It’s Time for Clinicians to Reconsider Their Proscription Against the Use of Soyfoods by Breast Cancer Patients

Abstract: The impact of soyfood intake on breast cancer risk has been intensely investigated. This focus can be attributed to soyfoods being uniquely rich dietary sources of isoflavones. Isoflavones are classified as both phytoestrogens and selective estrogen receptor (ER) modulators. The finding that dietary genistein, the primary soybean isoflavone, stimulates the growth of existing mammary tumors in ovariectomized athymic mice implanted with ER-positive breast cancer cells has led many oncologists to advise their patients against the use of soyfoods. However, the clinical evidence indicates that isoflavone exposure has little effect on markers of breast cancer risk. Furthermore, a pooled analysis that involved 9,514 breast cancer survivors found higher isoflavone intake was associated with a statistically significant 25% reduction in recurrence over the average 7.4-year follow-up period. Given the clinical and epidemiologic data, our position is that clinicians should allow soyfood use by patients for whom soyfoods already represent a normal part of their diet, and should not discourage other breast cancer survivors from moderate consumption.

Introduction

The relationship between soyfood intake and breast cancer has been rigorously investigated for 2 decades. The presence of isoflavones in soyfoods, diphenolic molecules classified as phytoestrogens, primarily accounts for the interest in this relationship. Initial focus was on the possible breast cancer-protective properties of soyfoods; a result of the (1) low historical breast cancer incidence rates in soyfood-consuming countries, (2) increased breast cancer incidence rates among Japanese immigrants to the United States, and (3) chemopreventive properties of isoflavones observed in vitro. [1] Compelling yet speculative evidence suggests that soyfoods reduce breast cancer risk, but to derive this proposed benefit requires consumption during childhood and/or adolescence.[2]

In recent years attention has turned to the possible role of isoflavones in stimulating the growth of estrogen-sensitive breast tumors, as has been demonstrated in a widely used ovariectomized athymic mouse model.[3] As a result, clinicians generally advise breast cancer patients against regular soyfood consumption. A Canadian survey found that 25% of estrogen receptor (ER)-positive breast cancer patients stopped consuming soyfoods after receiving their diagnosis.[4] This issue is of obvious public health importance. In the United States alone, of the estimated 13.7 million Americans currently alive with a history of cancer, 41% had received a diagnosis of breast cancer.[5]

However, recently published clinical and prospective epidemiologic research questions the need for the advised restriction against soy. Also, doubts have been raised about the utility of the ovariectomized athymic mouse model for understanding the impact of isoflavones in humans. Furthermore, findings from the Women’s Health Initiative trials illustrate the uncertainty surrounding even the long-term use of estrogen,[6] as opposed to combination hormone therapy,[7] in the etiology of breast cancer. It is argued here that it is now time for oncologists and other clinicians to reconsider proscription against the use of soyfoods by women with a history of breast cancer.

Isoflavones

Among commonly consumed foods, only soybean-derived products provide physiologically relevant amounts of isoflavones. The soybean contains 12 different isoflavone isomers: the three aglycones genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone), and glycitein (7,4'-dihydroxy-6-methoxyisoflavone); their respective β-glycosides genistin, daidzin, and glycitin; and three β-glicosides each esterified with either malonic or acetic acid.[8] (Isoflavone amounts used in this text refer to the...
aglycone equivalent weights.) When all forms of the individual isoflavones are considered, genistein, daidzein, and glycitein account for approximately 50%, 40%, and 10%, respectively, of the total soybean isoflavone content.[8]

There are approximately 3.5 mg of isoflavones per gram of protein in traditional soyfoods,[9] whereas in some more modern forms of soy as much as 80% of the isoflavone content is lost during processing. On average, there are 20–30 mg of isoflavones per serving of traditional soyfoods (eg, 250 mL soymilk, 100 g tofu), and older Japanese and Shanghai Chinese individuals consume about 30–50 mg of isoflavones per day.[9]

Isoflavones have a chemical structure similar to estrogens, bind to ERs, and exert estrogen-like effects under certain experimental conditions. For these reasons, isoflavones have been classified as phytosterogens despite their many other biological mechanisms of action.[1] Genistein, which is the main circulating and best-studied isoflavone, transactivates ERα and induces estrogenic effects with $10^{-3}–10^{-4}$ less potency than 17β-estradiol.[10]

However, serum isoflavone concentrations following a high-soy meal can reach low micromolar levels,[11] thereby exceeding postmenopausal total estrogen levels by $\sim 10^3$.

In addition to being phytosterogens, isoflavones are classified as selective ER modulators (SERMs).[12] The effect of any given SERM on a specific tissue depends upon the conformational shape of the ligand-receptor complex, the ERα:ERβ ratio, and the types of co-activators and co-repressors in cells. The tissue selectivity of isoflavones likely derives from their preferential binding to and transactivation of ERβ in comparison with ERα.[12] These two receptors have different tissue distributions and can have different functions. In the breast, activation of ERβ appears to inhibit the stimulatory and proliferative effects of ERα activation.[13]

The physiological implications of the preferential binding of genistein that occurs at the molecular level at certain concentrations are not fully understood. Nevertheless, there are numerous clinical examples of isoflavones exerting effects similar to those of estrogen on some tissues[14] without effects on other estrogen-sensitive endpoints,[15] although there is very limited evidence demonstrating anti-estrogenic effects.[16-18]

Finally, as mentioned previously, isoflavones potentially exert physiological effects independent of ER binding as they, especially genistein, affect signal transduction pathways in vitro by inhibiting the activity of enzymes (eg, tyrosine protein kinase, mitogen-activated kinase, DNA topoisomerase, etc.) and regulating cellular factors that control the growth and differentiation of cells.[1] The physiological relevance of many of these properties is unclear because the in vitro concentrations at which these effects are observed are generally far higher than can be achieved in vivo. Nevertheless, there is animal[19] and clinical[20] evidence of ER-independent effects of isoflavones.

**Preclinical Effects of Genistein**

Genistein exerts a biphasic effect on MCF-7 (an ER+ human breast cancer cell line) cell growth in vitro. At physiologically relevant concentrations, the estrogenic actions of genistein result in cell growth (in an estrogen-depleted media), whereas only at much higher concentrations do the ER-independent effects of genistein on signal transduction result in growth inhibition.[3] Because the estrogenic effects of genistein are minimized in an estrogen-rich medium/environment, it has been proposed that isoflavones function as estrogen antagonists in premenopausal women and as estrogen agonists in postmenopausal women. However, this conceptual framework is probably not applicable to breast tissue. Although circulating estrogen levels in postmenopausal women are only one-third those of premenopausal women, breast tissue estrogen concentrations are similar in women regardless of their menopausal status[21,22] because of local estrogen synthesis and uptake from the circulation.[23]

The in vitro stimulatory effects of genistein on MCF-7 cells were largely overlooked until this isoflavone was also found to stimulate the growth of mammary tumors in ovariectomized athymic mice implanted with these cells. It was subsequently shown that neither daidzein nor its metabolite equol has such effects[24] and genistein is without effect on ER-negative breast cancer cells.[25] In the basic model demonstrating stimulation, after tumors reach a cross-sectional area of $\sim 30–40$ mm$^2$, the estrogen pellet, which is implanted to stimulate tumor growth, is removed, resulting in tumor regression in mice consuming a soy-free diet.[3] In contrast, after an initial period of regression, tumor regrowth occurs in mice fed a soy-free diet that is supplemented with a variety of genistein/genistin-containing products.[3]

Research from the above-described model also shows that genistein inhibits the efficacy of tamoxifen[26] and letrozole,[27] and that despite containing similar amounts of genistein/genistin, tumor growth is positively related to the degree to which the isoflavone-containing product has been processed.[28] For example, soy flour (the least processed soyfood evaluated) does not stimulate tumor growth (although it does not allow regression to occur), whereas isolated genistein stimulates tumors to a greater extent than mixed isoflavones.[28] This processing effect has helped garner support for the use of minimally processed soyfoods.

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Soyfoods by breast cancer patients but has also led to strong warnings against the use of soy (isoflavone) supplements. However, this distinction among different genistein-containing products has not been tested clinically. Such investigations are warranted given that recent evidence indicates that the “processing effect” is not applicable to humans.[29]

Clinical Research Involving Markers of Breast Cancer Risk

Numerous studies have evaluated the effects of isoflavone exposure on markers of breast cancer risk, including reproductive hormone levels, mammographic density, nipple aspirate fluid contents, and cell proliferation (Tables 1 and 2).[30,31] Agents that raise breast cancer risk, eg, combined hormone therapy, increase mammographic density[32] and cell proliferation,[33] whereas agents that lower risk, such as tamoxifen, decrease these markers.[34] As discussed below, the totality of evidence indicates that regardless of the source, isoflavone exposure does not adversely affect breast tissue.

Reproductive hormones

In a meta-analysis by Hooper et al.[35] that included 35 studies involving postmenopausal women, isoflavones had no statistically significant effects on estradiol, estrone, sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH), or luteinizing hormone (LH), although there was a small statistically nonsignificant increase (~14%) in total estradiol. While acknowledging that higher circulating estradiol levels are related to a higher breast cancer risk,[36] Huber et al.[37] pointed out that in the meta-analysis,[35] a parallel decrease in estrone levels occurred in response to soy/isoflavones. Elevated estrone levels are associated with a similar increase in breast cancer risk among postmenopausal women.[36] Thus, the opposing small and nonsignificant effects on hormone levels are likely of no relevance to breast cancer risk.

Table 1

Effects of Soy Isoflavone Exposure on Mammographic Density

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Intervention</th>
<th>Product</th>
<th>Dose (mg/d)</th>
<th>Group (n)/Age</th>
<th>Group</th>
<th>Percent Density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>Premenopausal Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maskarinec 2003[72]</td>
<td>1 yr</td>
<td>Supplement</td>
<td>76</td>
<td></td>
<td>Placebo (15)/ 43.1 ± 1.7 yr IF (15)/ 41.1 ± 3.1 yr</td>
<td>Placebo  IF</td>
<td>49.5 ± 12.6</td>
</tr>
<tr>
<td>Maskarinec 2004[73]</td>
<td>2 yr</td>
<td>Soyfoods</td>
<td>58 ± 15.8 vs 5.0 ± 6.0</td>
<td>Control (111)/ 42.8 ± 2.9 yr IF (109)/ 43.2 ± 3.1 yr</td>
<td>Control  IF</td>
<td>48.1 ± 25.2</td>
<td>43.2 ± 24.3</td>
</tr>
<tr>
<td>Hooper 2010[41]</td>
<td>26 wk</td>
<td>ISP</td>
<td>50</td>
<td></td>
<td>Control (24)/ 44.6 yr IF (23)/ 44.8 yr</td>
<td>Control difference: 2.77 IF difference: 1.01</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verheus 2008[74]</td>
<td>1 yr</td>
<td>ISP</td>
<td>99</td>
<td></td>
<td>Control (56)/ 65.3 ± 4.0 yr IF (70)/ 66.3 ± 4.3 yr</td>
<td>Control  IF</td>
<td>15.4</td>
</tr>
<tr>
<td>Marini 2008[42]</td>
<td>3 yr</td>
<td>Supplement</td>
<td>54 mg (genistein)</td>
<td>Placebo (67)/ 53.5 ± 2.0 yr IF (71)/ 53.8 ± 2.9 yr</td>
<td>Image mean index (IMI) calculated in arbitrary units. Data in graph.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maskarinec 2009[75]</td>
<td>2 yr</td>
<td>Supplement</td>
<td>80, 120</td>
<td></td>
<td>Placebo (123)</td>
<td>54.8 ± 3.6 yr IF-80 (115) 55.2 ± 4.0 yr IF-120 (120) 54.7 ± 3.8 yr</td>
<td>Placebo  IF</td>
</tr>
<tr>
<td>Colacurcil 2012[43]</td>
<td>1 yr</td>
<td>Supplement</td>
<td>60</td>
<td></td>
<td>Placebo (62)/ 55.3 ± 7.6 yr IF (62)/ 5.7 ± 7.7 yr</td>
<td>Placebo  IF</td>
<td>1.75 ± 0.85</td>
</tr>
</tbody>
</table>

IF = Isoflavones; ISP = isolated soy protein.
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The authors were unable to conclude whether the changes in FSH and LH reflect an estrogenic or antiestrogenic effect,[35] and another group of investigators has noted that longer menstrual cycles are associated with a reduced breast cancer risk.[38]

Mammographic density

Greater breast tissue density as seen in radiographic images is associated with a higher breast cancer risk after adjusting for age, parity, and body weight. Although the effects of estrogen-only treatment vs estrogen plus progestin on density are quite modest, they have been observed across studies. For example, in the Postmenopausal Estrogen/Progestin Interventions (PEPI) randomized placebo-controlled clinical trial, conjugated equine estrogen (CEE) treatment resulted in a nonsignificant increase in mammographic density of 1.2% after 1 year compared with significant increases of 3.1% to 4.8% for different estrogen plus progestin regimens.[40]

In a meta-analysis by Hooper et al.[41] isoflavone exposure did not affect mammographic density in postmenopausal women (see Table 1 for a description of studies). Two other studies not included in the meta-analysis support this conclusion,[42,43] and a third shows isoflavone exposure does not lead to abnormal mammograms (cancer, cysts, or other abnormalities).[44] In premenopausal women, isoflavone exposure modestly increased breast density by 1.83%, but due to the small effect size the authors concluded that there were no immediate implications for practice (Table 1).[41]

Nipple aspirate fluid (NAF)

In nonlactating women, nipple aspiration is a noninvasive method to obtain breast fluid and epithelial cells, and it provides information on cellular and noncellular markers of breast cancer risk. Women who produce NAF appear to be at higher risk of developing breast cancer.[45] The first study to investigate the effects of soy on NAF was a single-arm intervention among 24 pre- and postmenopausal Caucasian women that intervened with 38 grams daily of isolated soy protein.[46] Each woman served as her own control and donated NAF monthly for 6 months of soy supplementation and 3 months preceding and following the active intervention. In the 14 premenopausal women, the volume of NAF increased two- to six-fold as compared to baseline during the intervention: 11.5, 18.2, 28.4, and 32.6 mL for months 1–3, 4–6, months 7–9, and months 10–12, respectively ($P = .03$). The presence of hyperplas-
Epithelial cells in the NAF in four women during the months of soy protein intake raised concern that NAF secretors may be sensitive to soy and react with increased secretion and cell proliferation.

Studies found an increase in cell proliferation in response to isoflavones relative to the placebo. One study did find cell proliferation increased relative to baseline in premenopausal women (Table 2) (1.71 to 2.18, \( P = .04 \)).

This finding has led to cautionary statements about the use of supplements, and to a lesser extent, soyfoods. However, our view is that this study provides strong evidence that isoflavone exposure consistent with intake levels among women in Asian countries is safe.

Of the total daily 235-mg dose of isoflavones used in this study, 150 mg were from genistein, the isoflavone shown to stimulate tumors in ovariec-tomized athymic mice. This much genistein is provided by approximately 15 servings of soyfoods. And yet, neither cell proliferation nor atypia were increased in postmenopausal women, the group presumed to be most vulnerable to the proposed breast tissue-proliferative effects of isoflavones.

Epidemiologic Research in Breast Cancer Survivors

Seven prospective epidemiologic studies have evaluated the impact of post-diagnosis soy intake on the prognosis of breast cancer survivors (Table 3). The largest investigations with the longest follow-up periods are the Shanghai Breast Cancer Survival Study (SBCSS), the Women’s Healthy Eating and Living (WHEL) study, and the Life Af-ter Cancer Epidemiology (LACE) study. The Chinese investigation found that when comparing the highest soy protein intake quartile (> 15.72 g/d) to the lowest, total mortality (hazard ratio [HR] = 0.71; 95% CI, 0.54–0.92) and recurrence (HR = 0.68; 95% CI, 0.54–0.87) were reduced by approximately 30%.

The relevance of these striking findings to non-Chinese women has been questioned because of the possibility that tumors that develop in Chinese women who consumed soy early in life respond differently to isoflavones than tumors in non-Chinese women who have not been previously exposed to soy. While this question cannot be definitively answered by the current studies, protective effects of soy consumption were also found in the LACE and WHEL studies, which comprised predominantly Caucasian women who were unlikely to have consumed soy when young.

Expected, isoflavone intake in the US studies was very low, raising concerns about the utility of the data. However, because a 95th percentile isoflavone intake category was created (women in this category consumed the equivalent of about one serving of a traditional soyfood per day), both US studies were able to examine soy intake at levels comparable to those of women living in Asian countries.

Recently, Nechuta et al pooled results from the SBCSS and the WHEL and LACE studies. The 9,514 breast cancer patients in this analysis were followed for a mean of 7.4 years. When comparing the highest isoflavone intake group with the lowest (≥ 10 mg/d vs < 4 mg/d), risk of total mortality, breast cancer–specific mortality, and breast cancer recurrence were reduced by 13% (HR = 0.87; 95% CI, 0.70–1.10), 17% (HR = 0.83; 95% CI, 0.64–1.07), and 25% (HR = 0.75; 95% CI, 0.61–0.92), respectively. Soy consumption tended to reduce recurrence to a greater extent in tamoxifen users than...
in non-users (HR = 0.63 vs 0.79), ER-negative vs ER-positive patients (HR = 0.64 vs 0.81), and postmenopausal vs premenopausal women (HR = 0.64 vs 0.93), although there were no statistically significant interactions observed among these strata.

The suggestion that soy intake was more beneficial in women with a history of tamoxifen use is especially notable because the opposite would have been predicted based on the results from the ovariectomized athymic mouse model discussed previously.[26] Interestingly, in the small study by Kang et al,[63] (Table 3) not only did soy intake not affect the efficacy of tamoxifen, it enhanced the efficacy of anastrozole, another finding which contrasts with that from the ovariectomized athymic mouse model.[27]

Finally, there is a need for better understanding of the impact of soy and isoflavone exposure on the prognosis of survivors according to the different biological subtypes of breast cancer, such as those expressing human epidermal growth factor receptor-2 (HER2). The research that exists specifically with respect to tumors expressing HER2 is far too limited to use even as a basis for speculation.[64,68]

**Summary**

The evidence to date convincingly suggests that soyfoods are not harmful to breast cancer survivors. In fact, the prospective epidemiologic data suggest benefit from consuming soy after a diagnosis of breast cancer. It is noteworthy that soy intake is associated with improved prognosis in epidemiologic studies, whereas intervention studies indicate no effect of isoflavone exposure on breast tissue. It is there-

**Table 3** Description of Epidemiologic Studies Evaluating the Effects of Soy Intake on Breast Cancer Prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Follow up (yr)</th>
<th>(N)</th>
<th>Intake Assessment Period</th>
<th>Age (range or mean)</th>
<th>Pre/Post</th>
<th>ER+/ER–</th>
<th>Tamoxifen Use</th>
<th>Median IF Intake (mg/d)</th>
<th>Deaths</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyapati 2005[62]</td>
<td>China</td>
<td>5.2</td>
<td>1,459</td>
<td>Enrollment (past 5 yr)</td>
<td>25–64</td>
<td>NR</td>
<td>383/142</td>
<td>NR</td>
<td>NR</td>
<td>296</td>
<td>NA</td>
</tr>
<tr>
<td>Guha 2009[61]</td>
<td>USA</td>
<td>6.3</td>
<td>1,954</td>
<td>23 mo post enrollment</td>
<td>18–79</td>
<td>387/1,203</td>
<td>1,594/337</td>
<td>1,443/410</td>
<td>NR</td>
<td>None</td>
<td>282</td>
</tr>
<tr>
<td>Shu 2009[59]</td>
<td>China</td>
<td>3.9</td>
<td>5,033</td>
<td>6, 18, 36, 60 mo post enrollment</td>
<td>20–75</td>
<td>2,461/2,572</td>
<td>3,181/1,772</td>
<td>2,622/2,408</td>
<td>47</td>
<td>444</td>
<td>534^a</td>
</tr>
<tr>
<td>Kang 2010[63]</td>
<td>China</td>
<td>5.1</td>
<td>524</td>
<td>Enrolment (past 5 yr)</td>
<td>Range NR</td>
<td>248/276</td>
<td>447/77</td>
<td>438/0</td>
<td>25.6</td>
<td>154</td>
<td>185</td>
</tr>
<tr>
<td>Caan 2011[60]</td>
<td>USA</td>
<td>7.3</td>
<td>2,736</td>
<td>~24 mo post enrollment (range, 2–48 mo)</td>
<td>18–70</td>
<td>306/2,426b</td>
<td>NR</td>
<td>1,816/920</td>
<td>0.23</td>
<td>271</td>
<td>448</td>
</tr>
<tr>
<td>Woo 2012[64]</td>
<td>Korea</td>
<td>2.7</td>
<td>339</td>
<td>Enrollment (past 12 mo)</td>
<td>25–77</td>
<td>207/132</td>
<td>NR</td>
<td>195/144</td>
<td>~13</td>
<td>None</td>
<td>25</td>
</tr>
<tr>
<td>Zhang 2012[65]</td>
<td>China</td>
<td>4.3</td>
<td>616</td>
<td>Enrollment</td>
<td>45.7 ± 6.2</td>
<td>326/290</td>
<td>378/238</td>
<td>350/266</td>
<td>17.3</td>
<td>79</td>
<td>NA</td>
</tr>
</tbody>
</table>

ER = estrogen receptor; IF = isoflavones; NA = not applicable; NR = not reported.

^aIncludes recurrences and breast cancer–specific deaths.

^bIncludes perimenopausal and postmenopausal women.
fore possible that soyfoods have effects that differ from the isoflavone products used in the interventions and/or that breast cancer prognosis is improved through mechanisms not detected by changes in cell proliferation or breast tissue density, such as by angiogenesis inhibition.[69]

The totality of the reviewed evidence provides no basis for advising breast cancer patients, especially postmenopausal women, against the consumption of soyfoods. However, since the epidemiologic data, but not the clinical data, are supportive of potential benefits, sufficient evidence to recommend soyfoods to breast cancer patients to improve prognosis does not exist at this time. Therefore, the most justifiable position for clinicians is to allow soyfood use by patients for whom soyfoods already represent a normal part of their diet (mainly vegetarians and patients of Asian ethnicity) and not to discourage other survivors from moderate consumption. This recommendation is consistent with the position of the American Cancer Society[70] and the American Institute for Cancer Research.[71]

Finally, we acknowledge that it would be easy for clinicians to advise patients against the use of soyfoods, especially in light of the lack of definitive clinical data, to avoid any potential adverse effects on prognosis. However, this decision may deprive women of a food that has nutritional benefits, especially with respect to cardiovascular disease. Breast cancer patients need to focus on an overall healthy lifestyle, which includes diet, because substantial numbers will live for many years without recurrence and therefore are at risk for other chronic diseases related to aging. Given the lack of human evidence for adverse effects, soyfoods can be part of a healthy lifestyle for breast cancer patients and survivors.

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45.

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women

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matory tumors following ovariectomy in Sprague-


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22.


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18.

Soyfoods are consumed by many because of cultural factors, for potential beneficial effects on overall health, and for the unproven hope that they will ease menopausal symptoms in women.[1] As Messina and colleagues nicely note in their article, over the last couple of decades the pendulum has swung back and forth concerning the effect of soy on breast cancer risk. In the 1980s, soy products were on the National Cancer Institute’s list of potential chemoprevention agents, based largely on the lower incidence of breast cancer in populations in the Far East, populations well known to consume more soy products than do Western populations. Subsequently, however, soy products generated breast cancer–related fear, based on cell culture and xenograft data; this information is also nicely reviewed by Messina et al. The authors additionally note that, in the recent past, many patients with a new diagnosis of breast cancer decreased or eliminated their consumption of phytoestrogen-containing soyfoods. This change is based, presumably at least in part, on healthcare provider recommendations.[2] Newer data, supporting the notion that soy products are more safe than dangerous, are also thoughtfully reviewed by Messina and colleagues, leading them to suggest that this pendulum should swing more towards an equilibrium position.

In reaching that conclusion, the authors comprehensively discuss the available basic research and clinical data regarding isoflavones in soyfoods, including literature about both their estrogenic and anti-estrogenic effects. These data basically delineate soy isoflavones as being selective estrogen receptor modulators, much in the way that tamoxifen and raloxifene (Evista) are categorized. Noting this comparison, it is worth remembering that it took tens of thousands of patients followed for many years to get a decent understanding of the effects of tamoxifen and raloxifene as chemopreventive agents. Similar data for soy products are neither currently available nor likely to be available in the future. These data, or lack thereof, should remind us that there are marked limitations in our knowledge regarding the effect of soyfoods on breast cancer–related issues.

Messina et al also review substantial epidemiologic data from observational studies regarding the potential risks and benefits of soy products. Keep in mind, however, that even more substantial amounts of data from observational studies were available regarding hormonal therapies (including estrogen alone and estrogen/progesterone combinations), and the fact that these data did not accurately predict what we learned about hormonal therapy through the Women’s Health Initiative prospective clinical trials. Results from these trials, which were not predicted by results from prior observational studies, demonstrated that these agents did not protect against cardiac vascular disease as previously thought,[3] but, rather, increased the risk of cardiac conditions[4]; that these agents did not protect against neurocognitive disorders,[5] but, rather, increased the risk of those conditions[6]; and that estrogen alone does not increase the incidence of new breast cancers.[7,8] These data should again remind us that there are marked limitations in our current knowledge regarding long-term effects of soyfoods on breast cancer–related issues.

Understanding that they should respect the limited knowledge regarding the effect of dietary soy on breast cancer–related issues, clinicians should be careful of what they proscribe for patients. Proscribing soyfood intake for patients who prefer to ingest soyfood is not justified based on the available evidence. As another recent example of our incorrect recommendations in the not-too-distant past, we proscribed upper-extremity exercise for women at risk for developing lymphedema, while new data support that we should prescribe it.[9]

This rule about clinicians being careful of what they proscribe might take on further meaning if we look at the other side of the coin—that being, that healthcare providers should be wary of prescribing therapies that might appear to be of benefit but which have not been proven to be beneficial, noting that many such therapies are eventually proven to cause net harm. A few
8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the half-life of the bevacizumab (approximately 20 days), the potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure.

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Anti-angiogenic activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Juvenile cynomolgus monkeys with open growth plates exhibited phsyseal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of phsyseal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were anemia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehiscence, hypokalemia, and hypotension. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, rash, and fatigue.

In Study 5, patients aged ≥65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. [See Warnings and Precautions (5.8)].

Of the 1424 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 232 (19%) were age 65 or older and 43 (8%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (2.1% vs. 1.4%). [See Warnings and Precautions (5.1)].

8.6 Females of Reproductive Potential

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (0%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See Warnings and Precautions (5.16) Adverse Reactions (6.1)].

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

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examples of these phenomena are not hard to detail, and include such things as arsenic treatment for cholera; high-dose chemotherapy with stem cell rescue for breast cancer; and radiation therapy for such conditions as acne and enlarged thymus glands.

To summarize the current review article, Messina et al state that “evidence to date convincingly suggests that soyfoods are not harmful to breast cancer survivors.” We, taking a slightly more conservative stance, might have changed a couple of words in that sentence so that it would read: “The evidence to date fails to support that soyfoods are harmful to breast cancer survivors.” We agree with the authors’ conclusion that patients who are already consuming soyfoods should not be discouraged from continuing to do so.

The story is different with regard to the use of soy as a pharmacologic product. At the present time, there is not good evidence to recommend pharmacologic doses of soy for any reason, including the treatment of hot flashes.[1]

On a final note, the recommendations we make now are much in sync with those expressed in a review article about the use of soy in breast cancer survivors, written more than a decade ago.[10] The concluding paragraphs from this review, which express sentiments that continue to be true today, are as follows:

“The available data…indicate a lack of any convincing information to substantiate either of two extreme and opposing claims, each of which has been prominently and repeatedly put forth in both the lay and scientific literature…: (1) soy is protective against breast cancer and because of this should be recommended for consumption by healthy women and breast cancer patients, and (2) soy is harmful for women with a history of or at high risk for breast cancer, and because of this should be avoided by such women.

The honest response to each of these diametrically opposed claims is that no convincing data exist to support either claim. In fact, there are strongly conflicting data regarding both. As such, if women (with or without breast cancer) enjoyed partaking of soy products, then it seems quite reasonable for them to partake of them. As with most things, moderation in intake is probably wise. In this regard, Asian soy intake may serve as a general guide for Western women.”

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THE MESSINA ET AL. ARTICLE REVIEWED: OUKSEUB LEE, SEEMA A. KHAN

A Fitting Prescription for All: Whole Soyfoods as Part of a Varied Plant-Based Diet

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The review in this issue of ONCOLOGY by Messina and colleagues concisely and appropriately summarizes the clinical and epidemiological evidence that consumption of soyfoods is not associated with higher breast cancer recurrence or risk of primary cancer. Consistent with the position of the American Cancer Society and the American Institute for Cancer Research, the authors recommend that clinicians should consider soyfood consumption as part of a healthy varied diet for breast cancer patients and survivors; they describe the lack of clinical evidence for adverse effects of soy on the course of breast cancer, and point to evidence of other health benefits of soyfoods, in particular those related to cardiovascular disease. Additional available data support this recommendation.

Metabolism of Isoflavones in Rodents vs Humans

Since human and mouse studies have shown conflicting results regarding the effect of soy isoflavones on mammary tumors, Setchell et al have studied whether the phase II metabolism of soy isoflavones differs between humans and rodents.[1] Doerge et al have pointed out that phase II metabolism by glucuronidation is a major pathway for the elimination of isoflavones in humans,[2] and others have reported that humans have a high capacity for conjugation of steroid and steroid-like molecules between the intestinal tract and liver, such as endogenous estrogens, thus circulating unconjugated isoflavones remain at a relatively low level.[3] Therefore, Setchell et al provided various soyfoods, or genistein, or pure S-(-) equol to healthy human subjects (adults and infants), Sprague-Dawley rats, and multiple mouse strains: athymic nude, C57BL/6, and transgenic Angptl4β6 mice (an angiogenesis model). They then analyzed the plasma concentrations of unconjugated (biologically active) vs conjugated forms of genistein by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Strikingly, the unconjugated genistein levels in plasma were found to be 20 to 150 times higher in the rodents than in all the human subjects.[1] These data further support the contention that rodents may not be appropriate models for gaining insight into the health effects of isoflavones in humans, because it is very unlikely that the high unconjugated plasma concentrations of genistein seen in rodents would occur in humans who consume soyfoods or isoflavone supple-

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Breast Concentration of Isoflavones

Two recent studies with pre- and postmenopausal female cynomolgus monkeys suggest that dietary exposure alone of soy protein for periods of 12 to 36 months, as the human equivalent of 129 mg/d of isoflavones (containing 91-mg genistein, 31-mg daidzein, and 7-mg aglycone equivalents of glycitein) is not a significant estrogen agonist for breast tissue.[4,5] This dietary exposure did not induce proliferation in mammary tissue; instead, mammary gland proliferation (Ki67 labeling index) induced by estradiol was antagonized by soy in postmenopausal monkeys. In humans, studies of breast tissue isoflavones concentrations following exposure to dietary soy products are also reassuring. In two small trials, women undergoing aesthetic breast reductions tested a several-day intervention of soy supplementation and/or soy milk, followed by measurement of isoflavones (genistein, daidzein, and equol) by LC-MS/MS in breast tissue compared with serum and urinary levels.[6,7] Both studies found that concentrations of total isoflavones were in the subnanomolar[7] to low nanomolar[6] ranges in hydrolyzed breast tissue, whereas they were generally 100-fold higher in the corresponding serum and urine samples; thus serum concentrations may overestimate tissue exposure.

Ethnic Differences in Metabolism of Isoflavones

The majority of intervention studies have consisted of women of European ancestry, and differences in biomarkers between Asians and Europeans have not often been compared. Asian women tend to have higher mammographic density (due to the smaller breast sizes) than Caucasians,[8] and are less likely to produce nipple aspirate fluid (NAF)[9,10] but more likely to produce equol.[11] Existing data suggest that soy ingestion may have a greater association with mammographic density[12] and possibly estrogen levels in Asians[13] than in Europeans. However, low NAF production and a lack of breast tissue measurement in Asian women have made it difficult for researchers to investigate the effect of soy on local breast biomarkers. Two possible mechanisms vary across populations and appear to be important in terms of beneficial effects of soy for breast cancer patients: (1) genetic variation in the metabolism of enzymes such as cytochrome P450 or catechol-O-methyltransferase[14,15]; and (2) the timing of soy exposure, occurring in early childhood in Asian women rather than as part of adult nutrition, which is more common among Western women. Gut microbiota colonize the intestine during infancy[16] and facilitate the hydrolysis of glycosides for improved bioavailability and the formation of equol from daidzein.[17]
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making a categorical statement about the role of radiation therapy in this risk-adapted approach difficult at this time.

In summary, we need to weigh the potential risks and benefits of consolidation RT for each patient in the context of ever-evolving prognostic factors and the chemotherapy regimen used. We need to keep in mind that for the same involved field—for example, the right axilla—the risk/benefit ratio for consolidation RT is quite different when this involved field is in a 20-year-old woman compared with when it is in a 70-year-old man. We also need to consider that the therapeutic ratio of RT will continue to improve with advances in such technologies as IMRT, IGRT, and respiration-gated treatment. There will continue to be subsets of patients for whom the benefits of RT outweigh the risk, and the decision to add RT needs to be individualized for each patient. ☑

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