary soy intake and breast cancer prognosis

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
Nechuta/ 2012/[176]	All women	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age at diagnosis, ER/PR status, stage, chemotherapy, radiotherapy, hormonal therapy, smoking, BMI, exercise, cruciferous vegetable intake, parity, menopausal status, study, race/ethnicity, and education
	Isoflavones (mg/day)				
	< 4.0	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	4.0–9.99	0.99 (0.78–1.25)	1.09 (0.81–1.48)	1.04 (0.80–1.36)	
	≥ 10	0.75 (0.61–0.92)	0.83 (0.64–1.07)	0.87 (0.70–1.10)	
	Chinese women				
	Isoflavones (mg/day)				
	< 4.0	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	4.0–9.99	0.91 (0.56–1.47)	0.98 (0.56–1.75)	1.07 (0.62–1.86)	
	≥ 10	0.69 (0.47–1.01)	0.75 (0.47–1.20)	0.84 (0.54–1.33)	
	US women				
	Isoflavones (mg/day)				
	< 4.0	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	4.0–9.99	1.03 (0.77–1.37)	1.10 (0.74–1.62)	1.02 (0.73–1.42)	
	≥ 10	0.76 (0.58–0.99)	0.84 (0.59–1.19)	0.93 (0.69–1.24)	
Guha/2009/[171]	Daidzein intake (µg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for soy supplement use, BMI 1 year before diagnosis, menopausal status, tobacco pack-years, tumor stage, ER status, age, race, and kilocalories
	0	1.0 (reference)	NA	NA	
	0.10–7.77	1.16 (0.81–1.68)			
	7.78–149.59	0.87 (0.60–1.26)			
	149.60–1,453.00	0.97 (0.68–1.41)			
	1,453.10–9,596.54	0.71 (0.45–1.11)			
	≥ 9,596.55	0.96 (0.52–1.76)			
	Genistein intake (µg/day)				
	0	1.0 (reference)			
	0.10–6.99	1.09 (0.76–1.58)			
	7.00–220.61	0.92 (0.64–1.34)			
	220.62–2,184.8	0.97 (0.67–1.40)			
	2,199.82–13,025.87	0.72 (0.46–1.13)			
	≥ 13,025.88	0.95 (0.52–1.75)			
	Glycitein intake (µg/day)				
	0–3.61	1.0 (reference)			
	3.62–8.16	1.01 (0.71–1.43)			
	8.17–14.99	0.68 (0.46–1.01)			
	15.00–78.53	0.75 (0.51–1.12)			
	78.54–795.39	0.78 (0.50–1.22)			
	≥ 795.39	0.80 (0.42–1.50)			
Shu/2009/[118]	Soy protein (g/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age at diagnosis, TNM stage, chemotherapy, radiotherapy, type of surgery received, BMI, menopausal status, ER/PR status, tamoxifen use, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity
	≤ 5.31	1.0 (reference)	NA	1.0 (reference)	
	5.32–9.45	0.77 (0.61–0.98)		0.77 (0.59–1.00)	
	9.46–15.31	0.69 (0.54–0.87)		0.72 (0.55–0.94)	
	> 15.31	0.68 (0.54–0.87)		0.71 (0.54–0.92)	
	Isoflavones (mg/day)				
	≤ 20.00	1.0 (reference)		1.0 (reference)	
	20.01–36.50	0.84 (0.67–1.06)		0.73 (0.56–0.95)	
	36.51–62.68	0.65 (0.51–0.84)		0.77 (0.59–1.00)	
	> 62.68	0.77 (0.60–0.98)		0.79 (0.61–1.03)	

Table 5 (continued)

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
Kang/ 2010/[170]	Isoflavones (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age at diagnosis, stage, ER/PR status, chemotherapy and radiotherapy
	Premenopausal		NA		
	< 15.2	1.0 (reference)		1.0 (reference)	
	15.3–25.4	0.96 (0.62–1.46)		0.95 (0.76–1.56)	
	25.5–42.3	0.86 (0.56–1.47)		0.92 (0.59–1.43)	
	> 42.3	0.88 (0.61–1.23)		1.05 (0.78–1.71)	
	Postmenopausal				
	< 15.2	1.0 (reference)		1.0 (reference)	
	15.3–25.4	0.74 (0.64–0.96)		1.12 (0.81–1.82)	
	25.5–42.3	0.72 (0.58–0.92)		1.02 (0.72–1.51)	
	> 42.3	0.67 (0.54–0.85)		0.88 (0.56–1.24)	
Caan/2011/[172]	Isoflavones (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for stage, grade, ER/PR status, menopausal status, chemotherapy treatment, radiation, age, education, race, soy supplements, intervention group, presence of hot flash symptoms, and tamoxifen use
	0–0.07	1.0 (reference)	NA	1.0 (reference)	
	0.07–1.01	0.89 (0.72–1.11)		0.75 (0.57–0.99)	
	1.01–16.33	0.99 (0.75–1.32)		0.79 (0.54–1.15)	
	16.33–86.9	0.78 (0.46–1.31)		0.46 (0.2–1.05)	
Zhang/2012/[169]	Isoflavones (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age, education level, smoking, alcohol drinking, family history of cancer, menopausal status, tamoxifen use, cancer stage, ER status, chemotherapy, and radiotherapy
	< 7.56	NA	1.0 (reference)	NA	
	7.56–17.32		0.79 (0.54–1.07)		
	17.32–28.83		0.64 (0.45–0.93)		
	> 28.83		0.62 (0.42–0.90)		
	Soy protein (g/day)				
	< 2.12		1.0 (reference)		
	2.12–7.03		0.72 (0.55–0.99)		
	7.03–13.03		0.73 (0.43–1.13)		
	> 13.03		0.71 (0.52–0.98)		
Woo/2012/[173]	Soy products (g/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for total energy intake, cancer stage, age, menopausal status, alcohol intake, Herceptin use, and tamoxifen use
	< 36.2	1.0 (reference)	NA	NA	
	36.2–65.7	0.25 (0.07–0.92)			
	≥ 65.7	0.71 (0.28–1.80)			
	Isoflavones (mg/day)				
	< 7.4	1.0 (reference)			
	7.4–15.2	0.59 (0.22–1.62)			
	≥ 15.2	0.56 (0.20–1.53)			
Ho/2021/[168]	Early Post-diagnosis Isoflavones (mg/1000 kcal/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age, educational level, menopausal status, cancer stage, comorbidity, ER status, PR status, HER2 status, hormonal therapy, and radiotherapy
	< 1.74	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	1.74–3.9	0.60 (0.36–0.99)	0.45 (0.21–0.93)	0.49 (0.25–0.97)	
	3.9–7.2	0.78 (0.48–1.26)	0.49 (0.23–1.01)	0.44 (0.22–0.89)	
	> 7.2	1.21 (0.76–1.93)	1.24 (0.66–2.32)	1.15 (0.63–2.10)	

Table 5 (continued)

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
Yang/2023/[174]	Fermented Soy Products (g/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age, alcohol consumption, smoking, tumor size, lymph node metastasis, and age at menarche,
	≤ 5.0	1.0 (reference)	NA	1.0 (reference)	
	> 5.0–15.0	0.592 (0.29–1.20)		0.665 (0.27–1.63)	
	> 15.0–28.5	0.457 (0.22–0.94)		0.462 (0.17–1.19)	
	> 28.5	0.336 (0.14–0.78)		0.173 (0.03–0.76)	
Song/2024/[175]	Isoflavone (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age, energy intake, hospital center, stage, ER status, time since surgery, menopausal status, history of chronic diseases, BMI, physical activity, American Cancer Society diet guidelines scores, alcohol drinking, dietary supplement use, and educational levels
	Tertile 1	1.0 (reference)	NA	NA	
	Tertile 2	1.44 (0.65–3.16)			
	Tertile 3	1.29 (0.60–2.78)			
	Soy protein (g/day)				
	Tertile 1	1.0 (reference)			
	Tertile 2	1.03 (0.48–2.17)			
	Tertile 3	0.87 (0.40–1.89)			
	Soy food (g/day)				
	Tertile 1	1.0 (reference)			
	Tertile 2	1.20 (0.57–2.54)			
	Tertile 3	1.03 (0.48–2.19)			

Abbreviations: BCa (breast cancer), BMI (body mass index), ER (estrogen receptor), HER2 (human epidermal growth factor receptor 2), HR (hormone receptor), NA (Not available), PR (progesterone receptor). [a]For completeness, studies that collected soy food dietary intake after diagnosis using a measure that included both pre- and post-diagnosis intake (as most assessments included the last year of usual intake) were included.

study (5 recurrences in the ER+ group and one recurrence in ER- group) and the 95% CI for women with ER- cancers was imprecise. Overall, the largest study to date suggests that the inverse association of isoflavones intake and breast cancer outcomes is strongest among women with ER- breast cancer, however, across all studies, evidence is inconsistent, potentially due to small sample sizes.

Outcomes According to Menopausal Status

In the pooled analysis, when comparing the highest (10 mg/d) with the lowest (<4 mg/d) isoflavone intake categories, the HRs (95% CI) for breast cancer-specific mortality and recurrence for postmenopausal women were 0.78 (0.54, 1.14) and 0.64 (0.48, 0.87), respectively, and for premenopausal women, they were 0.97 (0.66, 1.43) and 0.93 (0.69, 1.26), respectively. Thus, isoflavones appeared to be more protective against postmenopausal breast cancer. In contrast, in the study by Ho et al. [168], isoflavone intake had more favorable effects for premenopausal breast cancer. The HRs (95% CI) when comparing the highest (>7.2 mg/1000 kcal) with the lowest (<1.74 mg/1000 kcal) intake groups for all-cause mortality and recurrence for pre- and postmenopausal cancer were 0.76 (0.34, 1.68) and 0.90 (0.48, 1.66), respectively, and 1.74 (0.65, 4.66) and 2.15 (0.98, 4.64), respectively. However, none of the results were statistically significant.

Outcomes according to HER2 and triple negative breast cancer (TNBC) status

Few data are available on the impact of tumor subtypes beyond ER status for the association between postdiagnosis isoflavone intake and breast cancer outcomes. Woo et al. [173] found isoflavone intake was inversely associated with breast cancer recurrence among HER2- patients (n = 63) (HR: 0.23, 95% CI: 0.06, 0.89) and positively associated with recurrence 3.85 (0.43, 34.67) among HER2 + patients [173]. However, as also noted previously, there were only 17 and 8 recurrences in these two groups, respectively. Comparing the highest and lowest isoflavone intake groups, Ho et al. [168] found that the HRs (95% CIs) for breast cancer-specific mortality and recurrence for TNBC (n = 177) were 0.85 (0.31, 2.30) and 1.08 (0.44, 2.70), respectively. For those who did not have TNBC (n = 1231), the HRs (95% CIs) for breast cancer-specific mortality and recurrence were 1.20 (0.55, 2.58) and 1.14 (0.65, 2.00), respectively. See box 1 for further information about TNBC and isoflavones.

Box 1 Isoflavones and Triple Negative Breast Cancer

Triple negative breast cancer (TNBC) accounts for approximately 15% of all breast cancer cases [179, 180]. It is characterized by cellular expression of progesterone and estrogen receptors of ≤1% and human epidermal growth factor receptor 2 (HER2) expression between 0 and 1+, as determined by immunohistochemistry [181]. HER2 is a transmembrane protein that is a receptor for members of the epidermal growth factor family of extracellular protein ligands. TNBC is associated with aggressive histology, poorer prognosis, shorter survival, and unresponsiveness to hormonal therapy [179, 182]. There is a high prevalence of TNBC in women of African descent and women who carry a mutated copy of the BRCA1 gene [183]

Relatively little epidemiologic research about the association between soy or isoflavone intake and TNBC exists. Nevertheless, two studies of isoflavone intake and breast cancer prognosis have produced intriguing findings. For example, in a Korean prospective study by Woo et al. [173], isoflavone intake was significantly inversely related to recurrence among HER2- patients (HR: 0.23, 95% CI: 0.06–0.89), although this finding was based on only 17 recurrences among 256 patients. These results align with those from Ho et al. [168], who reported that the adjusted HR (95% CI) for patients with TNBC was 0.43 (0.17, 1.07) in the second isoflavone intake tertile (compared with the lowest tertile), which was numerically lower than the HR (95% CI) for those who did not have TNBC [0.75 (0.46, 1.21). However, neither result was statistically significant

In addition to the epidemiologic evidence there are preclinical and clinical data suggesting isoflavones may have a role in TNBC prognosis. For example, genistein (250 mg/kg diet) administration beginning when the primary tumor reached 2 mm in diameter resulted in a delay of tumor growth in two preclinical patient-derived xenograft orthotopic mouse models and significantly influenced expression of multiple tumor-regulated genes[184]. The authors of this study concluded that genistein has high potential as novel therapeutic approach for TNBC patients

Other research in mice showed that genistein may be useful for the prevention and reversal of aryl hydrocarbon receptor (which is often overexpressed in BRCA patients) -dependent BRCA1 hypermethylation, and the restoration of ER-mediated response [185]. Furthermore, based on docking and molecular dynamics simulation, Chatterjee et al. [186], found that genistein is a potential multi-target inhibitor of the six TNBC high penetrance genes. Also, the binding interaction of PTEN (a potent mediator of the PI3K signaling pathway in TNBC) and genistein was superior to that of PTEN-Olaparib. Olaparib is an extensively used FDA-approved chemotherapeutic drug for the treatment of TNBC [187, 188]

Finally, in breast tumor tissue from TNBC patients, Chinese researchers found that soy intake one year prior to diagnosis was significantly associated 14 miRNAs and 24 genes [189]. Thirteen of the 14 miRNAs (92.9%) and 9 of the 24 genes (37.5%), including tumor suppressors miR-29a-3p and IGF1R, showed overexpression whereas the remaining miRNAs and genes, including oncogenes KRAS and FGFR4, showed underexpression. Overall, soy intake was associated with underexpression of cell growth-related genes

Outcomes According to Endocrine Therapy

In the pooled analysis by Nechuta et al. [176], when comparing the highest isoflavone intake with the lowest, the HRs (95% CI) for overall mortality, breast cancer-specific mortality and recurrence among non-users of tamoxifen were 0.98 (0.65, 1.47), 1.16 (0.71, 1.90) and 0.79 (0.55, 1.14), respectively (Table 6). Among tamoxifen users, these values were 0.74 (0.52, 1.07), 0.84 (0.54, 1.31) and 0.63 (0.46, 0.87), respectively. The reduced risk of recurrence was strongest (37%) for women in the highest isoflavone intake category of 10 mg/d among users of tamoxifen. Reduced risk of recurrence was also found for intakes of 4.0–9.99 mg/day (20%) and <4.0 mg per day (22%), however, the results were not statistically significant for the 4.0–9.99 mg/day intake category. Non-significant inverse associations for isoflavone intake were also observed among tamoxifen users for mortality and among non-users of tamoxifen only for recurrence. The test for multiplicative interaction between tamoxifen use and isoflavone intake was not statistically significant. Among women with ER+ breast cancer in the pooling project, 67.6% (n = 2077), 81.5% (n = 1655) and 91.4% (n = 1446) used tamoxifen in the SBCSS, WHEL and LACE, respectively. Given the high correlation between ER+ breast cancer and tamoxifen use, these results seem somewhat inconsistent with the above noted findings from the pooling project that isoflavone intake appeared to be more protective against ER- breast cancer than ER + breast cancer. However, not all ER + women received tamoxifen therapy, and therefore a direct comparison cannot be made.

In the study from Hong Kong, the HRs (95% CI) for all-cause mortality and recurrence among non-users of tamoxifen were 0.90 (0.44, 1.85) and 1.66 (0.92. 3.02), respectively, and for users of tamoxifen were 0.81 (0.35, 1.87) and 0.76 (0.36, 1.60), respectively [168]. Although none of these findings were statistically significant, the results align with those of Nechuta et al. [176], which suggests isoflavone intake is more protective in tamoxifen users.

Lastly, Kang et al. [170] examined the impact of isoflavone intake on 524 breast cancer patients undergoing endocrine therapy (tamoxifen or anastrozole). During the median follow-up period of 5.1 years, there were 185 recurrences and 154 deaths. Isoflavone intake was unrelated to cancer outcomes among premenopausal women but was associated with a decreased risk of recurrence among postmenopausal women. The isoflavone cutoffs for Q1 and Q4 were < 15.2 and > 42.3 mg/d, respectively. Among postmenopausal women who used tamoxifen, isoflavones were not associated with recurrence (HR for Q4 vs Q1: 1.06; 95% CI: 0.76, 1.67) but among women on the AI anastrozole, higher isoflavone intake was associated with a decreased risk when comparing Q4 with Q1 [HR:0.65; 95% CI:0.47, 0.85]. It is important to note that soy intake was based on the 5 years prior to study enrollment (which was a median of 3 months after diagnosis) and included both pre- and postdiagnosis intake. However, a supplemental survey indicated that most women (n = 452, 86.3%) reported no change in intake of soy foods after diagnosis of breast cancer, 29 (5.5%) reported an increase after diagnosis and 43 (8.2%) reported a decrease after diagnosis [170].

Outcomes According to Dose

Of the nine studies in Table 4, the one by Yang et al. [174] only reported on fermented soy food intake, and is therefore uninformative about isoflavone dose. As already noted, in Korea, most soy is consumed in unfermented form [190]. Ho et al. [168] observed lower HRs for all three outcomes for more moderate isoflavone intakes (1.74–3.9 mg/2000 kcal and 3.9–7.2 mg/2000 kcal) compared to the highest intake category (>7.21 mg/2000 kcal). The highest cutoff for the highest intake group of any of the seven studies was in the SBCSS as the Q4 cutoff was at >62.68 mg/d (mean intake, 85.09 mg/d) [118]. The Q1 cutoff in this study was ≤20 mg/d (mean intake, 11.5 mg/d), which is similar to the high intake cutoff for the other studies. To have sufficient numbers in each intake category, the cutoff for the highest intake level in the pooled analysis by Nechuta et al. [176] was only ≥10.0 mg/d. Mean isoflavone intake (mg/d) in this category was 48.59 mg/d among all women, 50.82 for Shanghainese women, 26.64 for all US women and 26.68 for non-Asian US women.

In the pooled analysis, HRs for all-cause mortality, breast cancer-specific mortality and breast cancer recurrence were reported according to isoflavone intake deciles [176]. There was no significant trend for any of these outcomes. The HRs for the 2nd and 10th decile isoflavone intakes for all-cause mortality, breast cancer-specific mortality and breast cancer recurrence were 0.78 and 0.82, 0.74 and 0.71, and 0.72 and 0.64, respectively. These data suggest that even low isoflavone intakes improve breast cancer prognosis, and that protection is not lost at the highest intake levels. However, these results contrast with the results of the SBCSS, which was one of the three studies in the pooled analysis. Shu et al. [118] commented that the associations of isoflavone intake with mortality and recurrence appeared to follow a linear dose response pattern until about 40 mg/d, after which the association appears to level off or even rebound slightly.

Outcomes According to Isoflavone Delivery Vehicle (Supplement vs Foods)

Greater concern has been expressed about the safety of isoflavones provided in the form of supplements (tablets or concentrated sources of soy protein) than traditional Asian soy foods [109, 119]. In the Etude Epidemiologique aupres de Femmes de laMutuelle Generale de l'Education Nationale cohort, among women aged >50, current use of soy supplements containing isoflavones was associated with a decreased and increased risk of developing ER+ and ER- breast cancer, respectively. Also, the HRs for current use among women with a family history of breast cancer were above and below 1.0 for ER+ and ER- breast cancer, respectively (p-interaction = 0.03) [191]. Among the 76,442 women included in the analyses of this cohort, over the 11-year follow up period, between 1.4% and 5.3% indicated use of supplements at the four different time points evaluated. Among women who reported ever using soy supplements together with their brand names, 81% had used ≥ 1 of the 5 most-consumed soy supplements in the cohort, which contained between 3.75 and 37.5 mg soy isoflavones (present in their glucoside form in soy extract)/tablet, according to the manufacturers).

In the LACE and WHEL studies, only 2.7% (53/1954) and 2.1% (58/2736) women reported any use of isoflavone supplements, respectively. Results were not sub-analyzed according to supplement use due to too small sample size. None of the other studies in Table 4 reported on supplement use. Several other observational studies have examined the impact of soy/isoflavone supplement use on breast cancer risk, but none focused on postdiagnosis intake and breast cancer survival [191–195].

Concerns about isoflavone tablets and concentrated forms of soy protein include the assumed greater propensity to consume excessive amounts of isoflavones, the absence of potentially beneficial bioactives found in soybeans and many soy foods, the lack of historical precedent for use and the lack of epidemiologic support for their safety when consumed by women with breast cancer. These concerns may be valid except that on a mg/g protein basis, as already noted, concentrated sources of soy protein such as soy protein isolate and soy protein concentrate typically have a lower isoflavone content than traditional Asian soy foods [50, 71, 72]. Furthermore, in nearly all the RCTs that assessed mammographic density or cell proliferation previously discussed and listed in Tables 2 and 3, isoflavones were provided in the form of tablets or protein powders. Thus, there are more clinical data available for the safety of isoflavones provided in these forms than for traditional Asian soy foods.

Perhaps the most relevant finding related to concerns about supplements vs soy foods was published in 2004 by Allred et al. [114], who found that in mice, the degree to which soy flour is processed affects the estrogenicity of products containing the same amount of genistein. That is, tumor growth was least stimulated by soy flour (less processed) and most stimulated by isolated genistein (most processed). It was also later shown that soy flour affects gene expression in mammary tumors differently than isolated genistein [196]. In brief, tumors in athymic nude mice exhibited higher expression of tumor growth suppressor genes and lower expression of oncogenes in comparison to mice fed genistein. It was suggested that this difference could be because of the influence of bioactives in soy flour besides genistein.

However, in 2005, it was shown in mice that processing increased the percentage of unconjugated genistein relative

Table 6 Findings of prospective cohort studies of postdiagnosis[a] dietary soy intake and breast cancer prognosis by endocrine therapy

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
Nechuta/ 2012/[176]	Among cases with ER + breast cancer	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age at diagnosis, stage, chemotherapy, radiotherapy, hormonal therapy, smoking, BMI, exercise, cruciferous vegetable intake, parity, menopausal status, study, race/ethnicity, and education
	No tamoxifen use Isoflavones (mg/day)				
	< 4.0	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	4.0–9.99	0.99 (0.56–1.75)	1.54 (0.78–3.02)	1.37 (0.76–2.46)	
	≥ 10	0.79 (0.55- 1.14)	1.16 (0.71–1.90)	0.98 (0.65–1.47)	
	Tamoxifen use Isoflavones (mg/day)				
	< 4.0	0.78 (0.62–0.99)	0.96 (0.68–1.35)	0.83 (0.63–1.09)	
	4.0–9.99	0.80 (0.56–1.16)	1.05 (0.63–1.74)	0.85 (0.56–1.29)	
	≥ 10	0.63 (0.46–0.87)	0.84 (0.54–1.31)	0.74 (0.52–1.07)	
Guha/2009/[171]	Tamoxifen use Daidzein intake (μg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	All models were adjusted for soy supplement use, BMI 1 year before diagnosis, tobacco pack-years, tumor stage, menopausal status, age, race, and kilocalories
	0	1.0 (reference)	NA	NA	
	0.10–7.77	1.12 (0.75–1.69)			
	7.78–149.59	0.78 (0.52–1.19)			
	149.60–1,453.00	1.00 (0.67–1.50)			
	1,453.10–9,596.54	0.73 (0.45–1.20)			
	≥ 9,596.55	0.48 (0.19–1.21)			
	Genistein intake (μg/day)				
	0	1.0 (reference)			
	0.10–6.99	1.02 (0.68–1.54)			
	7.00–220.61	0.86 (0.57–1.31)			
	220.62–2,184.8	0.99 (0.66–1.48)			
	2,199.82–13,025.87	0.74 (0.45–1.21)			
	≥ 13,025.88	0.48 (0.19–1.22)			
	Glycitein intake (μg/day)				
	0–3.61	1.0 (reference)			
	3.62–8.16	1.26 (0.85–1.87)			
	8.17–14.99	0.82 (0.53–1.26)			
	15.00–78.53	0.69 (0.43–1.10)			
	78.54–795.39	0.77 (0.46–1.28)			
	≥ 795.40	0.85 (0.40–1.80)			

Table 6 (continued)

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
	No Tamoxifen use Daidzein intake (μg/day)				
	0	1.0 (reference)			
	0.10–7.77	1.63 (0.72–3.68)			
	7.78–149.59	1.31 (0.58–2.99)			
	149.60–1,453.00	0.93 (0.39–2.22)			
	1,453.10–9,596.54	0.69 (0.23–2.08)			
	≥ 9,596.55	2.40 (0.93–6.18)			
	Genistein intake (μg/day)				
	0	1.0 (reference)			
	0.10–6.99	1.70 (0.76–3.79)			
	7.00–220.61	1.25 (0.53–2.95)			
	220.62–2,184.8	0.96 (0.41–2.22)			
	2,199.82–13,025.87	0.70 (0.23–2.10)			
	≥ 13,025.88	2.42 (0.95–6.21)			
	Glycitein intake (μg/day)				
	0–3.61	1.0 (reference)			
	3.62–8.16	0.32 (0.13–0.78)			
	8.17–14.99	0.26 (0.10–0.73)			
	15.00–78.53	0.83 (0.40–1.74)			
	78.54–795.39	0.87 (0.37- 2.01)			
	≥ 795.40	0.68 (0.22–2.12)			
Shu/2009/[118]	No Tamoxifen use Soy protein (g/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age at diagnosis, stage, chemotherapy, radiotherapy, type of surgery received, BMI, menopausal status, ER/PR status, education level, income, cruciferous vegetable intake, total meat intake, vitamin supplement use, tea consumption, and physical activity
	≤ 5.31	1.0 (reference)	NA	1.0 (reference)	
	5.32–9.45	0.73 (0.41–1.32)		0.65 (0.33–1.29)	
	9.46–15.31	1.10 (0.65–1.88)		1.24 (0.69–2.22)	
	> 15.31	0.65 (0.36–1.17)		0.65 (0.33–1.29)	
	Isoflavones (mg/day)				
	≤ 20.00	1.0 (reference)		1.0 (reference)	
	20.01–36.50	0.84 (0.47–1.50)		0.72 (0.37–1.42)	
	36.51–62.68	1.04 (0.61–1.77)		1.15 (0.63–2.09)	
	> 62.68	0.71 (0.39–1.28)		0.74 (0.38–1.43)	
	Tamoxifen use Soy protein (g/day)				
	≤ 5.31	0.93 (0.58–1.51)		0.90 (0.52–1.57)	
	5.32–9.45	0.65 (0.39–1.09)		0.79 (0.45–1.39)	
	9.46–15.31	0.58 (0.34–0.98)		0.62 (0.35–1.12)	
	> 15.31	0.66 (0.40–1.09)		0.61 (0.34–1.08)	

Table 6 (continued)

Author/ year/Ref	Results				Comments
	Postdiagnosis soy intake	Hazard ratios (95% confidence interval)			
	Isoflavones (mg/day)				
	≤ 20.00	0.91 (0.56–1.48)		0.92 (0.53–1.60)	
	20.01–36.50	0.71 (0.43–1.18)		0.69 (0.39–1.23)	
	36.51–62.68	0.58 (0.34–0.98)		0.62 (0.34–1.12)	
	> 62.68	0.73 (0.44–1.19)		0.74 (0.42–1.29)	
Kang[b]/2010/[170]	Tamoxifen users Isoflavones (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	This analysis was among postmenopausal women using endocrine therapy (either tamoxifen or Anastrozole) and did not include a comparison group of non-users Adjusted for age at diagnosis, stage, ER/PR status, chemotherapy and radiotherapy
	< 15.2	1.0 (reference)	NA	NA	
	15.3–25.4	1.23 (0.78–1.86)			
	25.5–42.3	1.13 (0.79–1.71)			
	> 42.3	1.06 (0.76–1.67)			
	Anastrozole users Isoflavones (mg/day)				
	< 15.2	1.0 (reference)			
	15.3–25.4	0.72 (0.56–0.92)			
	25.5–42.3	0.71 (0.54–0.88)			
	> 42.3	0.65 (0.47–0.85)			
Caan/2011/[172]	Tamoxifen use Isoflavones (mg/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for stage, grade, ER/PR status, menopausal status, chemotherapy treatment, radiation, age, education, race, soy Supplements, intervention group, and presence of hot flash symptoms
	0–0.07	1.0 (reference)	NA	1.0 (reference)	
	0.07–1.01	0.91 (0.69–1.21)		0.79 (0.56–1.12)	
	1.01–16.33	0.97 (0.67–1.41)		0.81 (0.5–1.30)	
	16.33–86.9	0.59 (0.27–1.29)		0.26 (0.06–1.08)	
	No Tamoxifen use Isoflavones (mg/day)				
	0–0.07	1.0 (reference)		1.0 (reference)	
	0.07–1.01	0.82 (0.57–1.17)		0.61 (0.38–0.99)	
	1.01–16.33	1.09 (0.69–1.71)		0.79 (0.42–1.49)	
	16.33–86.9	0.96 (0.46–1.99)		0.68 (0.24–1.99)	
Ho/2021/[168]	No Tamoxifen use Early postdiagnosis isoflavones (mg/1000 kcal/day)	**Recurrence:**	**BCa deaths:**	**All deaths:**	Adjusted for age, menopausal status, educational level, comorbidity, and cancer stage
	< 1.74	1.0 (reference)	NA	1.0 (reference)	
	1.74–7.2	0.85 (0.49–1.47)		0.54 (0.28–1.02)	
	≥ 7.2	1.66 (0.92–3.02)		0.90 (0.44–1.85)	
	Tamoxifen use Early postdiagnosis isoflavones (mg/1000 kcal/day)				
	< 1.74	1.10 (0.54–2.25)		0.42 (0.14–1.29)	
	1.74–7.2	0.54 (0.29–1.01)		0.15 (0.05–0.41)	
	≥ 7.2	0.76 (0.36–1.60)		0.81 (0.35–1.87)	

Abbreviations: BC (breast cancer), BMI (body mass index), ER (estrogen receptor), NA (Not available), PR (progesterone receptor). [a]For completeness, studies that collected soy food dietary intake after diagnosis using a measure that included both pre- and post-diagnosis intake were included (see Table 4 for soy measurement details). [b]This study measured soy food intake after diagnosis and assessed intake for the previous five years.

to conjugated genistein in the circulation, the former of which is the biologically active form of the isoflavone [197]. The effect of processing on conjugation accounts for the difference in tumor-stimulating effects. Importantly, in contrast to mice, in 2011, Setchell et al. [55] showed that in women consuming isoflavones from different delivery vehicles, the degree of processing does not impact the relative percentage of genistein in conjugated form. Thus, at least with respect to the physiological effects of isoflavone exposure, it does not appear supplements differ from soy foods.

Do Tumors in Women Exposed to Genistein Prior to Diagnosis Respond Differently to Tamoxifen than Tumors in Women Without such Exposure?

Based on their findings in Sprague–Dawley rats, in 2017, Zhang et al. [198] recommended that women with breast cancer *continue* to consume soy foods after diagnosis but not to start if they were not previously exposed to this isoflavone. These authors found that lifelong genistein consumption increased latency (time to appearance of first tumor) in rats administered 7,12-dimethylbenz[a]anthracene and that in response to tamoxifen, lifelong genistein, prepubertal genistein and adult genistein (genistein given before tamoxifen) decreased the number of recurring tumors relative to the number in the control rats given tamoxifen. In contrast, when genistein exposure began only after tamoxifen was administered, the number of recurring tumors was increased (33 vs 23) relative to controls, although the difference was not statistically significant. However, the number of tumors fully responding to tamoxifen was statistically significantly lower (38% vs 54%) in the rats given genistein post-tamoxifen only, vs the controls not given genistein.

To what extent is there human evidence to address the findings by Zhang et al. [198]? In the SBCSS [118], there was no interaction between isoflavone intake and tamoxifen. According to the findings of Zhang et al. [198], the efficacy of tamoxifen should have been enhanced because it is likely high-soy-consuming women were consuming soy long before breast cancer diagnosis. Interestingly, in the LACE study [171], although the interaction between tamoxifen and isoflavone intake was not statistically significant, among women treated with tamoxifen, there was an approximate 50% reduction in breast cancer recurrence when comparing the highest genistein intake (≥ 13,025.88 ug/d) with the lowest (0 ug/d) (HR, 0.48; 95% CI: 0.19, 1.22, P-trend, 0.13).

Although purely speculative, it is unlikely the women in this study were regularly consuming soy prior to diagnosis. Of the 96 women in the high intake group, 84 were non-Asian. Among non-Asians in the US prior to the 1990s, only those adhering to plant-forward diets regularly consumed soy. Soy food consumption gained in popularity only after research began to suggest intake was associated with health benefits, especially related to chronic disease prevention [199, 200]. In the LACE study [171], breast cancer diagnoses occurred between 1997 and 2000 but breast tumors have to be quite large to be detected by mammography (1.0–1.5 cm) or self-breast examination (2–2.5 cm) [201]. Weedon-Fekjær et al. [202] estimated that it takes breast tumors on average 1.7 years to grow from 10 to 20 mm in diameter. Therefore, it is likely that the tumors in the women participating in the LACE study were well formed by the time genistein exposure may have occurred. And therefore, if the pre-diagnosis soy food intake influenced tamoxifen response as noted above among breast cancer survivors, the efficacy of tamoxifen should have been inhibited whereas the trend was for tamoxifen efficacy to be enhanced.

Research Needs

As noted at the onset, no RCT has evaluated the impact of postdiagnosis soy intake on breast cancer outcomes and for that reason the SBCC continues. It is worth noting that RCTs of dietary interventions and cancer prognosis have many potential limitations that can be difficult to address, including compliance concerns and lack of generalizability [203]. It may be that in the relatively near term, no such trial will be initiated. Even if it was, it would be many years before the results would be known. A RCT whose primary outcomes were recurrence and/or breast cancer-specific mortality, would require a large sample size and long duration. Alternatively, a small and shorter duration RCT could examine intermediate endpoints such as mammographic density, in vivo cell proliferation, changes in gene expression, and other relevant endpoints.

In addition to RCTs, well-designed prospective cohort studies can continue to inform this area of research. Contemporary cohorts examining postdiagnosis soy intake and breast cancer outcomes according to endocrine therapy use would be particularly informative. Further, cohorts with larger samples to enable well-powered investigations of the associations of postdiagnosis soy intake and breast cancer outcomes by tumor subtype are needed, including for TNBC (see box 1).

Summary and Conclusions

Dietary recommendations are often, if not always, based on imperfect data. Such is the case for any soy intake recommendation for women with breast cancer given that no RCT has evaluated the impact of postdiagnosis soy consumption on breast cancer recurrence or mortality. However, the wealth of clinical data that examined markers of breast cancer risk (e.g., breast tissue density and in vivo breast cell proliferation) is supportive of the safety of soy food consumption by women with breast cancer, although relatively few studies included women with this disease. The observational data are not only supportive of safety but suggestive of benefit. These data also indicate postdiagnosis soy intake does not interfere with the efficacy of tamoxifen, and to a much lesser extent, AIs, although most data come from one large cohort of Chinese women [118].

The evidence is too limited to recommend postdiagnosis soy intake specifically to improve the prognosis of breast cancer patients. However, evidence supports the safety of soy consumption by women with breast cancer regardless of whether they are undergoing endocrine therapy. Isoflavone intake in the RCTs typically exceeded 50 mg/d, the amount provided by approximately two servings of traditional Asian soy foods. In the SBCSS isoflavone intake was associated with protective effects even when exceeding this amount [118]. Nevertheless, because of the limited epidemiologic data overall, two servings daily providing approximately 50 mg isoflavones is a reasonable intake recommendation for those wanting to add soy foods to their diet. Although the source of isoflavones may not matter with respect to the physiological effects of isoflavones, there are non-isoflavone components of soy foods that may exert health benefits. Further, there is a potential indirect benefit of consuming soy foods if they replace less healthful foods in the diet. Therefore, although supplements can be used alone or in combination with soy foods to obtain isoflavones, emphasis is best placed on the latter.

Key references

- Viscardi G, et al. Effect of soy isoflavones on measures of estrogenicity: A systematic review and meta-analysis of randomized controlled trials. Adv Nutr 2024:10,032,710.1016/j.advnut.2024.100327.
    - o This research represents the first analysis of the clinical data to systematically demonstrate that isoflavones fundamentally differ from the hormone estrogen. It shows that in postmenopausal women, isoflavones do not affect the four outcomes evaluated that are affected by the hormone estrogen. This finding does not preclude isoflavones from exerting estrogen-like effects on outcomes not evaluated and in other subpopulations.
- Rock CL, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors**.** CA Cancer J Clin 2022;72:230–26210.3322/caac.21719.
    - o After extensively evaluating the epidemiologic research the American Cancer Society concluded that "Soy food consumption before diagnosis is associated with lower risk of overall mortality. There is also consistent evidence, albeit from fewer studies, that soy intake, whether prediagnosis or postdiagnosis, or postdiagnosis soy isoflavone intake is associated with a lower risk of recurrence."
- Messina M, Messina V, Nagata C. Perspective: Observational studies involving low soy intake populations have limited ability for providing insight into the health effects of soybean isoflavones. Adv Nutr 2024:10,021,010.1016/j.advnut.2024.100210.
    - o Numerous epidemiologic studies evaluating the impact of soy and isoflavone intake on risk of developing breast cancer and the impact of postdiagnosis intake on breast cancer outcomes, have been conducted. However, many of these studies have involved low-soy-intake populations. It is likely that any observed associations do not have a causal basis because intake is too low to exert a biological effect. For this reason, these studies should not carry much weight when reaching conclusions about the impact of soy or isoflavones.

Author Contribution MM and SN contributed equally to the review of the literature and the writing of the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations Author MM is an employee of Soy Nutrition Institute Global, which receives funding from the United Soybean Board. SN has no conflicts of interest to declare.

Competing Interests MM is an employee of Soy Nutrition Institute Global, which receives funding from the United Soybean Board and from company members involved in the soy food industry.

References

1. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63. https://doi.org/10.3322/caac.21834.
2. De Cicco P, Catani MV, Gasperi V, Sibilano M, Quaglietta M, Savini I. Nutrition and breast cancer: A literature review on prevention, treatment and recurrence. Nutrients 2019;11. https://doi.org/10.3390/nu11071514.
3. Becerra-Tomas N, et al. Postdiagnosis dietary factors, supplement use and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis. Int J Cancer. 2023;152:616–34. https://doi.org/10.1002/ijc.34321.
4. Messina M, Barnes S. The role of soy products in reducing risk of cancer. J Natl Cancer Inst. 1991;83:541–6.
5. Tominaga S. Cancer incidence in Japanese in Japan, Hawaii, and western United States. Natl Cancer Inst Monogr. 1985;69:83–92.
6. Barnes S, Grubbs C, Setchell KD, Carlson J. Soybeans inhibit mammary tumors in models of breast cancer. Prog Clin Biol Res. 1990;347:239–53.
7. Ziegler RG, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1993;85:1819–27.
8. Huang MH, et al. Development of an updated phytoestrogen database for use with the SWAN food frequency questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer. 2012;64:228–44. https://doi.org/10.1080/01635581.2012.638434.
9. Sharifi-Rad J, et al. Genistein: An integrative overview of its mode of action, pharmacological properties, and health benefits. Oxid Med Cell Longev. 2021;2021:3268136. https://doi.org/10.1155/2021/3268136.
10. Yang J, Shen H, Mi M, Qin Y. Isoflavone consumption and risk of breast cancer: An updated systematic review with meta-analysis of observational studies. Nutrients 2023;15. https://doi.org/10.3390/nu15102402.
11. Lamartiniere CA, Moore J, Holland M, Barnes S. Neonatal genistein chemoprevents mammary cancer. Proc Soc Exp Biol Med. 1995;208:120–3.
12. Lamartiniere CA, Moore JB, Brown NM, Thompson R, Hardin MJ, Barnes S. Genistein suppresses mammary cancer in rats. Carcinogenesis. 1995;16:2833–40.
13. Shu XO, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev. 2001;10:483–8.
14. Korde LA, et al. Childhood soy intake and breast cancer risk in Asian American women. Cancer Epidemiol Biomarkers Prev 2009;18:1050–10591055–9965.EPI-08–0405 [pii] https://doi.org/10.1158/1055-9965.EPI-08-0405.
15. Wu AH, Wan P, Hankin J, Tseng CC, Yu MC, Pike MC. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. Carcinogenesis. 2002;23:1491–6.
16. Baglia ML, et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int J Cancer. 2016;139:742–8. https://doi.org/10.1002/ijc.30117.
17. Hsieh CY, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor- positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res. 1998;58:3833–8.
18. Early Breast Cancer Trialists' Collaborative Group, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771-784. https://doi.org/10.1016/S0140-6736(11)60993-8.
19. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–1717. 10.1016/S0140–6736(05)66544–0.
20. Joe BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. In: UpToDate. Burstein HJ, Vora SR (eds.). Waltham, MA: UpToDate, 2019
21. Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805–16. https://doi.org/10.1016/S0140-6736(12)61963-1.
22. Vogel VG, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295:2727–41. https://doi.org/10.1001/jama.295.23.joc60074.
23. Cuzick J, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015;16:67–75. https://doi.org/10.1016/S1470-2045(14)71171-4.
24. Vogel VG, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila). 2010;3:696–706. https://doi.org/10.1158/1940-6207.CAPR-10-0076.
25. Goss PE, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381–91. https://doi.org/10.1056/NEJMoa1103507.
26. Cuzick J, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014;383:1041–8. https://doi.org/10.1016/S0140-6736(13)62292-8.
27. Bezerra PHA, Amaral C, Almeida CF, Correia-da-Silva G, Torqueti MR, Teixeira N. In vitro effects of combining genistein with aromatase inhibitors: Concerns regarding its consumption during breast cancer treatment. Molecules 2023;28. https://doi.org/10.3390/molecules28134893.
28. Seo HS, et al. Stimulatory effect of genistein and apigenin on the growth of breast cancer cells correlates with their ability to activate ER alpha. Breast Cancer Res Treat. 2006;99:121–34. https://doi.org/10.1007/s10549-006-9191-2.
29. Choi JH, Ko CM. Food and drug interactions. J Lifestyle Med 2017;7:1–9. https://doi.org/10.15280/jlm.2017.7.1.1.
30. Wu AH, et al. Tamoxifen, soy, and lifestyle factors in Asian American women with breast cancer. J Clin Oncol. 2007;25:3024–30. https://doi.org/10.1200/JCO.2006.10.5023.
31. Hwang CS, et al. Isoflavone metabolites and their in vitro dual functions: they can act as an estrogenic agonist or antagonist depending on the estrogen concentration. J Steroid Biochem Mol Biol 2006;101:246–253S0960–0760(06)00196–8 [pii] https://doi.org/10.1016/j.jsbmb.2006.06.020.
32. Deng K, et al. Soy foods might weaken the sensitivity of tamoxifen in premenopausal patients with lumina A subtype of breast cancer. Clin Breast Cancer. 2019;19:e337–42. https://doi.org/10.1016/j.clbc.2018.12.003.
33. Ju YH, Doerge DR, Allred KF, Allred CD, Helferich WG. Dietary genistein negates the inhibitory effect of tamoxifen on

growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. Cancer Res. 2002;62:2474–7.
34. Du M, et al. Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice. Carcinogenesis. 2012;33:895–901. https://doi.org/10.1093/carcin/bgs017.
35. Ju YH, Doerge DR, Woodling KA, Hartman JA, Kwak J, Helferich WG. Dietary genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) in vivo**.** Carcinogenesis 2008;29:2162–2168bgn161 [pii] https://doi.org/10.1093/carcin/bgn161.
36. American Cancer Society I: **American Cancer Society. Breast Cancer Facts & Figures 2022–2024.** Atlanta; 2022.
37. Buro AW, Nguyen T, Abaskaron M, Haver MK, Carson TL. Lifestyle interventions with dietary strategies after breast cancer diagnosis: a systematic review. Breast Cancer Res Treat. 2024. https://doi.org/10.1007/s10549-024-07278-x.
38. Willett W, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;393:447–92. https://doi.org/10.1016/S0140-6736(18)31788-4.
39. Grasso AC, Olthof MR, van Dooren C, Broekema R, Visser M, Brouwer IA. Protein for a healthy future: How to increase protein intake in an environmentally sustainable way in older adults in the Netherlands. J Nutr. 2021;151:109–19. https://doi.org/10.1093/jn/nxaa322.
40. Messina M, Messina V. The role of soy in vegetarian diets. Nutrients. 2010;2:855–88.
41. Rizzo G, Baroni L. Soy, soy foods and their role in vegetarian diets**.** Nutrients 2018;10. https://doi.org/10.3390/nu10010043.
42. Kanadys W, et al. Effects of soy isoflavones on biochemical markers of bone metabolism in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials**.** Int J Environ Res Public Health 2021;18. https://doi.org/10.3390/ijerph18105346.
43. Cui C, et al. Effects of soy isoflavones on cognitive function: A systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2020;78:134–44. https://doi.org/10.1093/nutrit/nuz050.
44. Rizzo J, et al. Soy protein containing isoflavones improves facial signs of photoaging and skin hydration in postmenopausal women: Results of a prospective randomized double-blind controlled trial**.** Nutrients 2023;15. https://doi.org/10.3390/nu15194113.
45. Ramin C, et al. All-cause and cardiovascular disease mortality among breast cancer survivors in CLUE II, a long-standing community-based cohort. J Natl Cancer Inst. 2021;113:137–45. https://doi.org/10.1093/jnci/djaa096.
46. Bostany G, et al. Cardiac dysfunction among breast cancer survivors: Role of cardiotoxic therapy and cardiovascular risk factors**.** J Clin Oncol 2024:JCO2301779. https://doi.org/10.1200/JCO.23.01779.
47. Blanco Mejia S, et al. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. J Nutr. 2019;149:968–81. https://doi.org/10.1093/jn/nxz020.
48. Jenkins DJA, et al. Cumulative meta-analysis of the soy effect over time. J Am Heart Assoc. 2019;8: e012458. https://doi.org/10.1161/JAHA.119.012458.
49. Laudani S, et al. Isoflavones effects on vascular and endothelial outcomes: How Is the gut microbiota involved? Pharmaceuticals (Basel) 2024;17. https://doi.org/10.3390/ph17020236.
50. Murphy PA, Barua K, Hauck CC. Solvent extraction selection in the determination of isoflavones in soy foods. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;777:129–38. https://doi.org/10.1016/s1570-0232(02)00342-2.
51. Damodaran S, Hortobagyi GN. Estrogen receptor: A paradigm for targeted therapy. Cancer Res. 2021;81:5396–8. https://doi.org/10.1158/0008-5472.CAN-21-3200.
52. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci U S A. 1996;93:5925–30.
53. Kuiper GG, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998;139:4252–63.
54. Paruthiyil S, Parmar H, Kerekatte V, Cunha GR, Firestone GL, Leitman DC. Estrogen receptor beta inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res. 2004;64:423–8.
55. Setchell KD, et al. Soy isoflavone phase II metabolism differs between rodents and humans: implications for the effect on breast cancer risk**.** Am J Clin Nutr 2011;94:1284–1294ajcn.111.019638 [pii] https://doi.org/10.3945/ajcn.111.019638.
56. Richardson H, et al. Baseline estrogen levels in postmenopausal women participating in the MAP.3 breast cancer chemoprevention trial**.** Menopause 2020;27:693–700. https://doi.org/10.1097/GME.0000000000001568.
57. Oseni T, Patel R, Pyle J, Jordan VC. Selective estrogen receptor modulators and phytoestrogens. Planta Med. 2008;74:1656–65. https://doi.org/10.1055/s-0028-1088304.
58. Brzezinski A, Debi A. Phytoestrogens: the "natural" selective estrogen receptor modulators? Eur J Obstet Gynecol Reprod Biol. 1999;85:47–51. https://doi.org/10.1016/s0301-2115(98)00281-4.
59. Setchell KD. Soy isoflavones--benefits and risks from nature's selective estrogen receptor modulators (SERMs)**.** J Am Coll Nutr 2001;20:354S-362S; discussion 381S-383S. https://doi.org/10.1080/07315724.2001.10719168.
60. Folman Y, Pope GS. The interaction in the immature mouse of potent oestrogens with coumestrol, genistein and other utero-vaginotrophic compounds of low potency. J Endocrinol. 1966;34:215–25.
61. Viscardi G, et al. Effect of soy isoflavones on measures of estrogenicity: A systematic review and meta-analysis of randomized controlled trials**.** Adv Nutr 2024:100327. https://doi.org/10.1016/j.advnut.2024.100327.
62. Akiyama T, Ogawara H. Use and specificity of genistein as inhibitor of protein-tyrosine kinases. Methods Enzymol. 1991;201:362–70.
63. Constantinou A, Huberman E. Genistein as an inducer of tumor cell differentiation: possible mechanisms of action. Proc Soc Exp Biol Med. 1995;208:109–15.
64. Constantinou A, Mehta R, Runyan C, Rao K, Vaughan A, Moon R. Flavonoids as DNA topoisomerase antagonists and poisons: structure-activity relationships. J Nat Prod. 1995;58:217–25.
65. Paul MK, Mukhopadhyay AK. Tyrosine kinase - Role and significance in Cancer. Int J Med Sci. 2004;1:101–15. https://doi.org/10.7150/ijms.1.101.
66. Wang JC. Cellular roles of DNA topoisomerases: a molecular perspective. Nat Rev Mol Cell Biol. 2002;3:430–40. https://doi.org/10.1038/nrm831.
67. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55:1–12. https://doi.org/10.1207/s15327914nc5501_1.
68. Konishi K, et al. Dietary soy intake is inversely associated with risk of type 2 diabetes in Japanese women but not in men. J Nutr. 2019;149:1208–14. https://doi.org/10.1093/jn/nxz047.
69. Messina M, Sievenpiper JL, Williamson P, Kiel J, Erdman JW. Perspective: Soy-based meat and dairy alternatives, despite classification as ultra-processed foods, deliver high-quality nutrition on par with unprocessed or minimally processed animal-based counterparts. Adv Nutr. 2022;13:726–38. https://doi.org/10.1093/advances/nmac026.

70. Codex General Standard for Soy Protein Products, Codex Standard 175–1989. 1989
71. Bhagwat S, Haytowitz DB: USDA Database for the Isoflavone Content of Selected Foods, Release 2.1. 2015. U.S. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory Home Page: https://data.nal.usda.gov/dataset/usda-database-isoflavone-content-selected-foods-release-21-november-2015/resource/1de757af.
72. Andrade JE, Twaddle NC, Helferich WG, Doerge DR. Absolute bioavailability of isoflavones from soy protein isolate-containing food in female BALB/c mice. J Agric Food Chem. 2010;58:4529–36. https://doi.org/10.1021/jf9039843.
73. Murai U, et al. Soy product intake and risk of incident disabling dementia: the JPHC Disabling Dementia Study. Eur J Nutr. 2022;61:4045–57. https://doi.org/10.1007/s00394-022-02937-5.
74. Chei CL, et al. Isoflavone and soy food intake and risk of lung cancer in never smokers: report from prospective studies in Japan and China. Eur J Nutr. 2023;62:125–37. https://doi.org/10.1007/s00394-022-02968-y.
75. Liu Z, et al. Intake of soy foods and soy isoflavones by rural adult women in China. Asia Pac J Clin Nutr. 2004;13:204–9.
76. Fang Y, et al. The burden of cardiovascular disease attributable to dietary risk factors in the provinces of China, 2002–2018: a nationwide population-based study. Lancet Reg Health West Pac. 2023;37:100784. https://doi.org/10.1016/j.lanwpc.2023.100784.
77. Shu XO, et al. Cohort profile: The Shanghai Men's Health Study. Int J Epidemiol. 2015;44:810–8. https://doi.org/10.1093/ije/dyv013.
78. Yang G, et al. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. Am J Clin Nutr. 2005;81:1012–7. https://doi.org/10.1093/ajcn/81.5.1012.
79. Shirabe R, et al. Fermented and nonfermented soy foods and the risk of breast cancer in a Japanese population-based cohort study. Cancer Med. 2021;10:757–71. https://doi.org/10.1002/cam4.3677.
80. Bai W, Wang C, Ren C. Intakes of total and individual flavonoids by US adults. Int J Food Sci Nutr. 2014;65:9–20. https://doi.org/10.3109/09637486.2013.832170.
81. Anderson LN, Cotterchio M, Boucher BA, Kreiger N. Phytoestrogen intake from foods, during adolescence and adulthood, and risk of breast cancer by estrogen and progesterone receptor tumor subgroup among Ontario women. Int J Cancer. 2013;132:1683–92. https://doi.org/10.1002/ijc.27788.
82. Zamora-Ros R, et al. Dietary intakes and food sources of phytoestrogens in the European Prospective Investigation into Cancer and Nutrition (EPIC) 24-hour dietary recall cohort. Eur J Clin Nutr. 2012;66:932–41. https://doi.org/10.1038/ejcn.2012.36.
83. Lee MJ, Kim JH. Estimated dietary isoflavone intake among Korean adults. Nutr Res Pract. 2007;1:206–11. https://doi.org/10.4162/nrp.2007.1.3.206.
84. Setchell KD, et al. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr. 2003;77:411–9.
85. Setchell KD, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J Nutr. 2001;131:1362S-1375S.
86. King RA, Bursill DB. Plasma and urinary kinetics of the isoflavones daidzein and genistein after a single soy meal in humans. Am J Clin Nutr. 1998;67:867–72.
87. Watanabe S, et al. Pharmacokinetics of soybean isoflavones in plasma, urine and feces of men after ingestion of 60 g baked soybean powder (kinako). J Nutr. 1998;128:1710–5. https://doi.org/10.1093/jn/128.10.1710.
88. Shelnutt SR, Cimino CO, Wiggins PA, Ronis MJ, Badger TM. Pharmacokinetics of the glucuronide and sulfate conjugates of genistein and daidzein in men and women after consumption of a soy beverage. Am J Clin Nutr. 2002;76:588–94.
89. Busby MG, et al. Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men. Am J Clin Nutr. 2002;75:126–36.
90. Burnett BP, Pillai L, Bitto A, Squadrito F, Levy RM. Evaluation of CYP450 inhibitory effects and steady-state pharmacokinetics of genistein in combination with cholecalciferol and citrated zinc bisglycinate in postmenopausal women. Int J Womens Health. 2011;3:139–50. https://doi.org/10.2147/IJWH.S19309.
91. Takimoto CH, et al. Phase I pharmacokinetic and pharmacodynamic analysis of unconjugated soy isoflavones administered to individuals with cancer. Cancer Epidemiol Biomarkers Prev. 2003;12:1213–21.
92. van der Velpen V, et al. Large inter-individual variation in isoflavone plasma concentration limits use of isoflavone intake data for risk assessment. Eur J Clin Nutr. 2014;68:1141–7. https://doi.org/10.1038/ejcn.2014.108.
93. D'Alessandro TL, et al. Metabolism of phytoestrogen conjugates. Methods Enzymol. 2005;400:316–42.
94. Pritchett LE, Atherton KM, Mutch E, Ford D. Glucuronidation of the soyabean isoflavones genistein and daidzein by human liver is related to levels of UGT1A1 and UGT1A9 activity and alters isoflavone response in the MCF-7 human breast cancer cell line. J Nutr Biochem. 2008;19:739–45. https://doi.org/10.1016/j.jnutbio.2007.10.002.
95. Debon E, et al. Deciphering the origin of total estrogenic activity of complex mixtures. Front Nutr. 2023;10:1155800. https://doi.org/10.3389/fnut.2023.1155800.
96. Setchell KD, Clerici C. Equol: history, chemistry, and formation. J Nutr 2010;140:1355S-1362Sjn.109.119776 [pii]. https://doi.org/10.3945/jn.109.119776.
97. Wu X, et al. Correlations of urinary phytoestrogen excretion with lifestyle factors and dietary intakes among middle-aged and elderly Chinese women. Int J Mol Epidemiol Genet. 2012;3:18–29.
98. Takeuchi S, Takahashi T, Sawada Y, Iida M, Matsuda T, Kojima H. Comparative study on the nuclear hormone receptor activity of various phytochemicals and their metabolites by reporter gene assays using Chinese hamster ovary cells. Biol Pharm Bull 2009;32:195–202JST.JSTAGE/bpb/32.195 [pii].
99. Setchell KD, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavones. J Nutr. 2002;132:3577–84.
100. Ju YH, Fultz J, Allred KF, Doerge DR, Helferich WG. Effects of dietary daidzein and its metabolite, equol, at physiological concentrations on the growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in ovariectomized athymic mice. Carcinogenesis. 2006;27:856–63.
101. Wang C, Kurzer MS. Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. Nutr Cancer. 1997;28:236–47.
102. Wang TT, Sathyamoorthy N, Phang JM. Molecular effects of genistein on estrogen receptor mediated pathways. Carcinogenesis. 1996;17:271–5.
103. Miodini P, Fioravanti L, Di Fronzo G, Cappelletti V. The two phyto-oestrogens genistein and quercetin exert different effects on oestrogen receptor function. Br J Cancer. 1999;80:1150–5.
104. Zava DT, Duwe G. Estrogenic and antiproliferative properties of genistein and other flavonoids in human breast cancer cells in vitro. Nutr Cancer. 1997;27:31–40. https://doi.org/10.1080/01635589709514498.

105. Pike AC. Lessons learnt from structural studies of the oestrogen receptor. Best Pract Res Clin Endocrinol Metab. 2006;20:1–14. https://doi.org/10.1016/j.beem.2005.09.002.
106. Petrakis NL, et al. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epidemiol Biomarkers Prev. 1996;5:785–94.
107. McMichael-Phillips DF, et al. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. Am J Clin Nutr. 1998;68:1431S-1435S.
108. Hargreaves DF, et al. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. J Clin Endocrinol Metab. 1999;84:4017–24.
109. Helferich WG, Andrade JE, Hoagland MS. Phytoestrogens and breast cancer: a complex story. Inflammopharmacology. 2008;16:219–26. https://doi.org/10.1007/s10787-008-8020-0.
110. Ju YH, Allred CD, Allred KF, Karko KL, Doerge DR, Helferich WG. Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. J Nutr. 2001;131:2957–62.
111. Santell RC, Kieu N, Helferich WG. Genistein inhibits growth of estrogen-independent human breast cancer cells in culture but not in athymic mice. J Nutr. 2000;130:1665–9.
112. Ju YH, Allred KF, Allred CD, Helferich WG. Genistein stimulates growth of human breast cancer cells in a novel, postmenopausal animal model, with low plasma estradiol concentrations. Carcinogenesis. 2006;27:1292–9.
113. Allred CD, Allred KF, Ju YH, Virant SM, Helferich WG. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. Cancer Res. 2001;61:5045–50.
114. Allred CD, Allred KF, Ju YH, Goeppinger TS, Doerge DR, Helferich WG. Soy processing influences growth of estrogen-dependent breast cancer tumors. Carcinogenesis. 2004;25:1649–57.
115. Bracken MB. Why animal studies are often poor predictors of human reactions to exposure. J R Soc Med. 2009;102:120–2. https://doi.org/10.1258/jrsm.2008.08k033.
116. Ten SR. points to improve reproducibility and translation of animal research. Front Behav Neurosci. 2022;16:869511. https://doi.org/10.3389/fnbeh.2022.869511.
117. Onoda A, Ueno T, Uchiyama S, Hayashi S, Kato K, Wake N. Effects of S-equol and natural S-equol supplement (SE5-OH) on the growth of MCF-7 in vitro and as tumors implanted into ovariectomized athymic mice. Food Chem Toxicol. 2011;49:2279–84. https://doi.org/10.1016/j.fct.2011.06.027.
118. Shu XO, et al. Soy food intake and breast cancer survival**.** JAMA 2009;302:2437–2443302/22/2437 [pii]. https://doi.org/10.1001/jama.2009.1783.
119. Kurzer MS. Phytoestrogen supplement use by women. J Nutr. 2003;133:1983S-1986S. https://doi.org/10.1093/jn/133.6.1983S.
120. Rock CL, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin. 2022;72:230–62. https://doi.org/10.3322/caac.21719.
121. Boyd NF, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356:227–36.
122. Boyd NF, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol. 2005;6:798–808.
123. Burton A, et al. Mammographic density and ageing: A collaborative pooled analysis of cross-sectional data from 22 countries worldwide. PLoS Med. 2017;14:e1002335. https://doi.org/10.1371/journal.pmed.1002335.
124. Jiang S, Bennett DL, Rosner BA, Colditz GA. Longitudinal analysis of change in mammographic density in each breast and its association with breast cancer risk. JAMA Oncol. 2023. https://doi.org/10.1001/jamaoncol.2023.0434.
125. Mokhtary A, Karakatsanis A, Valachis A. Mammographic density changes over time and breast cancer risk: A systematic review and meta-Analysis**.** Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13194805.
126. Engmann NJ, et al. Longitudinal changes in volumetric breast density with tamoxifen and aromatase inhibitors. Cancer Epidemiol Biomarkers Prev. 2017;26:930–7. https://doi.org/10.1158/1055-9965.EPI-16-0882.
127 Greendale GA, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med. 1999;130:262–9.
128. Lundstrom E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: differences according to treatment. Am J Obstet Gynecol. 1999;181:348–52.
129. Chlebowski RT, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. JAMA. 2020;324:369–80. https://doi.org/10.1001/jama.2020.9482.
130. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74. https://doi.org/10.1016/j.cell.2011.02.013.
131. Rahmanzadeh R, Huttmann G, Gerdes J, Scholzen T. Chromophore-assisted light inactivation of pKi-67 leads to inhibition of ribosomal RNA synthesis. Cell Prolif. 2007;40:422–30. https://doi.org/10.1111/j.1365-2184.2007.00433.x.
132. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 2000;182:311–22.
133. Tomasetti C, et al. Cell division rates decrease with age, providing a potential explanation for the age-dependent deceleration in cancer incidence. Proc Natl Acad Sci U S A. 2019;116:20482–8. https://doi.org/10.1073/pnas.1905722116.
134. Conner P, et al. Breast cell proliferation in postmenopausal women during HRT evaluated through fine needle aspiration cytology. Breast Cancer Res Treat. 2003;78:159–65.
135. Murkes D, et al. Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. Fertil Steril. 2011;95:1188–91. https://doi.org/10.1016/j.fertnstert.2010.09.062.
136. Conner P. Breast response to menopausal hormone therapy–aspects on proliferation, apoptosis and mammographic density. Ann Med. 2007;39:28–41.
137. Decensi A, et al. A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. J Natl Cancer Inst. 2003;95:779–90. https://doi.org/10.1093/jnci/95.11.779.
138. Takagi K, et al. Intratumoral concentration of estrogens and clinicopathological changes in ductal carcinoma in situ following aromatase inhibitor letrozole treatment. Br J Cancer. 2013;109:100–8. https://doi.org/10.1038/bjc.2013.284.
139. Maskarinec G, Williams AE, Carlin L. Mammographic densities in a one-year isoflavone intervention. Eur J Cancer Prev. 2003;12:165–9.
140. Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A 2-year soy intervention in premenopausal women does not change mammographic densities. J Nutr. 2004;134:3089–94.
141. Tice JA. Soy and tamoxifen for breast cancer prevention in high risk pre-menopausal women. Prepared for the US Army Medical Research and Material Command, Fort Detrick, Maryland. 2005. https://apps.dtic.mil/sti/tr/pdf/ADA460295.pdf
142. Ferraris C, et al. Red clover and lifestyle changes to contrast menopausal symptoms in premenopausal patients with hormone-sensitive breast cancer receiving tamoxifen. Breast

Cancer Res Treat. 2020;180:157–65. https://doi.org/10.1007/s10549-020-05534-4.
143. Labos G, et al. Efficacy and safety of DT56a compared to hormone therapy in Greek post-menopausal women. J Endocrinol Invest. 2013;36:521–6. https://doi.org/10.3275/8926.
144. Verheus M, et al. Soy protein containing isoflavones and mammographic density in a randomized controlled trial in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2008;17:2632–263817/10/2632 [pii] https://doi.org/10.1158/1055-9965.EPI-08-0344.
145. Marini H, et al. Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: a follow-up study. J Clin Endocrinol Metab. 2008;93:4787–96. https://doi.org/10.1210/jc.2008-1087.
146. Maskarinec G, et al. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. J Nutr. 2009;139:981–6. https://doi.org/10.3945/jn.108.102913.
147. Colacurci N, et al. Endometrial, breast and liver safety of soy isoflavones plus Lactobacillus sporogenes in post-menopausal women. Gynecol Endocrinol. 2012;201210(3109/09513590):738724.
148. Delmanto A, Nahas-Neto J, Traiman P, Uemura G, Pessoa EC, Nahas EA. Effects of soy isoflavones on mammographic density and breast parenchyma in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. Menopause. 2013;20:1049–54. https://doi.org/10.1097/GME.0b013e3182850270.
149. Rajaram N, et al. A randomized controlled trial of soy isoflavone intake on mammographic density among Malaysian women. Nutrients 2023;1510.3390/nu15020299.
150. Atkinson C, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial. Breast Cancer Res. 2004;6:R170-179.
151. Powles TJ, Howell A, Evans DG, McCloskey EV, Ashley S, Greenhalgh R. Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer. Menopause Int. 2008;14:6–12.
152. Wu AH, et al. Double-blind randomized 12-month soy intervention had no effects on breast MRI fibroglandular tissue density or mammographic density. Cancer Prev Res (Phila). 2015;8:942–51. https://doi.org/10.1158/1940-6207.CAPR-15-0125.
153. Hooper L, Madhavan G, Tice JA, Leinster SJ, Cassidy A. Effects of isoflavones on breast density in pre- and post-menopausal women: a systematic review and meta-analysis of randomized controlled trials. Hum Reprod Update 2010;16:745–760dmq011 [pii] https://doi.org/10.1093/humupd/dmq011.
154. Heinonen SM, Wahala K, Adlercreutz H. Identification of urinary metabolites of the red clover isoflavones formononetin and biochanin A in human subjects. J Agric Food Chem. 2004;52:6802–9. https://doi.org/10.1021/jf0492767.
155. Finkeldey L, Schmitz E, Ellinger S. Effect of the Intake of Isoflavones on Risk Factors of Breast Cancer-A Systematic Review of Randomized Controlled Intervention Studies. Nutrients 2021;13. https://doi.org/10.3390/nu13072309.
156. Chilibeck PD, et al. Effect of exercise training combined with isoflavone supplementation on bone and lipids in postmenopausal women: a randomized clinical trial. J Bone Miner Res. 2013;28:780–93. https://doi.org/10.1002/jbmr.1815.
157. Sartippour MR, et al. A pilot clinical study of short-term isoflavone supplements in breast cancer patients. Nutr Cancer. 2004;49:59–65.
158. Palomares MR, Hopper L, Goldstein L, Lehman CD, Storer BE, Gralow JR. Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. Breast Cancer Res Treatment 2004;88 (Suppl 1):4002 (Abstract)
159. Cheng G, Wilczek B, Warner M, Gustafsson JA, Landgren BM. Isoflavone treatment for acute menopausal symptoms. Menopause. 2007;14:468–73. https://doi.org/10.1097/GME.0b013e31802cc7d0.
160. Khan SA, et al. Soy isoflavone supplementation for breast cancer risk reduction: A randomized phase II trial. Cancer Prev Res (Phila). 2012;5:309–19. https://doi.org/10.1158/1940-6207.CAPR-11-0251.
161. Shike M, et al. The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. J Natl Cancer Inst 2014;106. https://doi.org/10.1093/jnci/dju189.
162. Jaskulski S, et al. Genistein and enterolactone in relation to Ki-67 expression and HER2 status in postmenopausal breast cancer patients. Mol Nutr Food Res 2017;61. https://doi.org/10.1002/mnfr.201700449.
163. Messina M, Messina V, Nagata C. Perspective: Observational studies involving low soy intake populations have limited ability for providing insight into the health effects of soybean isoflavones. Adv Nutr 2024:100210. https://doi.org/10.1016/j.advnut.2024.100210.
164. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev. 1999;8:855–61.
165. Lundstrom E, Hirschberg AL, Soderqvist G. Digitized assessment of mammographic breast density–effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo. Maturitas. 2011;70:361–4. https://doi.org/10.1016/j.maturitas.2011.08.009.
166. Coussement L, et al. Exploratory analysis of the human breast DNA methylation profile upon soymilk exposure. Sci Rep. 2018;8:13617. https://doi.org/10.1038/s41598-018-31767-x.
167. Qin W, et al. Soy isoflavones have an antiestrogenic effect and alter mammary promoter hypermethylation in healthy premenopausal women. Nutrition and Cancer 2009;61:238–244908919410 [pii] https://doi.org/10.1080/01635580802404196.
168. Ho SC, et al. Pre-diagnosis and early post-diagnosis dietary soy isoflavone intake and survival outcomes: A prospective cohort study of early stage breast cancer survivors. Cancer Treat Res Commun. 2021;27:100350. https://doi.org/10.1016/j.ctarc.2021.100350.
169. Zhang YF, Kang HB, Li BL, Zhang RM. Positive effects of soy isoflavone food on survival of breast cancer patients in China. Asian Pac J Cancer Prev. 2012;13:479–82.
170. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ 2010;182:1857–1862cmaj.091298 [pii] https://doi.org/10.1503/cmaj.091298.
171. Guha N, Kwan ML, Quesenberry CP Jr, Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat. 2009;118:395–405. https://doi.org/10.1007/s10549-009-0321-5.
172. Caan BJ, et al. Soy food consumption and breast cancer prognosis. Cancer Epidemiol Biomarkers Prev. 2011;20:854–8. https://doi.org/10.1158/1055-9965.EPI-10-1041.
173. Woo HD, Park KS, Ro J, Kim J. Differential influence of dietary soy intake on the risk of breast cancer recurrence related to HER2 status. Nutr Cancer. 2012;64:198–205. https://doi.org/10.1080/01635581.2012.635261.
174. Yang J, Chung M, Park Y. Association of fermented products with risk of cancer recurrence and mortality among breast cancer survivors: A prospective cohort study. Nutr Cancer. 2023;75:1189–99. https://doi.org/10.1080/01635581.2023.2186259.

175. Song S, et al. Dietary isoflavone intake and breast cancer prognosis: A prospective analysis and meta-analysis. Nutr Cancer. 2024;76:42–54. https://doi.org/10.1080/01635581.2023.2279220.
176. Nechuta SJ, et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr. 2012;96:123–32. https://doi.org/10.3945/ajcn.112.035972.
177. Fink BN, et al. Dietary flavonoid intake and breast cancer survival among women on Long Island. Cancer Epidemiol Biomarkers Prev. 2007;16:2285–92.
178. Zhang FF, et al. Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. Cancer. 2017;123:2070–9. https://doi.org/10.1002/cncr.30615.
179. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109:1721–8. https://doi.org/10.1002/cncr.22618.
180. Sporikova Z, Koudelakova V, Trojanec R, Hajduch M. Genetic markers in triple-negative breast cancer. Clin Breast Cancer. 2018;18:e841–50. https://doi.org/10.1016/j.clbc.2018.07.023.
181. Wolff AC, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med. 2014;138:241–56. https://doi.org/10.5858/arpa.2013-0953-SA.
182. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol. 2016;13:674–90. https://doi.org/10.1038/nrclinonc.2016.66.
183. Sorlie T, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98:10869–74. https://doi.org/10.1073/pnas.191367098.
184. Sharma M, et al. Therapeutic effects of dietary soybean genistein on triple-negative breast cancer via regulation of epigenetic mechanisms**.** Nutrients 2021;13. https://doi.org/10.3390/nu13113944.
185. Donovan MG, Selmin OI, Doetschman TC, Romagnolo DF. Epigenetic activation of BRCA1 by genistein In vivo and triple negative breast cancer cells linked to antagonism toward aryl hydrocarbon receptor**.** Nutrients 2019;11. https://doi.org/10.3390/nu11112559.
186. Chatterjee P, Banerjee S. Evaluating chemotherapeutic potential of soya-isoflavonoids against high penetrance genes in triple-negative breast cancer**.** J Biomol Struct Dyn 2023:1–2010.1080/07391102.2023.2243352.
187. Im SA, et al. Olaparib monotherapy for Asian patients with a germline BRCA mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis. Sci Rep. 2020;10:8753. https://doi.org/10.1038/s41598-020-63033-4.
188. Robert M, Frenel JS, Gourmelon C, Patsouris A, Augereau P, Campone M. Olaparib for the treatment of breast cancer. Expert Opin Investig Drugs. 2017;26:751–9. https://doi.org/10.1080/13543784.2017.1318847.
189. Guo X, et al. Long-term soy consumption and tumor tissue MicroRNA and gene expression in triple-negative breast cancer. Cancer. 2016;122:2544–51. https://doi.org/10.1002/cncr.29981.
190. Kim YJ, Park MY, Chang N, Kwon O. Intake and major sources of dietary flavonoid in Korean adults: Korean National Health and Nutrition Examination Survey 2010–2012. Asia Pac J Clin Nutr. 2015;24:456–63. https://doi.org/10.6133/apjcn.2015.24.3.04.
191. Touillaud M, et al. Use of dietary supplements containing soy isoflavones and breast cancer risk among women aged >50 y: a prospective study. Am J Clin Nutr. 2019;109:597–605. https://doi.org/10.1093/ajcn/nqy313.
192. Brasky TM, Lampe JW, Potter JD, Patterson RE, White E. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort**.** Cancer Epidemiol Biomarkers Prev 2010;19:1696–170819/7/1696 [pii] https://doi.org/10.1158/1055-9965.EPI-10-0318.
193. Rebbeck TR, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer. 2007;120:1523–8. https://doi.org/10.1002/ijc.22485.
194. Obi N, et al. The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study. Cancer Epidemiol Biomarkers Prev. 2009;18:2207–13. https://doi.org/10.1158/1055-9965.EPI-09-0298.
195. Boucher BA, Cotterchio M, Anderson LN, Kreiger N, Kirsh VA, Thompson LU. Use of isoflavone supplements is associated with reduced postmenopausal breast cancer risk. Int J Cancer. 2013;132:1439–50. https://doi.org/10.1002/ijc.27769.
196. Liu Y, et al. Isoflavones in soy flour diet have different effects on whole-genome expression patterns than purified isoflavone mix in human MCF-7 breast tumors in ovariectomized athymic nude mice. Mol Nutr Food Res. 2015;59:1419–30. https://doi.org/10.1002/mnfr.201500028.
197. Allred CD, et al. Soy processing affects metabolism and disposition of dietary isoflavones in ovariectomized BALB/c mice. J Agric Food Chem. 2005;53:8542–50.
198. Zhang X, et al. Lifetime genistein intake increases the response of mammary tumors to tamoxifen in rats. Clin Cancer Res. 2017;23:814–24. https://doi.org/10.1158/1078-0432.CCR-16-1735.
199. Messina MJ, Persky V, Setchell KD, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr Cancer. 1994;21:113–31.
200. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med. 1995;333:276–82.
201. Guth U, et al. Tumor size and detection in breast cancer: Self-examination and clinical breast examination are at their limit. Cancer Detect Prev. 2008;32:224–8. https://doi.org/10.1016/j.cdp.2008.04.002.
202. Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S. Breast cancer tumor growth estimated through mammography screening data. Breast Cancer Res. 2008;10:R41. https://doi.org/10.1186/bcr2092.
203. Giovannucci E. Nutritional epidemiology and cancer: A Tale of Two Cities. Cancer Causes Control. 2018;29:1007–14. https://doi.org/10.1007/s10552-018-1088-y.