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SOY & BREAST CANCER

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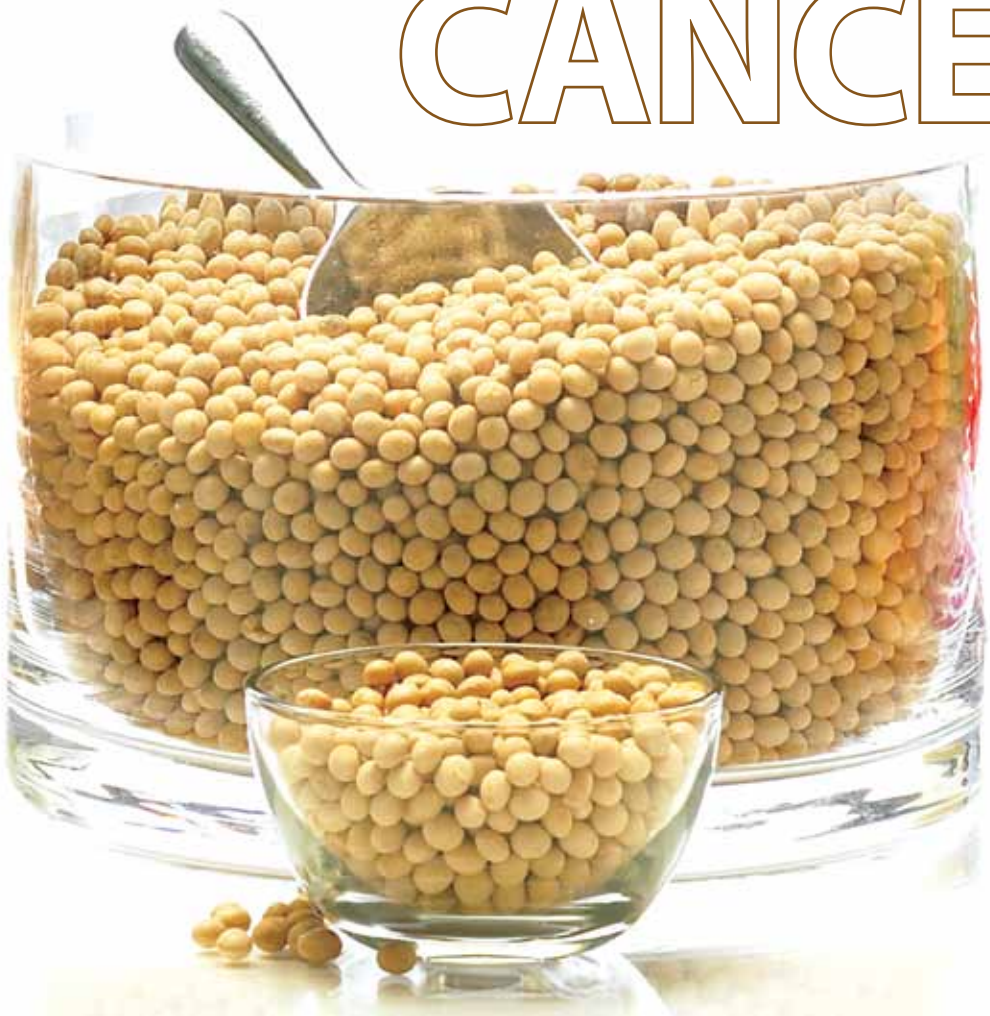

COURTESY OF THE UNITED SOYBEAN BOARD

The safety of soy foods for breast cancer patients has been in and out of the news for several decades. In this article, inform*'s Associate Editor Catherine Watkins examines current thinking.*

Catherine Watkins

Is it safe for postmenopausal women who have had breast cancer to eat soy foods?

On January 27, 2011, answering that question became much more than just an interesting intellectual exercise. That Thursday, at 3:47 p.m., the phone rang in my cubicle at AOCS headquarters.

"The biopsy shows breast cancer," my doctor informed me.

With those words, a journey of discovery began. Initial terror over my perceived imminent demise gave way to a period of intense research as I recuperated from my subsequent surgery. I found myself engaging in magical thinking about dietary silver bullets. Was there anything I should add to my diet, or was there a dietary supplement regimen that would drive a stake into the heart of any remaining cancer cells? As I read paper after paper, I found that most decisions about food and supplements were easy to make, either because there was a consensus about efficacy among scientists or because there were few questions about safety.

One potential dietary cancer-slayer was less clear: soy. Estrogen feeds between 60% and 75% of breast cancers, including my own. The standard oral therapy undertaken after initial treatment (known as "adjuvant therapy") for estrogen-sensitive cancers is either tamoxifen, which binds to estrogen receptors and stops cell growth signaling, or an aromatase inhibitor, which inhibits production of estrogen in the body.

Soy is a rich source of isoflavones (primarily genistein, daidzein, and glycitein), which exhibit estrogenic activity. The safety of isoflavone intake for women at high risk of breast cancer or those recovering from it may depend on whether isoflavones act as agonists by initiating cell growth signaling or as antagonists by suppressing a response.

Early research on soy and breast cancer in cell cultures and animal models pointed to possible negative effects from isoflavones. These findings remain firmly lodged in the public consciousness, despite several recent, well-designed epidemiological studies suggesting dietary soy not only is safe, but may also be protective against cancer recurrence in certain subgroups of women. The public memory is long, however; it takes a significant number of positive findings to displace memories of the negative ones.

To prove the point: When asked about the safety of soy intake, my oncologist said, "Didn't that fellow at the University of Illinois at Urbana-Champaign (UIUC; Illinois, USA) show it is bad for women who have had breast cancer? You should talk to him."

Early animal studies

"That fellow" is William Helferich, a professor of nutrition in the Department of Food Science and Human Nutrition at UIUC, just down the road from AOCS headquarters. Helferich and colleagues have demonstrated that dietary genistein and genistin (see sidebar) stimulate the growth of estrogen-sensitive breast cancers in mice (*Cancer Research 58*:3833–3838, 1998; *Carcinogenesis 22*:1667–1673, 2001).

He and his team injected MCF-7 cells under the skin of athymic ovariectomized mice and implanted estrogen pellets in them to fuel tumor growth. Tumors regressed completely in mice

CONTINUED ON NEXT PAGE

ABOUT ISOFLAVONES

Isoflavones are a subclass of the flavonoids, the plant secondary metabolites named for their function as yellow (in Latin, *flavus)* pigments.

Soy foods are the only source of physiologically relevant amounts of isoflavones. Each gram of soy protein in traditional soy foods such as tofu, soy milk, and miso delivers approximately 3.5 mg of isoflavones. People in Asia typically consume about 30–50 mg of isoflavones per day (8–10 g of soy protein). For reference, a traditional soy food contains about 25 mg of isoflavones per serving. The consumption by the upper quartile (25%) of Asian populations studied is about 75–100 mg of isoflavones/day. In the United States, isoflavone intake is about 1.5 mg/day, according to Mark Messina of Nutrition Matters, Inc., in Port Townsend, Washington, USA.

Soybeans are tiny isoflavone factories, producing 12 different isoflavone isomers. The key isoflavones in soybeans are genistin and daidzin (the glucoside form) and their aglycones, genistein (4′,5,7-trihydroxyisoflavone) and daidzein (4′,7-dihydroxyisoflavone). (A translation for nonchemists is in order: An aglycone is the nonsugar compound remaining after replacement of a glycosyl group from a glycoside by a hydrogen atom.) A third isoflavone is present in small amounts—glycitin and its aglycone form, glycitein (4′,7-dihydroxy-6-methoxyisoflavone).

"Perhaps the greatest misnomer has been the liberal classification of soy isoflavones as 'estrogens,'" writes Kenneth D.R. Setchell of the Children's Hospital Medical Center in Cincinnati, Ohio, USA (*Journal of the American College of Nutrition 20*:354S–362S, 2001).

He continues by pointing out that the isoflavones in soy are nonsteroidal in chemical structure. But because of their phenolic rings, they are able to bind to estrogen receptors (as does tamoxifen, the original antiestrogenic agent used as adjuvant treatment in breast cancer that continues in use for premenopausal women and some postmenopausal women with breast cancer).

Isoflavones bind preferentially to the estrogen receptor (ER)-β. Studies by X-ray crystallography have compared the binding of estrogens, the selective ER modulator raloxifene, and the soy isoflavone genistein. These studies show "distinct differences in positioning," Setchell notes, that determine whether the binding agent has an agonist (initiating a response) or antagonist (inhibiting a response) effect.

Genistein, it turns out, "sits in the ER-complex that is almost identical to that of raloxifene, and not like estradiol [the most potent estrogen in humans]," Setchell says. "So, rather than classifying soy isoflavones as 'estrogens,' they should more correctly be judged to act normally as natural selective estrogen receptor modulators . . . . As such, this suggests that soy isoflavones are likely to have the beneficial effects of estrogen without the negatives, especially in tissues such as the endometrium and breast."

TABLE 1. Cancer incidence and mortality worldwide[a] (2008)

	Male	Female	Both sexes
Population (thousands)	3,402,841	3,347,220	6,750,061
Number of new cancer cases (thousands)	6,617.8	6,044.7	12,662.6
Age-standardized rate (W)	203.8	165.1	181.6
Risk of getting cancer before age 75 (%)	21.2	16.5	18.7
Number of cancer deaths (thousands)	4,219.6	3,345.2	7,564.8
Age-standardized rate (W)	128.6	87.6	106.1
Risk of dying from cancer before age 75 (%)	13.4	9.1	11.2
Five most frequent cancers in descending order of prevalence	Lung	Breast	Lung
	Prostate	Colorectum	Breast
	Colorectum	Cervix uteri	Colorectum
	Stomach	Lung	Stomach
	Liver	Stomach	Prostate

[a]Glossary:
Age-standardized rate (W): A rate is the number of new cases or deaths per 100,000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.

Risk of getting or dying from the disease before age 75 (%): The probability or risk of individuals getting/dying from cancer. It is expressed as the number of newborn children (out of 100 or 1,000) who would be expected to develop/die from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

Source: GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10: International Agency for Research on Cancer (Lyon, France); 2010. Available from: http://globocan.iarc.fr.

fed a standard diet after removal of the pellet; tumors were stimulated in mice fed diets containing either isolated soy protein or isoflavone extracts.

One finding in Helferich's work that points to the potential safety of whole soy foods for breast cancer patients often is overlooked in media reports and is unknown by most oncologists: This same research demonstrated that minimally processed soy in the form of soy flour did not stimulate tumor growth (*Journal of Agricultural and Food Chemistry* 53:8542–8550, 2005).

The breast cancer patient is left trying to decide how much weight to place on research conducted in animals when making her postcancer nutrition plan. And I am here to report that the postcancer psyche is tricky. As much as I want to include all the magical anticancer foods and supplements possible, I just as passionately do not want to do anything at all that might cause recurrence. (Not everyone is aware that recurrent metastatic breast cancer is incurable, most often appearing in bone, lungs, or liver.)

Susan Love, a medical doctor and author of *Dr. Susan Love's Breast Book*—known to the community of breast cancer patients as the "breast cancer bible"—disagrees with generalizing animal data to women. (Love also heads the Dr. Susan Love Research Foundation, whose website [www.dslrf.org] is a treasure trove of well-organized information about the disease.)

"The issue is that in mice and rats, there's no question that dietary soy or genistein can increase metastases. [Those findings] gave everybody pause and led to the proscription by all oncologists to Never Eat Soy. Soy in the human diet, however, is different from giving artificial soy to mice and rats. The big mistake that we make is conflating the data, especially for causation or recurrence; mice are just not people. You have to be really careful."

Another reason to be careful about assigning too much importance to animal studies is that there are crucial differences in isoflavone metabolism between athymic mice and humans. "Because mice are poorly able to conjugate phenolic compounds such as isoflavones," writes Mark Messina in an article on soy and the breast cancer patient (http://tinyurl.com/MessinaSoy), "circulating levels of unconjugated genistein, the biologically active form, are much higher in these mice than they are in humans." Messina is an *inform* contributing editor and president of Nutrition Matters, Inc., in Port Townsend, Washington, USA.

"Furthermore, in mice, despite similar genistein exposure, the consumption of more concentrated or processed soy products leads to higher unconjugated genistein levels and greater tumor stimulation. This observation is generally cited as the basis for recommendations endorsing the use of soy foods but not soy supplements by breast cancer patients. However, in humans, processing does not affect genistein metabolism. Thus, at least in regard to isoflavone metabolism, there appears to be little basis for differentiating between the two types of isoflavone-containing products."

Research published in the September issue of *Food and Chemical Toxicology* (49:2279–2284, 2011) provides a different answer to a similar question and highlights the limitations of animal research, because it shows how slight changes in the model can produce different results.

In research led by Atsuko Onoda of the Saga Nutraceuticals Research Institute in Japan, scientists looked at the effect on ovariectomized mice implanted with MCF-7 cells of diets consisting of an isoflavone mixture or genistein vs. a control diet.

Unlike the earlier work, there were no significant differences in tumor growth among the treatment groups and control

group. (In other words, the dietary genistein did not promote tumor growth as it appears to have done in previous studies.) The major difference between the earlier and later work is in the estrogenic environment of the medium in which the MCF-7 cells were cultured before implantation. Onoda *et al.* used a low-estrogen environment; Helferich and his team used a high-estrogen environment. The question is, which cells or conditions best reflect the microenvironment in postmenopausal women. Perhaps future studies will provide a definitive answer.

Helferich, in an interview, called whole soy products such as tofu, soy milk, and miso "healthful foods," but urged breast cancer patients to eat a variety of legumes in the form of dried beans. (A study from the 1980s examined data from 41 countries and revealed that countries with the greatest consumption of beans had the lowest death rates due to breast, prostate, and colon cancer [*Cancer Research 41*:3685–3689, 1981].)

"Do not make soy your only legume," Helferich cautioned, adding that in his opinion, taking isoflavones in the concentrated form of dietary supplements is dangerous for both women at high risk of breast cancer and women who have had breast cancer.

Epi and clinical trump animal

Recent epidemiological and clinical studies (which trump animal studies in the hierarchy of research reliability) have found soy consumption to be safe for women with breast cancer and potentially even protective.

In a well-designed prospective study led by Xiao Ou Shu of Vanderbilt University (Nashville, Tennessee, USA), more than 5,000 surgically treated breast cancer patients in Shanghai, China, were followed for four years. The women who ate the most soy—more than 15 g of soy protein and 62 mg of isoflavones/day—saw a significant 30% reduction in cancer recurrence and mortality. The study appeared in the *Journal of the American Medical Association* (*302*:2437–2443, 2009).

"Higher soy intake was still beneficial, but there was a suggestion that as you started to consume more than 20 g of soy protein/day, some of the benefit was lost," notes Messina. "The trend was not significant, however."

Another study published in 2009 followed almost 2,000 US breast cancer patients for six years. Researchers led by Neela Guha of the University of California, Berkeley (USA) found that soy consumption may reduce the risk of recurrence in women who have not been treated with tamoxifen, and "furthermore does not appear to negate the effects of tamoxifen."

An unpublished clinical study led by Seema Khan of the Northwestern University Feinberg School of Medicine (Evanston, Illinois, USA) examined human breast cells obtained by fine needle aspiration from healthy women at high risk for breast cancer before and after exposure to isoflavone supplements. After six months of supplementation, there was no difference in markers indicating cell proliferation between the placebo and supplemented (150 mg/day of isoflavones) groups.

Khan, who is a surgical oncologist, noted that she and her group also measured the expression of a number of genes before and after supplementation. There was no change one way or the other in postmenopausal women, she said. But there was "a hint of cell growth" in premenopausal subjects after statistical adjustments.

"When my patients ask me about soy consumption," she said, "I tell them that if they like soy-containing foods, they shouldn't avoid them. I do, however, caution them about [isoflavone] supplements."

Khan's advice is more conservative than that of the American Cancer Society, which has since 2006 recommended that breast cancer patients can safely consume up to three servings of soy foods/day (http://tinyurl.com/ACS-Guidelines).

Do results in Asian women generalize?

The criticism most often leveled against the Shu epidemiological study (and several others) is that results in Asian women should not be extrapolated to Western women. The former group tends to have much greater intake of soy foods from early in life onward; the latter generally has barely any. Work by Leena Hilakivi-Clarke, a professor of oncology at Georgetown University (Washington, DC, USA) and others finds that when isoflavones are consumed before puberty and during early adolescence, they are protective against breast cancer.

"I believe that early exposure is the key in order to see the protective results in adult life," Hilakivi-Clarke said. "For that reason, we cannot make recommendations based on the Shu data—the exposure of Chinese women to isoflavones is very different."

Would she recommend soy foods to her best friend if the friend had breast cancer?

"If she had never consumed soy before and wants to improve her overall diet by adding it, it would be fine to include at the level of about 1/2 serving per day (or several full servings per week). But I would tell her she absolutely should not take isoflavone supplements."

Shu herself says that questioning the applicability of data in Asian women "is understandable." Thus, she and others pooled data from three US studies with her original data from Chinese women. In all, the team evaluated postdiagnosis soy food intake and breast cancer outcomes of 18,312 women between the ages of 20 and 83 years.

The pooled study was presented at the 102nd Annual Meeting of the American Association for Cancer Research in April 2011 (http://tinyurl.com/AACR-pooled). "We did not see any adverse effect related to eating soy food," Shu said of the study, adding that there was no sign of a risk of recurrence. "There was some suggestion that soy foods may be beneficial."

One of the pooled US cohorts in the research presented at AACR is from a study led by Bette Caan of Kaiser Permanente in Oakland, California, USA. Entitled Women's Healthy Eating and Living (WHEL), the study is a randomized, controlled trial of more than 3,000 early-stage breast cancer survivors, with a median follow-up of 7.3 years from the time of enrollment (*Cancer Epidemiology, Biomarkers & Prevention 20*:854–858, 2011). Results showed that consuming up to 1/2 serving of soy foods per day did not increase breast cancer recurrence among women previously diagnosed with breast cancer, and was associated with lower mortality among such women. (Neither result reached significance.)

"When one considers the limitations of animal research, that the clinical data show isoflavone exposure doesn't adversely affect markers of breast cancer risk, and the epidemiologic data from China and the United States indicating postdiagnosis soy

consumption improves the prognosis of women with a history of breast cancer, it is pretty clear that the totality of the evidence has shifted in favor of the safety and potential benefit of soy foods," says Mark Messina.

Moving forward

As is the case with all things scientific, more work is needed. But my months of research and reading have left me feeling perfectly comfortable with continuing to eat a variety of whole soy foods. [A note of caution: Each breast cancer patient needs to do her own review of the research and make her own decision. If it isn't wise to generalize data from Asian women to Western women, it is even less wise to blindly follow the decision of one health and nutrition writer.]

My daily—costly—supplement regimen now includes long-chain omega-3 fatty acids in the form of triglycerides, curcumin with piperine, glucosamine and chondroitin, and 6,000 International Units of vitamin D3 with co-factors.

Curcumin (a phytochemical in turmeric) has shown promise as an anticancer agent; I added it (with co-factor piperine, which is necessary to increase the bioavailability of curcumin) to my armamentarium. Resveratrol (one of the bioactive phytochemicals in red grapes) has also shown promise, but it is a mixed agonist/antagonist. Until there is more literature to review demonstrating that it doesn't aid cell proliferation, I will not take it in supplement form.

Why the D3? Studies show that women with serum 25-hydroxyvitamin D levels above 40 nanograms/milliliter have less debilitating joint pain and stiffness, a very common side effect of adjuvant therapy with aromatase inhibitors. Why omega-3 fatty acids? Because an observational study focusing on post-initial treatment breast cancer patients monitored over a seven-year period found that women in the highest third of long-chain omega-3 consumption (more than 153 mg/day) were 40% less likely to die from breast cancer compared with women in the lowest third.

Even more important, however, in terms of holding recurrence at bay—or reducing the risk of breast cancer, for that matter—is weight loss and exercise. Adipose tissue manufactures estradiol, the most potent of the body's estrogens, and outcomes of obese breast cancer patients are not as good as slender patients. Then, too, at least 15–20 metabolic equivalents of exercise per week has been associated with a significant reduction in the risk of recurrence of breast cancer. (To learn more about metabolic equivalents, see www.dslrf.org/pdfs/Great_Reads_MarieMurphyBCRisk.pdf.)

And now for the question that remains unanswered: Have I pulled the welcome mat for recurrent cancer or am I just making very expensive urine? Only time will tell.

Catherine Watkins is associate editor of inform. *She can be reached at cwatkins@aocs.org.*

WHAT IS AN MCF-7 CELL, ANYWAY?

MCF-7 is a breast cancer cell line isolated in 1970 from a 69-year-old Caucasian woman. The acronym refers to the Michigan Cancer Foundation (now the Karmanos Cancer Institute in Detroit, USA), where Herbert Soule and co-workers established the cell line in 1973. The cell line exhibits tumorigenicity in mice, but only with estrogen supplementation.

The patient, whose name—Frances Mallon—is unknown to the vast majority of cancer researchers, died in 1970. Her cells are the source of much of the current knowledge about breast cancer. At the time of sampling, she was a nun in the convent of the Immaculate Heart of Mary in Monroe, Michigan, USA, under the name of Sister Catherine Frances.

MCF-7 and two other breast cancer cell (BCC) lines, named T-47D and MDA-MB-231, account for more than two-thirds of all abstracts reporting studies on mentioned BCC lines, as concluded from a Medline-based survey published in 2004. Cell lines established prior to MCF-7 did not live longer than a few months.

Source: Wikipedia, accessed August 1, 2011

About *inform* and AOCS

As the AOCS member magazine, *inform* offers international news and features about vegetable oils, fats, surfactants, detergents, personal care products, and related materials.

AOCS (American Oil Chemists' Society; www.aocs.org) is a global professional scientific society for all individuals and corporations with interest in the fats, oils, surfactants, detergents, and related materials fields. For more than 100 years, AOCS has promoted the science and technology of lipids in the fats and oils industries through analytical methods, proficiency testing, peer-reviewed technical publishing, and by providing venues for technical discussions and educational opportunities. Today, AOCS is a global partner in the science and technology industry with over 4,500 members throughout 90 countries.