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Impact of Soy Foods on the Development of Breast Cancer and the Prognosis of Breast Cancer Patients

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Keywords
Soy foods · Isoflavones · Breast cancer · Prevention · Patients · Summary

Summary
The relationship between soy food intake and breast cancer has been rigorously investigated for more than 25 years. The identification of isoflavones as possible chemopreventive agents helped fuel this line of investigation. These diphenolic compounds, which are found in uniquely-rich amounts in soy beans, possess both estrogen-dependent and -independent properties that potentially inhibit the development of breast cancer. Observational studies show that among Asian women higher soy consumption is associated with an approximate 30% reduction in risk of developing breast cancer. However, evidence suggests that for soy to reduce breast cancer risk consumption must occur early in life, that is during childhood and/or adolescence. Despite the interest in the role of soy in reducing breast cancer risk concerns have arisen that soy foods, because they contain isoflavones, may increase the likelihood of high-risk women developing breast cancer and worsen the prognosis of breast cancer patients. However, extensive clinical and epidemiologic data show these concerns to be unfounded. Clinical trials consistently show that isoflavone intake does not adversely affect markers of breast cancer risk, including mammographic density and cell proliferation. Furthermore, prospective epidemiologic studies involving over 11,000 women from the USA and China show that postdiagnosis soy intake statistically significantly reduces recurrence and improves survival.

Schlüsselwörter
Soja-Lebensmittel · Isoflavone · Brustkrebs · Prävention · Patienten · Übersicht

Zusammenfassung
Der Zusammenhang zwischen dem Verzehr von Sojaprodukten und Brustkrebs wird seit mehr als 25 Jahren intensiv untersucht. Die Identifizierung von Isoflavonen als möglichen chemopräventiven Wirkstoffen hat dazu beigetragen, diese Forschungsrichtung voranzutreiben. Diese Diphenolverbindungen – in einzigartig großen Mengen in Sojabohnen vorhanden – haben sowohl östrogenabhängige als auch -unabhängige Eigenschaften, die potenziell die Entstehung von Brustkrebs hemmen. Beobachtungsstudien zeigen, dass ein erhöhter Sojakonsum unter asiatischen Frauen mit einer Reduzierung des Brustkrebs-Risikos um etwa 30% assoziiert ist. Allerdings deutet die Datenlage darauf hin, dass Soja in frühen Lebensphasen konsumiert werden muss, um das Risiko für Brustkrebs zu senken, d.h. in der Kindheit und/oder Pubertät. Obwohl die Frage, welche Rolle Soja für die Senkung des Brustkrebs-Risikos spielt, Interesse hervorruft, gibt es Bedenken, Soja-Lebensmittel könnten die Wahrscheinlichkeit für die Entstehung von Brustkrebs bei Frauen mit ohnehin hohem Risiko noch steigern und die Prognose von Brustkrebs-Patientinnen verschlechtern, weil sie Isoflavone beinhalten. Umfangreiche klinische und epidemiologische Daten belegen jedoch, dass diese Sorgen unbegründet sind. In klinischen Studien wurde durchgängig nachgewiesen, dass die Aufnahme von Isoflavonen keinen ungünstigen Effekt auf Brustkrebs-Risikomarker ausübt, einschließlich der Mammografiedichte und Zellproliferation. Darüber hinaus zeigen prospektive epidemiologische Studien mit über 11 000 Frauen aus den USA und China, dass Sojakonsum nach einer Diagnose die Rezidivrate statistisch signifikant reduziert und das Überleben verbessert.

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Introduction

The relationship between soy food intake and breast cancer risk has been rigorously investigated for at least 25 years [1]. The historically low breast cancer incidence and mortality rates in soy food-consuming countries [2] helped fuel initial interest in this relationship as did the identification of isoflavones as possible chemopreventive agents [3, 4]. These diphenolic compounds, which are found in uniquely-rich amounts in soy beans [5], possess both estrogen-dependent [6] and -independent [6, 7] properties that potentially enable them to inhibit the development of breast cancer. In addition, substantial clinical research suggests the estrogen-like properties of isoflavones may be especially beneficial for peri- and postmenopausal women. For example, isoflavones alleviate hot flashes [8], may improve arterial health [9], and reduce wrinkles [10]. Also, new research using novel methodology reported that isoflavones increase bone calcium content in postmenopausal women [11].

However, the estrogen-like properties of isoflavones raised concern that soy foods might increase the risk of developing breast cancer among high-risk women and worsen the prognosis of women with this disease. This concern is supported by studies showing that in athymic ovariectomized mice implanted with estrogen-sensitive human breast cancer cells (MCF-7) isoflavones stimulate the growth of existing tumors [12, 13]. However, the clinical data [14] show isoflavone exposure is safe for all women, and the prospective epidemiologic data [15] show isoflavone exposure improves the prognosis of breast cancer patients. This brief review addresses the relationship between soy intake and breast cancer in healthy women and breast cancer patients. Before exploring this relationship, background information on isoflavones is provided.

Isoflavones

Among commonly consumed foods, only the soy bean contains nutritionally relevant amounts isoflavones. This point is illustrated by the mean daily isoflavone intake of 30 to 50 mg among older individuals in Japan [16], whereas in the United States [17] and Europe [18], per capita intake is less than 3 mg. Not surprisingly, the intake of soy foods, and therefore isoflavones, among Western vegetarians, and especially vegans, greatly exceeds that of nonvegetarians [19].

Isoflavones have a similar chemical structure to estrogen, bind to estrogen receptors (ERs), and exert estrogen-like effects under certain experimental conditions. For these reasons, they are classified as phytoestrogens. However, isoflavones are also classified as selective estrogen receptor modulators (SERMs) [20]. SERMs, which include the breast cancer drugs tamoxifen and raloxifene, are selective for tissue type; depending upon the tissue, they can have estrogen agonistic effects, antagonistic effects, or no effects at all even in tissues affected by estrogen. In the case of isoflavones, tissue selectivity is thought to occur because they preferentially bind to and activate ERβ in comparison to ERα [20].

These 2 ERs have different tissue distributions and often perform different functions in the body when activated. Emerging evidence suggests that ERβ functions as a tissue-specific tumor suppressor with antiproliferative actions [21]. In breast tissue, ERβ activation is thought to inhibit the stimulatory and proliferative effects of ERα activation [22]. There are numerous clinical examples of isoflavones exerting estrogen-like effects in some tissues [8] but having no effect on other estrogen-sensitive endpoints [23], although there is limited evidence demonstrating antiestrogenic effects [24–26]. In addition to the classic estrogen receptors, isoflavones bind to and activate G protein-coupled estrogen receptor 1 (GPER), formerly referred to as G protein-coupled receptor 30 (GPR30) [27, 28].

The isoflavones in soy beans and unfermented soy foods are present primarily as glycosides; fermentation converts the glycosides to aglycones to varying degrees [29]. It is not clear if the isoflavone form impacts biological activity, but there is often confusion about the amount of biologically-active isoflavones in a food since the sugar accounts for 40% of the weight of the glycoside. The recommended approach and the approach used in this article when referring to an amount of isoflavones is to refer to the aglycone equivalent weight.

When all forms of the individual isoflavones are considered, the 3 isoflavones (genistein, daidzein, and glycitein) account for approximately 50%, 40%, and 10%, respectively, of the total soy bean isoflavone content [29]. Each of the 3 soy bean isoflavones is a distinct chemical entity with different ER binding affinities, but for most endpoints genistein is considered to be the most potent isoflavone [30]. For example, Taku et al. [8] found that only soy bean isoflavone supplements providing sufficient genistein alleviated menopause-related hot flashes. On the other hand, a mixture of isoflavones was shown to increase bone calcium content in postmenopausal women to a greater extent than a similar amount of isoflavones containing a higher proportion of genistein [11].

Finally, traditional soy foods contain approximately 3.5 mg of isoflavones per gram of protein [16]; highly processed soy can lose as much as 80% of its isoflavone content [29]. On average, traditional soy foods contain 20–30 mg of isoflavones per serving (e.g., 250 ml of soy milk made from whole soy beans or 100 g of tofu).

Breast Cancer Prevention

Not surprisingly, much of our understanding about the potential role of soy in breast cancer prevention comes from epidemiologic studies. When considering these data, it is important to recognize the importance of distinguishing between studies involving typical Western and Asian populations. Although epidemiologic studies involving Western populations are routinely conducted, their ability to provide meaningful insight into the health effects of soy foods is doubtful because of the very low soy intake [31]. There is almost certainly no causal basis for the statistically significant relationships that are occasionally observed.

Overall, findings from the epidemiologic studies are supportive of a protective role of soy food intake against breast cancer. To this point are the results of a recently published meta-analysis by Chen et al. [32], which included 30 studies involving premenopausal women and 31 involving postmenopausal women. Of the 30 studies involving premenopausal women, 10 were cohort or nested case-control studies (4 studies in Asian countries and 6 studies in Western countries), and 20 studies were case-control studies (13 studies in Asia and 8 studies in Western countries). Of the 31 studies involving postmenopausal women, 12 were cohort or nested case-control studies (5 studies in Asia and 7 in Western countries), and 19 were case-control studies (13 studies in Asian countries, 7 in Western countries).

In premenopausal women, the odds ratios (ORs) plus 95% confidence interval (CI) when comparing high versus low soy intake for Western and Asian studies were 0.90 (0.77–1.04) and 0.59 (0.48–0.69), respectively. In Western and Asian studies involving postmenopausal women, the ORs plus 95% CI were 0.92 (0.83–1.00) and 0.59 (0.44–0.74), respectively. When stratified by study type, the results show that, although risk was lower for both cohort and case-control studies, it was statistically significantly reduced only for the latter. More specifically, the ORs (95% CI) for Asian studies involving premenopausal women for cohort/nested case-control and case-control studies were 0.77 (0.37–1.18) and 0.56 (0.45–0.66), respectively. For postmenopausal women, these figures were 0.84 (0.54–1.14) and 0.50 (0.34–0.66), respectively.

Not surprisingly, no primary prevention studies have evaluated the effects of soy intake on the risk of developing breast cancer. However, numerous clinical studies have evaluated the impact of isoflavone exposure via tablets, soy protein, or soy foods on markers of breast cancer risk, including mammographic density and breast cell proliferation. These studies have involved healthy women, women at risk of developing breast cancer, and women with breast cancer. These data show no evidence of protective effects. For example, a meta-analysis by Hooper et al. [33] found no effects of isoflavone exposure on mammographic density in postmenopausal women and a slight increase in density in premenopausal women, the possible clinical significance of which was unable to be determined by the authors. More recently, in a year-long trial which included at-risk women and breast cancer patients, Wu et al. [34] found no evidence isoflavones affect breast MRI (magnetic resonance imaging) fibroglandular tissue density or mammographic density. Similarly, and even more importantly, none of the 6 studies [35–40] that evaluated in vivo breast cell proliferation (and in some cases apoptosis) found an affect despite in several cases [37, 39, 40], isoflavone exposure exceeding typical Japanese intake several fold.

Overall, with few exceptions, it is difficult to find any clinical evidence to support the protective effect of soy consumption against the development of breast cancer observed in the Asian epidemiologic studies. One explanation for this discrepancy is that soy intake is protective against breast cancer in Asian studies not because of adult consumption but because of intake early in life [41, 42]. Since childhood dietary habits track into adulthood, it is reasonable to speculate that adult high-soy consumers also consumed more soy when young [43].

The notion that early soy intake is protective against breast cancer was first proposed in 1995 [44, 45]. A series of rodent experiments from the laboratory of Coral Lamartiniere (University of Alabama at Birmingham, AL, USA) has shown that just brief genistein exposure during the early postnatal period reduces chemically-induced mammary cancer by approximately 50% [46]. In addition, genistein further reduces mammary cancer incidence when exposure also occurs late in life, but only in animals first exposed to genistein when young [46].

The existing epidemiologic data, although limited, supports the 'early-intake' hypothesis. All 4 case-control studies that have retrospectively evaluated the impact of soy intake during adolescence on later risk of developing breast cancer have found protective effects [47–50]. Also, indirectly, the results of the Oxford arm of the European Prospective Investigation into Cancer (EPIC) provide support for the early-intake hypothesis.

As noted above, because of the low soy intake, Western observational studies involving the general population are unable to provide meaningful insight into the health effects of soy foods or isoflavones. However, because the EPIC-Oxford oversampled for vegetarians, isoflavone intake was similar to that reported in Asian epidemiologic studies. And yet, in contrast to the Asian studies, high isoflavone intake in this cohort was unrelated to breast cancer risk [51]. One explanation for this lack of protection is that the high-soy consumers in the EPIC-Oxford adopted their dietary pattern late in life, so they did not consume soy when young.

Finally, several mechanisms for the protective effects of early isoflavone exposure have been proposed [52–56]. It appears that isoflavones change cells in the developing breast in ways that make them permanently less likely to be transformed into cancer cells. The notion that early soy intake reduces breast cancer risk is consistent with a growing recognition that childhood and adolescent lifestyle and environmental exposures are linked with subsequent risk of cancers arising in adulthood [57]. Interestingly, it is known that pregnancy – which results in elevated estradiol levels – early in life is protective against breast cancer [58]. There may be some similarities between the protective effect of early isoflavone exposure and early pregnancy.

Although still speculative, given the evidence and that in the epidemiologic studies 1 serving daily was associated with protection against breast cancer, it is reasonable to recommend that young females incorporate at least modest amounts of soy into their diet. With respect to adults, while soy consumption can be recommended for many reasons (e.g., soy foods are good sources of high-quality protein [59] and both essential fatty acids [60], isoflavones alleviate hot flashes [8] and may improve arterial health [9] and increase bone calcium content [11] in postmenopausal women), breast cancer prevention does not appear to be one of them.

Soy and the Breast Cancer Patient

As noted at the onset, research showing isoflavones stimulate existing tumor growth in an athymic ovariectomized mouse model fueled concern about the impact of soy on women with breast cancer [12, 13]. Even without these data, there was theoretical concern over the 'estrogenic' effects of isoflavones. However, research suggests neither the animal data nor the estrogen-like effects of isoflavones are a basis for concern.

First, as already noted, there is ample clinical evidence indicating isoflavones differ from estrogen. For example, in contrast to estrogen, isoflavones do not stimulate vaginal tissue [61] or increase platelet aggregation [62]. Furthermore, the evidence that estrogen therapy increases breast cancer risk or worsens the prognosis of breast cancer patients is in doubt. In fact, in the Women's Health Initiative trial, regardless of the age at which therapy was initiated, those in the estrogen group (0.625 mg/d conjugated equine estrogens) were less likely to develop invasive breast cancer in comparison to the women in the placebo group [63]. Considerable data show that it is estrogen plus progestin, rather than estrogen alone, which worsens breast cancer risk [64]. Soy has no progestin activity.

Second, in regard to the animal data, not only do mice metabolize isoflavones differently than humans [65] but when the ovariectomized athymic mouse model is just slightly tweaked, isoflavones no longer affect tumor growth [66]. More specifically, Onoda et al. [66] found that when MCF-7 cells are cultured in physiological concentrations of estrogen prior to implantation, rather than in pharmacological concentrations, isoflavones do not affect tumor growth.

Arguably, the most important data in support of the safety of soy foods for women with breast cancer are the prospective epidemiologic studies which involve over 11,000 breast cancer patients. In 2009, Shu et al. [67] were the first to report that postdiagnosis soy intake favorably affected prognosis. They found that in the Shanghai Breast Cancer Survival Study (N = 5,042) after 3.9 years of follow up, the hazard ratio (HR) plus 95% CI for recurrence/breast cancer-specific mortality for women in the 4th isoflavone intake quartile was 0.77 (0.60–0.98) [67]. Three years later, a pooled analysis which included this study and 2 prospective studies [68, 69] from the United States (n = 9,514) found that after 7.4 years of follow up, the HR (95% CI) for recurrence for women in the highest isoflavone group was 0.75 (0.61–0.92) [70]. Importantly, the HR (95% CI) of 0.69 (0.47–1.01) for breast cancer recurrence among Chinese women was similar to the HR (95% CI) of 0.74 (0.56–0.97) among non-Asian US women [70].

Finally, a meta-analysis (N = 11,206) by Chi et al. [15] that included the 3 prospective studies in the pooled analysis plus 2 additional Chinese prospective studies [71, 72] found soy food intake after diagnosis was associated with reduced mortality (HR 0.84, 95% CI 0.71–0.99) and recurrence (HR 0.74, 95% CI 0.64–0.85). The prospective data also suggest that soy intake may enhance the efficacy of both tamoxifen [70] and the aromatase inhibitor, anastrozole [71]. These findings directly contradict results from the aforementioned athymic ovariectomized mouse model [73, 74].

The mechanism by which soy consumption may improve the prognosis of breast cancer patients is not obvious, especially in light of the previously discussed clinical data which show isoflavones do not affect breast tissue density or cell proliferation [14, 15]. Some animal research shows isoflavones are capable of inhibiting angiogenesis [75, 76] and metastasis [77, 78], with the latter finding also having some human support [79]. Also, in a 3-year clinical trial involving osteopenic postmenopausal women, BRCA1 and BRCA2 mRNA levels were unchanged in the group consuming 54 mg/d genistein, whereas in the placebo group levels decreased [80]. Finally, there is some indication that, at least among women with breast cancer, soy acts as an ER antagonist [81], although in the previously referred to pooled analysis [70] and meta-analysis [15] isoflavone intake was associated with protective effects in both ER– and ER+ breast cancer patients.

Implications

Despite the abundance of data in support of the benefits of isoflavones for postmenopausal women, soy foods have not been embraced by the medical community to an extent that the evidence justifies. Much of this reluctance is likely due to concerns over safety and, in particular, to the fear that isoflavones may increase breast cancer risk. However, as outlined in this brief review, evidence published over the past decade attests to the safety of isoflavone exposure with respect to the breast. Furthermore, after an extensive literature review, the European Food Safety Authority recently concluded that in postmenopausal women, isoflavones do not adversely affect breast tissue, thyroid function, or the uterus – the 3 organs that were reviewed [82]. Therefore, the medical community may now be more likely to recommend soy foods to their postmenopausal patients.

Finally, there are some signs that the nutrition and medical communities may be ready to embrace the notion that a reasonable and prudent recommendation is for young females to consume soy on a daily basis. To this point, a review published in 2014 identified eating soy during childhood/adolescence as 1 of 6 steps to reducing cancer risk [83]. Also, a recent commentary in the 'American Journal of Epidemiology' concluded that '… growing evidence … links childhood and adolescent lifestyle and environmental exposures with subsequent risk of cancers arising in adulthood' [57]. Conversely, the dearth of clinical research investigating the effects of soy food consumption in young women may cause some health professionals to be reluctant to recommend soy. A recent cross-sectional study found that soy consumption was unrelated to the age of menses onset; perhaps a clinical study investigating this endpoint would help to fill this void [84].

Of course, generating clinical data in support of the 'early-soy intake' hypothesis would also make it easier for health professionals to recommend that young females consume soy foods. A cross-sectional study by Wang et al. [85] may provide the basis for such a study. These authors found that cancer-related proteins in the circulation were favorably altered in girls excreting large amounts of

genistein and small amounts of bisphenol A (BPA) when compared to girls excreting small amounts of genistein and large amounts of BPA [85]. In rodents, these changes reflect decreases and increases in cancer risk, respectively [86, 87]. An intervention study in young girls examining these cancer-related proteins may provide a reasonable option for generating clinical data.

Disclosure Statement

Mark Messina regularly consults for companies and/or organizations that manufacture and/or sell soy foods and/or isoflavone supplements.

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