Point-Counterpoint: Soy Intake for Breast Cancer Patients

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Should breast cancer patients consume soy, either as soy foods or soy supplements? Postmenopausal patients, as well as patients experiencing early menopause induced by adjuvant chemotherapy, may be inclined to use soy products as a "natural" alternative to hormone replacement therapy (HRT). Others may be motivated to consume soy products based on the belief that they may improve their prognosis or prevent a recurrence. Such beliefs lack the support of clinical data, as relatively few studies of soy have yielded information relevant to individuals diagnosed with breast cancer. Moreover, concern has arisen over a potential adverse impact of soy intake by breast cancer patients because of the estrogen-like effects of the isoflavones, notably genistein and daidzein, contained in soy. Estrogens have been linked to breast cancer promotion and progression, and some preclinical studies suggest that soy or its isoflavones may indeed increase proliferation of breast cancer cells. Other laboratory research indicates, however, that genistein and daidzein exert a wide range of anticancer activities as well.

The estrogenic effects of soy have led to controversy among both researchers and health professionals over the use of soy (and particularly soy-derived supplements) by breast cancer patients. Dr. William Helferich, an associate professor of nutrition at the University of Illinois, has publicly expressed concern that postmenopausal women with estrogen-dependent breast cancer may be harmed by soy supplements. Dr. Gregory Burke, chairman of the public health sciences department at Wake Forest University School of Medicine in Winston-Salem, North Carolina, is worried that women may overdose on isoflavone pills, which may provide doses up to 10 times as much as women consume in Japan. Dr. Daniel Sheehan, a research biologist at the Food and Drug Administration’s National Center for Toxicological Research in Jefferson, Arkansas, contends that there are different degrees of susceptibility in different organs, depending on age, and that consequently the same individual may show both beneficial and adverse outcomes. Such intense debate has caused considerable perplexity and consternation among breast cancer patients currently undergoing treatment, as well as among postmenopausal survivors.

Unfortunately, human studies of soy and cancer have focused primarily on prevention, not treatment. Soy is thought to play a role in the low rates of breast cancer seen in Asian populations, in which soy consumption is an order of magnitude higher than in Western populations. One meta-analysis of observational studies in Asia and the United States concluded that increased soy consumption is associated with a 20% reduction in the risk of breast cancer in premenopausal women, while having no effect in postmenopausal women. In the 2 U.S. studies to date, median soy intake levels were so low that they may only have been a marker for healthier eating patterns in general. The remaining studies were conducted in Asia, where soy is consumed from early childhood. Asian women living in their native country are exposed to soy’s effects in the critical adolescent years of breast development. In animal studies, neonatal and early-life exposures to soy genistein prevented the development of dimethylbenz[a]anthracene (DMBA)-induced mammary adenocarcinomas, whereas exposure in adulthood had little or no effect. During the 1990s, Coral Lamantiniere of the University of Alabama and Leena Hilakivi-Clarke of Georgetown University independently postulated that during this early-life period, the estrogenic effects of soy may stimulate breast cells to differentiate in a manner that protects them against carcinogenic agents.
The arguments of Lamartiniere and Hilakivi-Clarke suggest that soy may be helpful if consumed in early life, but confer no benefit if consumed later in life. This line of argument, however, does not rule out a possible therapeutic effect of soy after tumors have already developed; nor does it rule out the possibility that soy could help prevent the recurrence of tumors following cytoreduction. In this latter regard, animal studies have indicated that soy may magnify the chemopreventive effects of tamoxifen. Andreas Constantinou and colleagues recently reported that the incidence of DMBA-induced mammary tumors was reduced 29% with tamoxifen, 37% with soy protein isolate, and 62% by the combination; tumor latency increased only in the combination group. In contrast, the evidence from in vitro studies has been mixed, with some studies suggesting synergism and others indicating antagonism between soy and tamoxifen.

Several mechanisms have been proposed for the cancer-inhibiting effects of soy, including inhibition of tyrosine kinase, inhibition of DNA topoisomerase, inhibition of cell cycle progression and angiogenesis, and antiestrogenic effects (competition with estrogen for binding to receptors). Soy genistein may prevent metastasis by down-regulating the production of matrix metalloproteinases (MMPs) or up-regulating MMP inhibitors. The precise dosage of soy needed to modulate these different mechanisms remains unknown, although many researchers believe that very high, supraphysiologic doses are needed for maximal effects. The question of soy's interaction with other estrogen-modulating components of the diet (e.g., fat, fiber, indole-3-carbinol) merits attention as well.

Given the range of potential therapeutic effects, do concerns with regard to the estrogenic effects of the soy isoflavones have merit? Should breast cancer patients be consuming soy? How do soy researchers reconcile the well-substantiated chemopreventive properties of soy foods with the apparent ability of soy isoflavones to stimulate the growth of breast cancer cells?

Scientists concerned about soy use also conclude from the data on stimulation of breast cancer cells, animal tumor growth and weak estrogenic effects of soy in humans that cancer patients have reason to be concerned about soy use. Recommendations by these scientists include such cautions as avoiding consumption of soy isoflavone supplements and avoidance of soy by women who do not have cancer but are at high risk for estrogen receptor positive (ER+) cancer. According to these recommendations, cancer patients who have not previously consumed soy would not increase soy intake as part of a cancer treatment program. Although women who already consumed soy before breast cancer diagnosis may continue to include it in their diets.

The question of whether to consume soy continues to plague women with breast cancer and to baffle physicians who would like to support their patients' self-care choices in a way that promotes, than impedes, recovery from cancer. In our Point-Counterpoint feature this issue, we explore several dimensions of the controversy based on opinions from researchers who have investigated the potential effects of soy and considered its impact on women with breast cancer. We will consider data indicating that soy consumption may affect the course of malignant disease and thus the survival of breast cancer patients. We provide responses of several soy researchers and clinicians to specific questions with regard to the possible impact of soy after a diagnosis of breast cancer. Some of the panelists provided a written response to the questions that included citations. Others elected to respond either verbally or in writing without citing the medical literature. The resulting roundtable discussion provides a diverse range of perspectives. An integrative clinical perspective follows the individual responses.

—Keith Block

Question 1:

What is your (brief) assessment of the state of research on the estrogenic effects of soy at this time?

Constantinou: We are only beginning to understand the diverse estrogen-modulating effects of soy and its components in a variety of tissues. We've identified a surprisingly large number of biological responses that can be modulated by soy and its main components. The main components of soy are the soy isoflavones genistein and daidzein, saponins, Bowman-Birk protease inhibitor, and phytic acid. Processes that are modulated at the cellular level are cell growth and differentiation, cell cycle progression, and expression of estrogen responsive genes. In rodents, soy prevents carcinogen-induced mammary tumors, prostate cancer, and colon cancer. At the human level, soy is known to alter hormonal levels and change the menstrual cycle in women. Apparently, studies suggest that soy may reduce the frequency and severity of symptoms associated with menopause including osteoporosis and hot flashes. Soy clearly provides cardiovascular benefits in both men and women, and it may also reduce the risk of breast cancer in women and prostate cancer in men. Despite all these effects of soy foods such as soy protein isolate, soy milk, and tofu, it is presently not clear whether these benefits are due to specific components of soy (i.e., isoflavones).

In a recent set of studies submitted to Nutrition and Cancer, there were significant effects of dietary soy in the form of soy protein isolate (SPI), with or without isoflavones, for preventing mammary tumors. This
suggests that, rather than the isoflavones, other components contained within soy may be responsible for the antitumor effects. Alternatively, a combination of isoflavones and other dietary components (either from soy or nonsoy sources) may be needed. We should not underestimate the effects of isoflavones, particularly daidzein, which seems to have a stronger effect than genistein. At the present time, I'm carrying out in vivo studies as well to evaluate the effects of either genistein or soy protein, to see whether the growth of mammary tumors can be suppressed. So far, however, we've seen only marginal effects on the prevention of mammary tumors. Effects on existing tumors are even less clear.

Hilakivi-Clarke: Soy contains an estrogenic component genistein. At physiological concentrations, genistein has been shown to actively bind to estrogen receptors. The implications of this activity are unclear, however, because soy foods also contain many other components that might interfere with genistein's estrogenic properties. Thus, we do not yet know how soy products, as food, might affect women with breast cancer. That is to say, we don't know whether it will have an estrogenic impact or not.

Hughes: The estrogenic actions of the isoflavones in soy are reasonably well understood. These compounds are weak agonists at the ER-β and moderate agonists at the ER-α. The key to understanding the target tissues of actions of isoflavones will be to discern the intracellular signaling pathways mediated by these estrogen receptors and potentially other nuclear or nonnuclear receptors in people who have breast cancer. Isoflavones should be expected to be weak estrogenic agonists.

Tice: Soybeans contain isoflavones, phenolic compounds that are structurally similar to estradiol, bind to estrogen receptors (ERs), and have higher relative binding affinities for ER-β than for ER-α. Thus, soy has the potential to have either estrogenic or antiestrogenic effects. However, there are few data documenting estrogenic effects of soy on humans at this time. Most studies have found no effect of soy protein or isolated isoflavones on the vaginal maturation index, a measure of estrogenic effect on vaginal mucosa. Other studies have found no effect of soy on the endometrium. However, there is evidence that soy affects both menstrual cycle length and hormone levels in menstruating women. Furthermore, 3 studies have suggested modest estrogenic effects of soy on the breast. The data on relief of hot flashes is mixed, with some studies reporting a modest beneficial effect and others reporting no benefit compared with placebo.

Tripathy: It's always difficult to extrapolate from laboratory or epidemiologic research to clinical practice. The epidemiologic studies indicate that younger women are at lower risk of developing breast cancer if they eat more soy. The question is whether that research has any clinical relevance, and specifically whether soy would modify the risk of breast cancer recurrence in a woman who already has cancer. Consider the case of estrogen. We know that estrogen replacement therapy or oral contraceptives for 10 years or more is associated with a higher risk of getting breast cancer. But if you've already been diagnosed with breast cancer, we don't know whether either estrogen replacement therapy or oral contraceptives increase your risk of recurrence. The small studies that have been done so far suggest this is not the case. The first point, then, is it's difficult to extrapolate epidemiologic studies of primary prevention onto the clinical goal of secondary prevention. We need clinical trials to actually demonstrate that effect.

The second general area is this whole question of how to interpret laboratory data in terms of the estrogenic potential of some of the compounds in soy—the isoflavones genistein and daidzein—and again translate this into something of clinical relevance. The conservative view is that we simply don't know the impact of soy, either at normal or very high doses. We don't know whether moderate or high doses of soy protein are helping or possibly harming the patient with breast cancer. In the absence of prospective randomized trials, it's difficult to make any clinical recommendations for breast cancer patients.

In some cell culture studies, high doses of soy protein have shown stronger anticancer effects than low doses, which appear to be either ineffective or growth-stimulatory. One also sees this bimodal effect with serum estradiol. That is, with very low concentrations you have growth, whereas high concentrations give you growth inhibition. Because phytostrogens are bound by proteins, however, it's unlikely that even very high doses will have a substantial effect. (Estradiol and other estrogens are bound to proteins as well.) The effects that you see with phytostrogens in vitro appear to be greatly attenuated in vivo.

**Question 2:**

Are soy foods safe for postmenopausal breast cancer patients in moderate amounts? How about for premenopausal patients?

What can we say about safety with regard to estrogen-receptor status (ER+ vs. ER−) in these 2 groups of patients?

Are there doses that you feel are safe/unsafe?

**Constantinou:** The epidemiological data suggest that consumption of soy products is safe. Asians regularly consuming soy products have substantially lower rates of breast and prostate cancer than people from the West consuming diets that are devoid of soy. The risk associated with high soy intake is probably about 25% less for breast cancer and possibly the same for prostate cancer. Only a few studies evaluated the effects of soy diets in non-Asians. With respect to human intervention studies, unfortunately, the data are not very strong. There is definitely an effect of soy diet on hormonal levels, and you will see what appear to be estrogen-modulating effects. Patients' estrogen levels, menstrual cycle patterns, and excretion of harmful
estrogen metabolites will change in a favorable direction in terms of lowering breast cancer risk. The data have been focused mainly on evaluating tumor markers and hormonal levels. Although intervention data indicate that soy diets alter hormonal levels in both men and women, studies of tumor markers are inconclusive and conflicting. In a pilot study by Petrakis and colleagues, Western women eating soy showed a higher proliferative index as measured by nipple aspirate. Other studies indicate that proliferative markers actually decrease, which of course would be protective. We are currently studying the effects of soy on nipple aspirate in a more controlled way. The Petrakis study had several design problems that seriously limit our interpretation because they compromise the reliability and validity of the findings.

With respect to ER status and safety, there are no data at present in human populations, at least to my knowledge. The general thinking at this time is that if you’re an ER+ breast cancer patient, you shouldn’t take soy products because genistein in soy acts as an estrogen and is going to increase the proliferation of tumor cells. Frankly, I think the premise that ER+ cancer patients may be placed at a higher risk by eating soy products is narrow minded. This thinking is based rather simplistically on the estrogenic effects of soy genistein. However, we have to consider the 2 main types of estrogen receptors as well, namely, ERα and ERβ. Genistein binds to the ERβ with a much higher affinity compared to ERα, and the greater binding activity of ERβ may lead to biological responses that are not well understood. For instance, the genistein-ERβ complex may result in an antiproliferative (and antiestrogenic) response in tumor cells that are ERβ+. More studies are needed, because at this point we are attempting to answer the question almost entirely at a theoretical level.

Hilakivi-Clarke: We do not know whether soy foods are safe for postmenopausal breast cancer patients (or postmenopausal women not diagnosed with breast cancer). Animal data would suggest that they are not safe, but human studies have not indicated that soy intake would increase breast cancer risk. Findings obtained in animals with intact ovaries (premenopausal) suggest that soy is either protective or has no effect. Human data clearly indicate that premenopausal breast cancer risk is reduced in women consuming soy.

Genistein binds preferentially to ERβ, and we do not know what the function of this receptor is. It might reduce breast cancer risk, but it might also be linked to poor prognosis. Women with ER− tumors are ERα− but may be ERβ+. Thus, at this point it cannot be concluded whether soy is “safer” in ER− compared to ER+ women.

Hughes: If a moderate amount is on the order of a serving per day or less, then I think so. When you get to multiple servings per day, it is hard to say whether it would be safe. In terms of the safety with regard to estrogen-receptor status (ER+ vs. ER−) in these 2 groups of patients, we can say virtually nothing specific. If there is concern about use of small amounts of a potent estrogen agonist (such as a small transdermal skin patch) in a patient, then the concern about the dietary intake of a moderate to large amount of a weak estrogen agonist should be comparable. If there is no concern about the former, then there is logically no concern about the latter. The dosage issue is also unclear. Nonetheless, a general interpretation can be made based on epidemiological studies of soy intake. These studies have used estimates of dietary intake from traditional diets from Asia, India, and the Middle East, and it is logical to assume that those intake levels are safe.

Tice: Our first duty to our patients is to do no harm. There are too few data to make strong recommendations. The epidemiologic data consistently suggest that women who eat large amounts of soy are at lower risk for breast cancer, but the relationship is by no means proven to be causal. Women in Asia where soy is consumed daily have a substantially lower lifetime risk of breast cancer compared to women in Western countries. However, most of the animal data suggest that exposure early in life (during the period of breast tissue maturation) appears to be critical for the protective effects of soy. As indicated above, there are data in women suggesting that phytoestrogens act like estrogens in breast tissue and increase breast epithelial proliferation, potentially increasing a woman’s risk for recurrent or new disease. Furthermore, studies in nude mice with engrafted tumors reported that genistein, the major isoflavone in soy, stimulated tumor growth. Thus, I would not recommend that women with breast cancer start consuming soy either as foods or as supplements.

The evidence to date does not suggest that women receiving estrogen replacement therapy after treatment for breast cancer are at increased risk for recurrence or a second primary. However, these studies are small, with relatively short follow-up time. Soy isoflavones may be estrogenic in the breast, but only weakly, and thus are probably safe given that estrogens at worst minimally increase a woman’s risk for tumor recurrence or a second primary tumor. Therefore, I don’t counsel women who consume soy as part of their regular diet to stop after a diagnosis of breast cancer. Dietary consumption of soy in Asia averages 20 to 80 mg of isoflavones per day (1 to 3 servings of soy foods), and this level of intake is probably safe.

There are no data to support different recommendations for premenopausal versus postmenopausal women nor women with ER+ versus ER− tumors. In vitro studies using both ER+ and ER− breast cancer cell lines show that isoflavones stimulate cell growth at low to moderate concentrations and inhibit growth at higher concentrations.

Tripathy: Soy foods would probably be safe for both premenopausal and postmenopausal patients, whether or not the tumors in question are ER+. I’ve heard mainly theoretical soft opinions against soy.
Nonetheless, I do not know of any scientist or soy researcher out there who is clamoring to get rid of soy. I don’t think you’ll find any strong arguments against it. As a food, it’s hard to argue that there would be a strong effect.

Question 3:

Are soy isoflavone supplements safe for postmenopausal or premenopausal breast cancer patients? Do you feel there is much of a difference in soy versus isoflavones in terms of possible benefits versus risks?

Constantinou: While we can say that soy isoflavone supplements have not been proven safe, we cannot infer that they are unsafe, because at the present time no epidemiological studies have been designed to answer this question. There are risks of overdosing with supplements, but clearly we do not have that information with soy protein or concentrates. When you provide a soy concentrate, my guess is that there would be no adverse effects. When you extract certain key components from the soy, they are more likely to exert negative effects as well as positive effects. The negative effects become more prominent when the soy protein isolate is not there to provide a buffer or some measure of protection.

All the components in soy that may have anticancer effects seem to be safe for human ingestion. They are not toxic, they do not make people sterile or feminized, and they do not cause reproductive failure (sterilization or infertility). Currently, there are no data on the safety of isoflavone supplements in humans. There may be risks, especially with high-dose intakes, but it’s only speculation at this point.

In terms of inducing differentiation and apoptosis, it’s generally true that a more moderate dose induces differentiation whereas a higher dose induces apoptosis. My lab demonstrated this about 4 years ago. Higher doses induce apoptosis. Differentiation is induced at between 15 and 30 micromolar, whereas apoptosis requires doses of between 50 to 150 micromolar, a pharmacological dose. We do, however, see biological effects at lower levels, related to estrogenic effects.

We’re talking about tumor cell lines specifically. There are few exceptions to the dosage issue, but not that many. I would say that about 80% of the tumor cell lines have responded to induction of differentiation of genistein.

I would like to point out that higher doses of soy, as provided by supplements, may certainly be desirable in order to achieve the higher doses needed for apoptosis. This appears to be only of theoretical interest, however, because you may never be able to attain the high levels you need in order to induce apoptosis in tumor cells. The maximum we seem to be able to attain in vivo, following oral intake, is 15 to 20 micromolar, but this is substantially lower than one needs to attain the levels needed for apoptosis. Evidently, the soy isoflavones are rapidly metabolized and broken down, so a threshold is reached fairly quickly. A potential concern here is that the 15 to 20 micromolar range may actually induce estrogenic effects, which of course would be undesirable. In other words, instead of anticancer effects, you may get cancer-promoting effects at these low levels. For this reason, taking supplemental soy may not necessarily be a good thing unless you’re receiving chemotherapy at the same time. This is because genistein shows synergies with some chemotherapy drugs. One possibility is that certain chemotherapy agents may tend to induce apoptosis more readily with adjunctive use of genistein.

Thus, the anticancer effects are only attainable at very high levels, which are unattainable unless you make certain modifications in genistein itself. Some research indicates that if you conjugate genistein to surface receptors that recognize tumor antigens, you can introduce genistein at high levels into the tumor cell, and at these high levels you can induce apoptosis. Therefore, you have to do pharmacological modification in order to introduce genistein into tumor cells at these very high levels. So of course at this point it becomes a drug issue.

Hilakivi-Clarke: If estrogenic effect is the goal (bone, etc.), then isoflavones may be more effective than soy. However, if an estrogenic effect needs to be avoided, soy is a better alternative. Most likely, postmenopausal women should not consume isoflavone supplements. In general, it is advisable to use “normal” dietary exposures rather than be exposed to a specific component isolated from a food product (carrot vs. β-carotene), and this may also apply to genistein versus soy.

Hughes: If the supplement in question actually contains what it claims, and if anything is known about the pharmacokinetics of that product, then it makes no sense to think that it matters how a molecule of a particular isoflavone was delivered to the bloodstream. I doubt there is any difference between soy foods versus soy isoflavones in terms of possible benefits versus risks for breast cancer patients.

Tice: We just don’t know. Soy isoflavone supplements may act differently from soy foods. They are riskier because women may be tempted to think that “more is better” and consume levels of isoflavones several times higher than those consumed in traditional soy-rich diets. Furthermore, if soy does prove to be effective for breast cancer prevention, it may be due to components other than those included in supplements. Soy contains many potentially bioactive compounds including phytoestrogens, calcium, fiber, protein, and fatty acids.

Tripathy: When it comes to effects of isoflavones or soy supplements, this is where you might get a bit more division. There are concerns that soy supplements could be problematic for postmenopausal women. I have one colleague [Petrakis] who found that soy increased the secretion of nipple aspirate fluid, which is a risk factor for breast cancer. He was concerned about this. But I think that dietary amounts are okay.
Although I have no strong opinion either way about ER+ or ER-, I would be more concerned with high-dose soy supplements in ER+ women. When we're talking about soy supplements, we just have to be conservative. As physicians, we have to keep in mind that above all, we don't want to do any harm.

I generally counsel my patients that, in the absence of clear data, it makes sense to avoid unphysiologic concentrations of anything—whether it's vitamins or other dietary components. I think as a rule we have to assume that there could be harm when soy or soy isoflavones are taken in concentrations that you wouldn’t get in the diet. That's when I get concerned; even though I recognize very well that the high dose might help, we can't rule out the possibility that high doses may hurt. Dietary amounts are okay, but megadose or supraphysiologic amounts of soy don't make sense. It would be important to do a study of high-dose soy concentrate, soy protein, or soy isoflavones in breast cancer patients before recommending these supplements.

**Question 4:**

Would soy foods with low isoflavone contents be safe for these patients?

**Constantinou:** I would have to say yes. Low isoflavone intake in general should be safe. Now, I cannot say whether people would be better off consuming low amounts of dietary isoflavones versus high amounts, or whether people would get more protection from one than the other. The epidemiological data are only suggestive in terms of safety and efficacy because there are too many confounders in the existing studies.

**Hilakivi-Clarke:** This is not known.

**Hughes:** If a patient consumes a broad-based diversified diet and thus eats only one serving of soy per day or every other day or every third day, then isoflavone content is rather irrelevant.

**Tice:** In general, a diet with 1 to 3 servings of soy each day is probably safe for women with breast cancer, irrespective of the isoflavone content. Soy in modest amounts, as part of a low-fat diet rich in fresh fruits and vegetables, is likely to be safe and healthful.

**Tripathy:** Yes.

**Question 5:**

What would you advise about soy consumption for patients taking tamoxifen?

**Constantinou:** Fortunately, we just received 2 grants to study this issue. We will be looking at soy protein preparations with and without isoflavones to study their effects in combination with tamoxifen. We hope to be able to evaluate how the tamoxifen receptors may be affected by soy and to determine whether we can inhibit tamoxifen resistance in tumors. We obtained some preliminary animal data last year based on experiments in which we combined SPI with tamoxifen and compared them to data based on experiments with tamoxifen alone. We observed a significant reduction in tumor numbers in the combination group. Specifically, we saw a 65% reduction in tumor burden with the combination versus 39% with SPI and 29% with tamoxifen alone. So, clearly, there is an additive effect of SPI and tamoxifen. I'm not a statistician, so I can't say whether this effect is synergistic. To obtain these effects in patients, I calculate that 70 g of soy protein (as SPI) would be sufficient to provide the benefit with tamoxifen. People in Southeast Asia are consuming somewhere between 50 and 75 g at the highest level of dietary intake.

At this point, we don't know the number of years that might be needed to see a protective effect of tamoxifen. It's assumed that 5 years is the optimal amount of time, but we don't know for sure. What we do know is that, in animals, if you give tamoxifen, they eventually develop tamoxifen-resistant tumors. We'd like to know whether soy protein or soy genistein could in some way reduce the rate of tamoxifen-resistant tumors. Unfortunately, the mechanism behind tamoxifen resistance is poorly understood. We do know that tamoxifen resistance occurs more often in ER− tumors. After 1 to 2 years of tamoxifen, you begin to see tamoxifen-resistant tumors. A number of questions may be asked. Could soy combined with tamoxifen further augment the chemopreventive effects of tamoxifen? Could soy possibly reduce the required dose of tamoxifen, so that we might only need to use the lowest possible dose of tamoxifen? Some animal studies suggest that this might be the case. That would be good news for cancer patients but perhaps not all that great for the drug companies.

One final note about SPI. It may not translate into dietary consumption. SPI is an isolate of soy, but it does contain most of the original soy. It is about 90% protein. Normally, soy is about 40% protein, so this raises the protein concentration substantially. SPI is a powder that can be easily placed in beverages or turned into a bar, as some companies have already done. Finally, I'm not recommending 70 g of soy protein per day. I'm only saying that this is what can be deduced by extrapolating from the experimental and epidemiological data.

**Hilakivi-Clarke:** Tamoxifen might interact with genistein. Some studies suggest that there is a positive interaction—that is, that genistein increases tamoxifen's ability to inhibit cell proliferation. Other studies suggest that genistein may inhibit tamoxifen's action.

**Hughes:** It hardly matters. Drugs like tamoxifen are such potent antiestrogens that their actions surely abrogate any weak estrogenic actions of isoflavones.

**Tice:** Again, there are few data. One study in animals found that soy enhanced the beneficial effects of tamoxifen. In vitro data demonstrate that the binding affinity of tamoxifen for estrogen receptors is
much higher than that of soy isoflavones, suggesting that soy should have no significant effects in the setting of tamoxifen therapy (assuming that the soy acts through isoflavones interacting with the estrogen receptor). I would not encourage a woman already consuming soy to change her diet, nor would I recommend that women on tamoxifen add soy to their diet. To date, the evidence suggests no harm, but we need careful studies to look for interactions between tamoxifen and the constituents of soy.

Tripathy: In terms of tamoxifen, again, dietary amounts are probably okay and may even support the effects of tamoxifen. I recognize that soy in some women may help reduce hot flashes, although a recent study by Charles Loprinzi of the Mayo Clinic did not show any benefit in reducing hot flashes. In a subset of women, however, there may be an effect. Right now, it’s all trial and error. So if people want to take it for symptoms, they should take dietary amounts. If they want to include it in their diet, there should be no problem.

**Question 6:**

Do you have any suggestions for physicians who would like to begin incorporating soy into the clinical decision-making process?

Constantinou: I firmly believe we have an obligation to present our research to the general public, especially in situations such as this that have a direct impact on lifestyle and health. The data may never be conclusive. We have to present our knowledge even if much of the information has limited rigor, because it lacks the backing of randomized clinical trials. We have to go with the best available evidence and make some educated guesses. If you are a physician counseling a woman with breast cancer, and she wants to do something more than just chemotherapy and wants to do something to possibly reduce her risk of recurrence, you can go 1 of 2 ways. You may say to her simply, “I have no answer for you.” Or you may say that soy may be an option for you, it may help prevent the risk of recurrence. The possibility that it does prevent recurrences is worth trying now, in the clinical setting, in order to save lives.

Hughes: There is still no reason to think that there is any dietary advice superior to that of advising patients to eat a broad-based diversified diet that is not dominated by some tiny number of food items. There are many different healthful compounds in foods that are not isoflavones and do not occur in soybeans.

Hilakivi-Clarke: We do not know whether starting soy intake after being diagnosed with breast cancer is safe. No recommendations can be made at this time.

Tripathy: I do think that practical recommendations for soy can be made. One can look at theoretical data and say that, as much as we can tell, low doses of soy are not going to have a detrimental impact, and may even have a helpful impact. The effects of high doses of soy protein, in contrast, are completely unknown. We don’t know to what extent these high doses would influence estrogen receptor biology.

At this point in time, then, I would recommend against soy supplements across the board, as a group, because the effect could go either way—it could be helpful or it could be harmful. So whether or not the woman is premenopausal or postmenopausal, whether or not her breast tumor is ER+ or ER-, I feel she should avoid soy supplements unless she’s part of a clinical trial. In that case, I think the intervention should include a high-dose component in order to see which way the effect goes, and I believe it’s likely that there would be an effect. We just don’t know the direction of that effect. Without doing the study, we’re operating in the dark here. My approach is to be cautious.

Finally, we do know that there’s reasonably strong evidence that higher circulating estrogen in postmenopausal women increases the risk not only of getting cancer but of having a recurrence of cancer following initial efforts at cytoreduction. If you gain weight after getting cancer, this is counterproductive because your estrogen and insulin levels will tend to rise. If a patient is obese, she may want to work on losing weight. So I do strongly encourage women to maintain an ideal weight. If you’re using diet to lower or manage weight, then a low-fat diet makes sense. The exact dietary composition in terms of fat, however, is still a bit controversial because of the problem of cachexia in advanced-stage cancer. With advanced metastatic breast cancer, the caloric intake has to be watched carefully, and that usually means more liberal intake of dietary fat. But at this point, the main focus should be on maintaining normal weight with exercise and a low-fat diet in women who are not experiencing cachexia.

**Integrative Clinical Perspective**

Examining the responses to our questions by the panel of experienced researchers and clinicians who have authored this article is a valuable—and challenging—exercise in the assessment of controversy and consensus in the area of soy and breast cancer. Soy is a food that is of great interest, and potential value, for patients in integrative cancer care. Most integrative practitioners counsel vegetarian or semivegetarian diets, or at least some reduction in intake of specific meats. Soy has to be regarded as an important component of vegetarian diets: soy foods in general are easy to cook, soy is a good protein source, and the versatility of soy allows it to take the form of everything from sandwich “meats” to powders for incorporation into smoothies and shakes. Soy may contribute to the management of hot flashes that are problematic for women undergoing natural or treatment-induced menopause, although this effect is not completely supported in the litera-
ture; the apparently beneficial impact on bone makes it an attractive option for patients who are concerned about osteoporosis. Thus, for a variety of reasons, soy foods could play a productive role in the diets of women with breast cancer.

The Estrogenicity of Soy

Even with all these potential benefits, soy would, in fact, be the wrong choice for breast cancer patients if it promotes cancer recurrence, as those concerned about the estrogenic effects of soy have warned. Our panel of researchers points out both the reality of the estrogenic effect and the clinical context of that effect. The soy isoflavones genistein and daidzein are known to bind to estrogen receptors. Genistein is a weak agonist of ERα and a moderate agonist of ERβ. Genistein increases the proliferation of estrogen-sensitive breast cancer cell lines in the laboratory; several in vitro studies have also reported biphasic effects in which growth is stimulated at low doses but suppressed at high doses. These data surely do give pause to women with estrogen-receptor positive cancers, especially postmenopausal women whose endogenous estrogen levels are low.

Our panelists point out, however, that the relevance of these in vitro studies is less clear in the context of humans, where soy might play either estrogenic or antiestrogenic roles. Soy has been shown to increase menstrual cycle length, to reduce circulating estrogen levels, and to reduce excretion of potentially tumor-promoting estrogen metabolites. Soy protein isolate contributes to tumor prevention in animal studies. Soy does not affect the vaginal mucosa or endometrium, indicating lack of estrogenicity in these tissues. But 3 studies have shown evidence of some weak estrogenic effect on the breast. Two of these, by Petrikas et al. and McMichael-Phillips et al., found evidence of increased breast cell hyperplasia and increased DNA synthesis in breast cells in studies where women were fed genistein-containing products, but the third, by Hargreaves et al., found no effect on cell proliferation. Because of questions about the experimental design of these studies, the estrogenic effect of soy on breast cells must still be regarded as not having been fully validated.

Our panelists also point out that soy contains other substances besides genistein that may have anticancer effects. In fact, genistein itself has other activities that may play an important role in inhibiting the growth of breast tumors. Genistein may inhibit the activity of estrogen-metabolizing enzymes necessary for estradiol secretion from the ovaries in premenopausal women. This may account for the estradiol-lowering effects of a soy-supplemented diet. It may also inhibit enzymes that participate in the reduction of estrene to estradiol in adipose and other tissues. Genistein may also suppress growth of breast cancer cells stimulated by estrogen and other growth factors associated with breast cancer. Finally, it should be noted that even if soy or genistein have clinically significant estrogenic effects, it is not certain that giving estrogen to breast cancer patients, such as would be done in hormonal therapy, increases the risk of cancer recurrence, although more studies in this area need to be done.

What can we conclude from the variety of sometimes conflicting data our panel has reviewed? We certainly must admit that much remains to be done in determining the health benefits and risk of soy phytoestrogens. However, our panel members generally point out that harmful estrogenic effects of soy foods in humans are still not established; the many phytochemicals and other components of soy may contribute to an overall attenuation of the in vitro estrogenic activities of genistein and daidzein.

Safety of Soy Foods for Breast Cancer Patients

Our panelists agree that soy foods can be eaten as part of an overall healthful diet. Although the reports of binding of soy isoflavones to estrogen receptors raise concern mainly among ER+ patients, there are insufficient data to support distinguishing dietary recommendations depending on receptor status at this time. Premenopausal women actually seem to be at lower risk of breast cancer if they consume soy, so the level of concerns for them might be quite low. Potential concerns even for postmenopausal women consuming soy foods were not thought to be large by most panelists. A reasonable level of soy food for patients would be around 1 serving per day. An exception to this general view was expressed by one panelist who affirmed the idea that if a woman is already consuming soy as part of her diet when her cancer is diagnosed, she may continue to do so, but that patients should not be encouraged to add soy to their diets after diagnosis. Nonetheless, a majority of panelists felt that consumption of soy foods did not raise serious clinical concerns.

Safety of Soy Isoflavone Supplements

Our respondents generally felt that soy isoflavone supplements are less advisable for breast cancer patients, although one pointed out that it does not matter where isoflavones come from since they are, in fact, the same substance whether they are found in soybeans or in capsules. No epidemiological or clinical studies have been conducted on the safety or efficacy of such supplements in breast cancer patients, and our panel felt that such studies would be necessary before recommending supraphysiologic levels of these, or
other, natural dietary components. This is especially true of soy, in which activities other than the isoflavone-based estrogenicity might be important in anticancer effects.

Safety of Low-Isolavone Soy Foods
Many processed soy foods, which may appeal to patients as convenience items, are actually low in isoflavones. A database of isoflavone contents of various soy foods can be found on the Internet at the following Web site: http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html. Most of our panel felt low-isoflavone foods would be safe in reasonable quantities, although some pointed out that not much is known about such foods, and that they may lack some of the potential beneficial elements of natural soy foods. It should be pointed out that at this time, we are not certain whether the effects of soy isoflavones would be harmful or beneficial in different populations of breast cancer patients. It is conceivable that they may eventually be found to be beneficial to some or all breast cancer patients. For now, however, we must exercise caution in our recommendations of soy isoflavone preparations because it is still not clear whether isoflavones stimulate the growth of breast tumors.

Safety of Soy Use During Tamoxifen Intake
Constantinou has recently published work indicating that soy protein isolate given with tamoxifen reduced tumors in animals compared to tamoxifen alone, and has recently received funding to study this further. Other animal studies also suggest positive effects. Panelists also pointed out that because tamoxifen is such a potent drug, and because it binds to estrogen receptors more strongly than isoflavones, it would likely overwhelm any effects of isoflavone intake. Whether benefits of soy intake with tamoxifen will be established experimentally is obviously not clear yet, but there does not appear to be any directly harmful effect.

Advice for Physicians Counseling Patients
There are a number of investigators who express concerns about the use of soy. Margo Woods, PhD, an associate professor at Tufts University School of Medicine, suggests that "we can only make an educated estimation of what should be recommended to breast cancer patients at this time." Woods is particularly concerned about the biphasic response to soy, and specifically the possibility that low doses may be harmful. She contends that no one seems to know with certainty how much soy is necessary to attain the higher levels that may be required to override the potential estrogenic effects. This will need to be studied in breast cancer patients exposed to different doses and forms of soy, with careful monitoring. Until we have such research, Woods recommends that breast cancer patients consume soy foods as part of a well-designed dietary plan; isoflavone tablets and soy protein concentrates, on the other hand, should be strictly avoided.

Although one of our panelists feels that no recommendations about soy consumption can be made at this time, some other members agree with Woods's advice that soy foods can be taken as part of an overall healthy diet, although isoflavone supplements should be avoided, as they have a potential for abuse not present with soy foods. In discussing this possibility with patients, physicians need to discuss the available data with them even if it is inconclusive; soy is certainly not the only area of contemporary cancer treatment that lacks clear evidence at this time, and few physicians shrink from discussions of other controversial areas with their patients. Trials on soy foods and constituents certainly need to be done in patients who are actively combating breast cancer, and these trials may eventually help clarify this situation. In view of the overall context of both the estrogenic and the anticancer effects of soy, it does not appear necessary to prohibit soy use to interested patients.

Soy may contribute in a useful way to helping patients normalize their weight as part of a healthy, low-fat, generally vegetarian diet. Although soy is higher in fat than many other legumes and thus should be taken in limited quantities, it is lower in fat than many of the meats and other foods that it might replace in the diet. The availability of soy protein powders may also be helpful for patients with advanced disease to aid in supporting protein intake. Although the use of isoflavone supplements by breast cancer patients is generally not supported by the panel, and although there is as yet no specific evidence that soy consumption will lower the risk of disease recurrence, our panel feels that, based on current research findings, breast cancer patients who wish to include soy in healthful eating plans may do so.

—Keith Block

References


