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# A Review of Soy Intake in the Prevention and Treatment of Breast Cancer

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*Soyfoods and soybean constituents have grown in popularity in recent years. Increasingly, people are choosing these products to supplement or substitute elements in their diets. But what is the real value of soy to menopausal women? What role does soy play in the prevention and treatment of breast cancer? A review of the literature offers some answers to these and other questions.*

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## Introduction

During the past 10 years, soyfoods and soybean constituents have attracted widespread research attention in the West for their purported health benefits. Many newly developed “Westernized” soy products specifically target women because of reports that soy may be helpful for conditions and diseases associated with menopause. Soy is considered a possible alternative to conventional hormone therapy, in large part because it is a unique natural dietary source of isoflavones, a chemical class of compounds with estrogen-like properties.

Soy products are especially attractive to breast-cancer patients<sup>1,2</sup> since these women frequently seek alternatives to estrogen and progestogen therapy (EPT)<sup>3-5</sup> for fear that estrogen may stimulate breast tumor growth<sup>6,7</sup> and because of speculation that soy intake reduces breast cancer risk and, possibly, decreases recurrence.<sup>8,9</sup> The National Cancer Institute (NCI) has been investigating the anticancer effects of soy since 1991.<sup>10-13</sup> Nevertheless, somewhat paradoxically, there is concern that the estrogen-like effects of isoflavones actually may stimulate the growth of estrogen-sensitive tumors<sup>14</sup> and also inhibit the efficacy of tamoxifen.<sup>15</sup> Con-

sequently, many oncologists and several health organizations have issued cautionary statements about breast cancer patients and women at high risk of the disease—especially those on tamoxifen—consuming soy. This review will discuss whether soy intake is contraindicated for these women and answer some questions about the soy controversy.

## Background on Isoflavones

Isoflavones are a subclass of a larger and more ubiquitous group of phytochemicals called flavonoids. Japanese adults typically consume about 10 g soy protein/day and about 35 to 40 mg of isoflavones.<sup>16</sup> This amount is equal to approximately 1 to 2 servings of traditional soyfoods (one serving equals one cup of soymilk or 3 to 4 ounces of tofu). In traditional soyfoods 1g of soy protein generally provides about 3 to 4 mg of isoflavones. Fasting serum isoflavone levels in Japanese adults are approximately 200-500 nM, considerably lower than the postprandial levels of 1-5  $\mu$ M noted in subjects fed 2 to 3 servings of soyfoods. Although there are several putative anticarcinogens in soy, the focus has been on the isoflavones, in part because the primary soybean

isoflavone genistein inhibits the growth of a wide range of hormone-dependent and hormone-independent cancer cells in vitro.<sup>8,12</sup> In addition to genistein (4', 5, 7-trihydroxyisoflavone), soybeans contain daidzein (4', 7-dihydroxyisoflavone) and small amounts of a third isoflavone known as glycitein (7, 4'-dihydroxy-6-methoxyisoflavone). Also, in approximately 30% to 50% of subjects fed soy, intestinal bacteria convert the isoflavone daidzein into the isoflavonoid, equol.<sup>17</sup>

Isoflavones are present in the soybean primarily as  $\beta$ -glycosides, which can have an acetyl or malonyl group attached for a total of 12 different isoflavone isomers.<sup>18</sup> The various types of processing involved in the production of soyfoods only slightly affect total isoflavone content since, for the most part, these molecules are not heat labile. However, processing will affect isoflavone profile. The bioavailability of isoflavones from different soyfoods does not appear to be greatly affected by differences in isoflavone isoform profile.

Isoflavones are referred to as “phytoestrogens” because they bind to estrogen receptors (ERs) and exert some estrogen-like effects on cells. They have a low relative binding affinity (RBA) for ER $\alpha$ , although their binding affinity,

especially that of genistein, for ER $\beta$ , is only slightly lower than 17 $\beta$  estradiol.<sup>19,20</sup> Genistein has a similar RBA for ER $\alpha$ , as tamoxifen but has a much higher RBA than tamoxifen for ER $\beta$ . However, the RBA of 4-OH-tamoxifen for both receptors is considerably higher than the RBA of genistein, tamoxifen, and even 17 $\beta$ -estradiol.<sup>19</sup> Arguably, isoflavones are more accurately classified as selective estrogen-receptor modulators (SERMs) than phytoestrogens. Although they may exert estrogen-like effects in some tissues, such as the bones,<sup>21,22</sup> isoflavones are different from estrogen. For example, they do not increase endometrial cell proliferation;<sup>23,24</sup> and, unlike estrogen, they do not increase serum triglyceride levels.<sup>25</sup>

The potential antiestrogenic effects of weak estrogen-like compounds such as isoflavones, which were first noted in mice nearly 40 years ago,<sup>26</sup> certainly provide a possible mechanism for the hypothesized protective effects of soy consumption against breast cancer. Although it is by no means evident that soyfoods exert antiestrogenic effects on breast tissue, there are multiple mechanisms by which such effects can occur. However, it is the effects of genistein on signal transduction, such as the inhibition of tyrosine protein kinase,<sup>27,28</sup> MAP kinase,<sup>29</sup> and DNA topoisomerase,<sup>30</sup> which appear to be responsible for the *in vitro* inhibitory effects of this isoflavone on cancer cells.<sup>31-35</sup> For these reasons, even classifying isoflavones as phyto-SERMs is probably an incomplete characterization.

### Soy Intake and Breast Cancer Prevention

Findings published in 1990 showed that the addition of soy protein to a typical laboratory diet significantly decreased chemically induced rat mammary cancer.<sup>36</sup> This finding and the low breast cancer mortality rates in Asian countries<sup>37</sup> were two key observations that first convinced the NCI to allocate funding for research on the anticancer effects of soy.<sup>12</sup> Since then, the relation-

ship between soy intake and breast cancer risk has been intensely investigated.

**Animal and epidemiologic data.** The animal data are somewhat inconsistent. However, they generally show that the substitution of soy protein for casein (the reference animal protein used in rodent diets) and the addition of isolated isoflavones to a standard laboratory diet reduces chemically induced mammary tumor multiplicity (the number of tumors per rat) by 25% to 50%, although incidence (percentage of animals with tumors) is much less often affected.<sup>36,38-42</sup> Several studies also have noted increases in tumor latency (ie, average time to first tumor).<sup>43</sup> In contrast, despite low breast cancer mortality rates in Asia, there is little epidemiologic evidence from case-control or prospective studies supporting the hypothesis that adult soy intake reduces postmenopausal breast cancer risk. Nonetheless, there exists some modest support for a protective effect against premenopausal breast cancer.<sup>44</sup> A few widely publicized case-control studies involving Western subjects did find soy intake or urinary isoflavone excretion to be inversely related to breast cancer risk, but the significance of these findings is unclear since soy intake in these studies was negligible.<sup>45</sup> The reduction in breast cancer risk in these studies may be associated with soy intake because—among Westerners—soy consumption may be a marker for a healthy lifestyle.

**Clinical studies.** Human intervention studies involving intermediate endpoints of breast cancer risk have produced mixed results. For example, Kurzer noted that although no studies found statistically significant effects, 7 of 8 reported a trend toward an increase in menstrual cycle length;<sup>46</sup> longer cycles are associated with a reduced breast of cancer.<sup>47</sup> Also, several studies found a decrease in urinary estrogens and increased ratios of urinary 2-(OH) to 16 $\alpha$ -(OH) and 2-(OH) to 4-(OH) estrogens, findings that again suggest a protective effect.<sup>46</sup>

In contrast to these favorable findings, two studies suggest soy actually has estrogen-like effects on breast tissue. In one of these, Petrakis et al<sup>48</sup> found that daily soy consumption (38 g soy protein isolate, 80 mg isoflavones) over five months was associated with an increase in breast nipple aspirate fluid (NAF) secretion and breast cell hyperplasia in premenopausal women. Previous epidemiological research by these investigators showed that nonlactating women who can secrete breast fluid are at an increased breast cancer risk compared with those who cannot<sup>49</sup> and that abnormal NAF cytology is associated with a further increased breast cancer risk.<sup>50</sup> However, this study did not include a control group, and fluid secretion continued to increase even after soy consumption was discontinued. This suggests that repeated nipple aspiration may have contributed to the putative effect.

In the other study of biopsies taken from premenopausal women who consumed 60 g textured soy protein containing 45 mg isoflavones for two weeks, the expression of two proteins, pS2 and apolipoprotein D, found in breast cells were up-regulated and down-regulated, respectively, which is similar to the effects of estrogen. However, there was no effect of soy on estrogen and progesterone receptor status, apoptosis, mitosis, or Bcl-2 expression or cell proliferation. Consequently, although the authors of this study concluded that soy exerts a weak estrogenic effect on breast tissue, they also noted that the long-term implications of these effects were unclear. Certainly, the short duration of this study is a major limitation, since two weeks may not be sufficient for antiestrogenic and/or antiproliferative effects of soy to become evident. Furthermore, *in vitro* genistein was found to increase pS2 levels in estrogen-receptor positive (ER+) MCF-7 breast cancer cells at the same concentration at which growth was inhibited.<sup>15</sup>

Recently, two laboratories examined

the effect of isoflavone supplements on breast tissue density. (Neither study has been published in full manuscript form.) Mammographic density appears to be an excellent short-term marker of the effect on the breast of potential preventive interventions for breast cancer.<sup>51-53</sup> In one study, 175 women aged 49 to 65 with Wolfe's P2 or DY mammographic patterns were randomly assigned to receive either 40 mg isoflavones derived from red clover or placebo for one year. There were no significant differences between the isoflavone and placebo groups overall; but when subjects were divided into tertiles of age, breast tissue density significantly decreased ( $P < 0.05$ ) in women between the ages of 56-65 who received isoflavones, whereas women of the same age who received a placebo had a slight, but insignificant, increase. In the second study, 34 premenopausal women were randomly assigned to receive either 100 mg isoflavones (derived from soy) or placebo for one year. No differences in breast tissue density were noted between groups.

These two studies show that in contrast to EPT, isoflavones do not increase breast tissue density.<sup>54</sup> It should be noted that this discussion does not detail the work of Dr. Gertraud Maskarinec, which really should be mentioned. Her findings on soy and mammographic density, which are published in the peer-reviewed literature, show interesting ethnic differences.

Early soy intake. There is considerable interest in the possible protective effects of early soy consumption on adult breast cancer risk. This hypothesis is particularly intriguing because migration data indicate that early life events greatly influence breast cancer development in adults.<sup>55-57</sup> For example, Lamarinere and colleagues have shown consistently that exposing rats to oral or intravenous genistein for brief periods during the perinatal and prepubertal periods reduces chemically induced mammary tumor multiplicity by approximately 50%.<sup>58</sup> These investigators have

found that genistein inhibits mammary cancer when the compound was given to adult animals that were exposed to it while they were young. Recently, Badger has confirmed the findings of Lamarinere and colleagues using isolated soy protein.<sup>59</sup> These authors have shown that exposure to isoflavones causes breast tissue differentiation and reduces the number of terminal end buds, the anatomical structure within the rodent mammary gland that is the likely site of tumor development.<sup>58,60</sup>

Two recently published epidemiologic studies support the migration data and animal research. One showed that Chinese women who consumed an average of approximately 11 g of soy protein per day during their teenage years were 50% less likely to develop breast cancer, compared to women who rarely consumed soy during this period of life.<sup>61</sup> Soy consumption during adulthood did not affect these findings. In the other study, which involved Asian Americans, soy intake reduced breast cancer risk by 35% in women who consumed soy throughout their lives but was not protective in women only consuming soy during adulthood.<sup>62</sup>

Overall, the data are equivocal as to the question of whether adult soy intake reduces breast cancer risk. Clearly, without epidemiologic support it will be difficult to present a convincing case that adult soy intake is protective. Short-term clinical trials utilizing intermediate endpoints, such as breast tissue density, may continue to provide important insights. In the meantime, the most intriguing—but still highly speculative—hypothesis is that early soy intake reduces breast cancer risk later in life. Epidemiologic findings suggest the consumption of relatively little soy during teenage years (approximately 1 to 2 servings per day) is sufficient to markedly reduce adult breast cancer risk.

#### **Does Soy Increase Breast Cancer Risk or Cancer Recurrence in Breast Cancer Patients?**

In vitro genistein exerts a biphasic

effect on the growth of ER+, but not ER-, breast cancer cell lines.<sup>63-65</sup> At concentrations between 10 nM and 1  $\mu$ M, growth is typically stimulated, whereas at concentrations above 10  $\mu$ M growth is markedly inhibited. At lower concentrations, the estrogen-like effects of genistein predominate; whereas, at higher concentrations, the effects of genistein on signal transduction come into play and result in growth inhibition.

In theory, these in vitro findings suggest caution in the use of soyfoods because the lower concentrations represent physiologic levels. In serum, most genistein is conjugated and biologically inactive, whereas the in vitro concentrations refer to unconjugated genistein. However, not only do in vitro conditions not accurately reflect in vivo conditions, but Dalu et al also found that dietary genistein down-regulated epidermal growth factor receptor expression in the prostate despite genistein prostatic concentrations in the low nanomolar range.<sup>66</sup> Thus, it appears that genistein actually is more potent in vivo than would be expected on the basis of the in vitro data.

**Animal Studies.** Hsieh and colleagues conducted the one animal study primarily responsible for raising concerns about the possible estrogenic effects of soy on breast tissue.<sup>64</sup> In this study, dietary genistein markedly stimulated the growth of mammary tumors in athymic ovariectomized mice implanted with MCF-7 cells. In a follow-up study, isolated soy protein containing graded amounts of genistein produced similar effects as isolated genistein.<sup>67</sup> In contrast, Shao et al<sup>68</sup>—using very low doses (0.1-0.5 mg/kg body weight) of genistein injected subcutaneously—and Zhou et al<sup>69</sup>—using dietary genistein (the glycoside form of genistein)—observed tumor inhibition in intact nude mice given estrogen pellets and orthotopically implanted with MCF-7 cells.<sup>69</sup> Although still speculative, these rodent studies collectively suggest that in a low-estrogen environment

genistein is estrogenic and has a proliferative effect on breast tissue, while it has an antiproliferative and possibly antiestrogenic effect in a high-estrogen environment.<sup>64,67,68</sup> It is not clear which model is most applicable to humans. Although serum estrogen levels differ markedly between pre- and postmenopausal women, locally produced estrogens are thought to drive breast cancer cell growth.

**Study observations.** As noted by Messina and Loprinzi<sup>9</sup> and others,<sup>70</sup> considerable evidence indicates that at least in regard to breast cancer development in healthy women, the combination of hormones—not estrogen alone—increases breast cancer risk. If correct, this notion is potentially significant to the soy-breast cancer controversy because neither soy nor isoflavones have progesterone activity.<sup>71</sup> Evidence includes the observations that, compared to estrogen alone, the combination of estrogen and progesterone is associated with greater breast tissue density,<sup>51,72-74</sup> as well as increased breast<sup>75</sup> and mammary<sup>76</sup> cell proliferation. This same evidence also suggests that breast cell replication is four times greater during the luteal phase of the menstrual cycle when endogenous serum progesterone levels are high, compared to the follicular phase when progesterone levels are low.<sup>77</sup>

In addition, several epidemiologic studies have found that estrogen alone increases breast cancer risk only slightly, or not at all, whereas the combination of hormones markedly increases risk.<sup>78-81</sup> Finally, the most telling observation may prove to be the results from the Women's Health Initiative (WHI). In this trial, breast cancer risk was increased in women receiving both estrogen (0.625 mg/d of conjugated estrogens) and progestin (2.5 mg of medroxyprogesterone acetate), whereas no increase in breast cancer risk has been observed in the estrogen-only arm of this trial thus far.<sup>82</sup> However, this arm of the WHI is still underway; and final results regarding breast can-

cer will not be available for some time.

Despite the theoretical basis and some *in vitro* and animal support, overall evidence suggesting that soy intake increases risk of breast cancer in high-risk women or increases recurrence in breast cancer survivors is unimpressive.

### **Soy, Isoflavones, and Tamoxifen: Are There Clinically Relevant Interactions?**

Treatment outcomes of Asian breast cancer patients typically are better than those of U.S. women, even after controlling for stage of diagnosis.<sup>83-86</sup> Nevertheless, there is some concern that isoflavones may inhibit the efficacy of tamoxifen. Certainly, there is a biological basis for such speculation since both isoflavones and tamoxifen compete for binding to estrogen receptors. Jones et al found that *in vitro* genistein inhibited the effects of tamoxifen on the growth of T47D ER+ breast cancer cells.<sup>87</sup> In contrast, in MCF-7 cells<sup>88</sup> and MDA-MB-435 cells,<sup>89</sup> an ER-cell line, genistein enhanced the effects of tamoxifen.

Several investigators have examined the combination of soy and tamoxifen on mammary tumor growth in rodents. Most importantly, Ju and colleagues reported that genistein negated by about 60% the inhibitory effects of tamoxifen on mammary tumor growth in ovariectomized athymic mice implanted with MCF-7 cells.<sup>90</sup> In contrast, the fermented soy product miso acted synergistically with tamoxifen to inhibit N-nitroso-N-methylurea-induced rat mammary tumor multiplicity and incidence,<sup>91</sup> and isolated soy protein acted in an additive manner with tamoxifen to inhibit the development of 7,12-dimethylbenz[a]anthracene (DMBA) induced mammary tumors.<sup>92</sup>

There is some question about the applicability of these findings to breast cancer patients, since these models specifically address effects on tumor development. However, researchers also have found miso to enhance the efficacy of tamoxifen on the growth of existing tumors. At the same time, the

combination of miso and tamoxifen inhibited the growth of existing DMBA-induced mammary tumors by 15%; whereas in control rats and in rats given tamoxifen only, tumors grew by 41% and 60%, respectively.<sup>91</sup>

Although no human data on the interaction between soy and tamoxifen are available, there is limited information on the interaction between EPT and tamoxifen. In three clinical trials examining the impact of tamoxifen on breast tumor recurrence and in which a subset of the women were also taking EPT, no negative interactions were noted.<sup>93</sup>

### **Possible Benefits of Soy and Isoflavones**

Understandably, the overwhelming concern about soyfoods on the part of breast cancer survivors is how the decision whether or not to use these products will impact their cancer recurrence and survival. Nevertheless, it is notable that there is considerable evidence suggesting soyfoods and isoflavones exert both skeletal and coronary benefits. For example, a recent one-year study found that genistein increased bone mineral density at the hip and Ward's triangle about as much as EPT and only slightly less at the spine.<sup>94</sup> Isoflavones also have been shown to enhance systemic arterial compliance<sup>95,96</sup> and may improve endothelial function,<sup>97</sup> although studies are conflicting on the latter point. Soy protein also modestly lowers serum cholesterol as recognized by the U.S. Food and Drug Administration and the American Heart Association.<sup>98</sup>

Interestingly, three short-term studies suggest isoflavones and isoflavone-rich soyfoods improve certain aspects of cognitive function, although only one of these studies has been published to date.<sup>99</sup> Results from studies examining the effects of soy or isoflavone supplements on hot flashes are mixed, but a recently published analysis found that treatment efficacy is related to initial hot flash frequency. Thus, women with frequent hot flashes may find soy

efficacious, even though no benefits were noted in two studies specifically involving breast cancer patients.<sup>100,101</sup> Finally, and importantly, there is little evidence to suggest isoflavones or soyfoods cause the adverse effects reported for EPT in the WHI and the HERS I/II.<sup>102</sup> However, it should be noted that neither soyfoods nor isoflavones have been studied in long-term clinical trials utilizing disease outcome as an endpoint; therefore, definitive conclusions about health benefits cannot be made.

The estrogen-like effects of isoflavones have led some to conclude that soyfood consumption should be avoided by breast cancer patients and women at high risk of the disease. In this author's opinion, the evidence does not warrant such restrictions. It is not necessary to advise women to stop current use of soyfoods if they develop breast cancer. Expecting women for whom soyfoods are an important part of their diet to give them up is an unnecessary burden. Although isoflavones have some estrogen-like properties, they are different from estrogen and are more accurately classified as SERMs. Furthermore, isoflavones have nonhormonal properties that likely contribute to their physiological effects.

Although one animal study did find genistein increased mammary tumor growth in ovariectomized athymic mice, other animal studies show isoflavones inhibit tumor growth in mice orthotopically implanted with ER+ breast cancer cells. In humans, two studies suggested soy exerted estrogen-like effects on breast tissue but the findings from both are difficult to interpret because of methodological issues. Therefore, any possible implications regarding breast cancer risk are unclear. Furthermore, two year-long studies, one in premenopausal and the other in postmenopausal women, did not find that isoflavone supplements increased breast tissue density. In fact, in the latter group, there was a suggestion that isoflavones were protective against breast cancer.

Finally, an impressive body of data

suggests estrogen in combination with a progestin, but not estrogen alone, increases breast cancer risk. If this proposition is true, it would suggest that soy would not increase breast cancer risk. Although there is a biological basis for concern that soyfood consumption might interfere with the efficacy of tamoxifen, overall the data actually are more supportive of soy enhancing, rather than inhibiting, the effects of this drug; but this is highly speculative.

## Conclusion

Clearly, there are insufficient data to recommend that breast cancer patients, regardless of tamoxifen use, specifically begin consuming soy solely to enhance survival. However, these women may want to start eating soyfoods because they are transitioning to a more plant-based diet or because of the hypothesized coronary and skeletal benefits of soy. This seems appropriate, but these women should be advised of both the potential risks and benefits of doing so. Evidence suggests the consumption of approximately two servings of soy per day, which provide about 15 g soy protein and 50 mg isoflavones, is sufficient to derive health benefits. ■

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