Risks and Benefits of Soy Isoflavones for Breast Cancer Survivors

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Purpose/Objectives: To present state-of-the-art information about the risks and benefits of soy isoflavones for breast cancer survivors.

Data Sources: Published research articles, pertinent articles and books, and computerized databases.

Data Synthesis: Some epidemiologic data suggest that soy isoflavones play an important role in preventing breast cancer in Asian women and promoting women's health in a variety of ways. However, the use of soy isoflavones in women with breast cancer is controversial. Risks and benefits exist regarding the use of soy isoflavones by breast cancer survivors.

Conclusions: The use of soy isoflavones to promote health in breast cancer survivors remains controversial because of scant scientific data.

Implications for Nursing: Nurses should not only provide updated information to the public but also interpret research results carefully. More clinical trials need to be conducted on a longitudinal basis with the enrollment of breast cancer survivors.

Key Points . . .

- As a complementary therapy, soy has the potential to prevent breast cancer and may alleviate menopausal symptoms in women.
- The use of soy isoflavones to promote health in women with breast cancer remains controversial.
- Nurses have the responsibility to interpret research results carefully, provide updated information, and educate the public about soy.

Goal for CE Enrollees:

To enhance nurses' knowledge about the current research related to the risks and benefits of soy isoflavones for breast cancer survivors.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Identify the proven and proposed health benefits of soy isoflavones.
2. Describe the results of research related to the effects of soy isoflavones on menopausal symptoms.
3. Discuss the current research related to the use of soy isoflavones by breast cancer survivors.

Breast cancer is the most common malignancy and second leading cause of death for American women (American Cancer Society, 2004). In 2004, an estimated 215,990 American women are expected to be diagnosed with breast cancer and more than 40,000 will die from the disease (American Cancer Society). As a result of improvements in early detection and advances in cancer therapy, the number of breast cancer survivors and their life expectancy has increased (American Cancer Society; Beckmann et al., 2001; Vassilopoulou-Sellin & Theriault, 1994).

Breast cancer survivors are a unique population with different concerns and perspectives than women without cancer. Physical effects of breast cancer and treatments may persist up to 10 years after therapy has been completed (Ganz et al., 2002). Fear of cancer recurrence is a dominant issue that influences survivors' psychological well-being (Carter, 1993; Dow, 1999; Ferrell et al., 1996; Wyatt, Kurtz, & Liken, 1993). Breast cancer survivors who undergo premature menopause associated with adjuvant chemotherapy may experience vasomotor symptoms that are more frequent or severe (Burstein & Winer, 2000; Carpenter, 2000; Ganz, Rowland, Desmond, Meyerowitz, & Wyatt, 1998; Knobf, 2001). Hormone replacement therapy (HRT) generally is contraindicated for women with breast cancer (Poniatowski, Grimm, & Cohen, 2001; Vassilopoulou-Sellin & Theriault, 1994). The benefits of HRT on menopausal symptom distress are well established, but breast cancer survivors must explore alternative options for menopausal symptom relief.

Soy has the potential to alleviate menopausal symptoms (Boon et al., 2000; Burstein, Gelber, Guadagnoli, & Weeks, 1999; Burstein & Winer, 2000) and has been explored as an alternative to HRT for women with breast cancer. However,

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two issues are related to soy use in breast cancer survivors. First, soy isoflavones may act as an estrogen agonist in breast tissue, potentially increasing the risk of breast cancer (Petrakis et al., 1996), and soy isoflavones may increase breast cell proliferation (Messina, 2000). In contrast, soy isoflavones may lower the risk of breast cancer by stimulating sex hormone-binding globulin (Adlercreutz et al., 1987; Adlercreutz & Mazur, 1997). At this point, the data are inconclusive regarding whether soy isoflavones increase or decrease the risk of breast cancer. Evidence-based studies do not always support the potential benefits of soy that are promoted by the media and food and drug industries. Thus, whether women with breast cancer can safely use isoflavones to alleviate menopausal symptoms or promote general health is a daily dilemma.

Soy and Soy Isoflavones

In 1998, the U.S. Food and Drug Administration (FDA) announced that soy protein can improve high cholesterol levels, a common health risk for cardiovascular disease in the United States. The potential health benefits of soy increasingly have attracted more Americans to include soy in their diets. According to annual nationwide surveys sponsored by the United Soybean Board (2002, 2003), 70% of Americans changed their eating habits in response to health or nutrition since 1998 (United Soybean Board, 2003). Seventy-four percent of consumers believed that soy is healthy, 26% of the women surveyed believed that soy may help to manage symptoms of menopause (United Soybean Board, 2003), and 16% of Americans were aware that soy may have a role in cancer prevention (United Soybean Board, 2002). Although healthcare professionals are playing important roles in health education and providing health information, only 6% of Americans obtained information about soy from their healthcare professionals (United Soybean Board, 2002). Multimedia sources served as an information gateway for the majority of Americans (82%) in 2002 (United Soybean Board, 2002). Healthcare professionals have not promoted soy heavily, yet the public believes that soy has many positive benefits. Soy is a low-cost item, which makes it available to people from all socioeconomic levels. It does not contain cholesterol, is low in saturated fat, and contains significant amounts of nutrients such as dietary fiber, vegetable protein, vitamin B, calcium, zinc, iron, and most importantly, phytochemicals (e.g., isoflavones).

Soy Isoflavones

The fact that soy contains high levels of isoflavones has been known since 1930 (Adlercreutz & Mazur, 1997). Isoflavones are groups of food chemicals produced naturally by legumes and are found almost exclusively in soy. Soy isoflavones are biologically active components. They are subclasses of the flavonoid family, which is a member of the polyphenol family. Although soy isoflavones can be classified further into 12 different isoflavone isomers, genistein and daidzein are the two that are studied most commonly in the United States (Messina & Loprinzi, 2001) (see Patient Education Fact Sheet). In *The Simple Soybean and Your Health,* Messina, Messina, and Setchell (1994) proposed that soy isoflavones are end-products of the natural defense reaction of the soy plant when it encounters stress such as dryness and heat during its growth. They further suggested that these isoflavone products might be beneficial to the human body by strengthening its ability to fight stressors such as illnesses. Although the researchers were unable to determine exactly what kind of stressors soy isoflavones can fight, genistein and daidzein have been proven to have antifungal properties (Harborne, Baxter, & Moss, 1999).

Soy Isoflavones in Plants and Foods

The amount of soy isoflavones in plants and foods is inconsistent. In plants, the location of the crop; the time of harvest; conditions such as dryness, heat, and light during growth; condition of the soil; and genetic technology affect the production of soy isoflavones (Albertazzi et al., 1998; Eldridge & Kwolek, 1983; Glisson, Crawford, & Street, 1999; Greenwood et al., 2002; Knight & Eden, 1996; Messina, Messina, et al., 1994). Soy isoflavones are sensitive to heat and, thus, can be lost in food processing. Therefore, greater amounts of heat in the processing of a soy product will result in fewer isoflavones in the product (Glisson et al.; Greenwood et al.). Soy beverages have the most abundant soy isoflavones that are well absorbed by the human body (Barnes, Sfakianos, Coward, & Kirk, 1996). The metabolites of soy isoflavones also may be found in meat and dairy products because of the soy intake by livestock (Adlercreutz & Mazur, 1997). Soy isoflavones, however, do not exist in all soy products. Soy sauce, for example, a fermented soy product that commonly is used by Asians for seasoning, does not contain any soy isoflavones (Vincent & Fitzpatrick, 2000). The intake of soy isoflavones in the Asian population, therefore, mainly comes from soy foods such as tofu and soy drinks. Because soy has a high concentration but an inconsistent amount of isoflavones, pharmaceutical companies have tried to produce soy products that provide large quantities of purified isoflavones with a standardized dosage for more convenient use by people in Western countries.

Absorption, Metabolism, and Elimination

Although soy isoflavones are biologically active components, they remain inactive in the soy plant. Isoflavones genistin and daidzin do not convert into the biologically active form until ingested by animals and humans. Bacteria in the small intestine are necessary to convert them into the active products genistein and daidzein. Therefore, the number of bacteria in the small intestine of an individual will affect the number of isoflavones that can be converted into active forms (Adlercreutz, 1995; Adlercreutz & Mazur, 1997; Cerrato, 1998; Knight & Eden, 1996; Messina, Persky, Setchell, & Barnes, 1994). The activated soy isoflavones then undergo metabolism and absorption in the small intestine. In adults, genistein and daidzein further convert into metabolites (Adlercreutz, 1995; Baird et al., 1995; "Soy Isoflavones," 1998). Then, the majority of soy isoflavones is transported to the liver and eliminated through the blood via the portal vein, with a smaller percentage being eliminated by the kidneys in the urine.

Studies suggest that the rate and amount of absorption, metabolism, and elimination of soy isoflavones are highly variable between each animal and each individual (Albertazzi et al., 1999; Kelly, Joannou, Reeder, Nelson, & Waring, 1995; Lu, Anderson, Grady, Kohen, & Nagamani, 2000; Murkies et al., 2000; Vincent & Fitzpatrick, 2000). Two factors that influence absorption and metabolism are a change in intestinal

Patient Education Fact Sheet: What Women Need to Know About Soy

What is soy?

- Soy is a legume that has been a dietary staple of Asians for more than 1,000 years.
- Soy is a low-cost item with no cholesterol, low saturated fat, and high vegetable protein, dietary fiber, vitamin B, calcium, zinc, iron, and isoflavones.
- Soy is a key component of a vegetarian diet.

What is soy protein?

- Soy protein is vegetable protein.
- In 1998, the U.S. Food and Drug Administration (FDA) announced that consuming 25 g of soy protein per day can reduce the risk of heart and vessel disease.
- Soy products need to have at least 6.25 g of soy protein per serving to make the above claim.
- Soy protein contains high levels of isoflavones.

What are soy isoflavones?

- Soy isoflavones are plant-form chemicals that have similar structures to human estrogen.
- Genistein and daidzein are the two most common soy isoflavones.
- Soy isoflavones are biologically inactive in the soy plant and become active when ingested by bacteria in the small intestine.
- The absorption, metabolism, and elimination of isoflavones are highly variable from one individual to another.
- Isoflavones are sensitive to heat and can be lost in food processing.
- Not every soy product has isoflavones. Soy milk contains the most isoflavones, and soy sauce does not contain any.
- Soy isoflavones can have estrogenic or antiestrogenic effects, depending on gender, menopausal status, and concentration of estrogen in the body.

What forms of soy are available in grocery and specialty food stores?

- Soy products can be classified into three categories.
  - Soy products that mainly are made from soybeans with little or no other components added (e.g., soybeans, soy milk, soy flour, tofu or soybean curd, miso or soybean paste, tempeh or soybean cake, soy bar, vegetarian meat products)
  - Nonsoy products that are added with some soy components such as drinks and juices that are soy protein and/or soy isoflavone fortified
  - Soy supplements that contain megadosing soy components (e.g., soy protein isolates, soy isoflavones tablets)

What have researchers learned about soy and women's health?

- The mechanism of action of soy isoflavones as either an estrogen or antiestrogen is not fully explained.
- Asian women have a lower incidence of breast cancer and report fewer menopausal symptoms. Whether these low breast cancer rates and reduced menopausal symptom distress are associated with their high intake of soy is not clear.
- In some studies, soy has been shown to improve hot flashes in healthy women.
- Two studies have tested soy in women with breast cancer who are experiencing hot flashes. Neither study showed that soy products were better than nonsoy products in reducing hot flashes in women with breast cancer.
- The safety of soy in women with breast cancer is unknown.
- Soy may act like a weak estrogen. The safety of estrogen in women with a history of breast cancer is controversial.
- Whether women need to consume a soy diet early in life to get health benefits is not clear.
- The safe and effective dosage of soy isoflavones is unknown.
- The toxicity of high-dose soy isoflavones is unknown.
- The safety of long-term use of soy supplements is unknown.
- Genetically modified soy products commonly are sold in the United States and are not required to be labeled. Genetically modified soy products may differ from conventional soy. The safety and nutritional value of genetically modified soy products are unknown.
- Although unknown, soy isoflavones may not be safe for women with breast cancer because isoflavones are known to have estrogen-like properties.

Recommendations for women considering a soy diet

- Although natural, soy isoflavones are food chemicals.
- When consuming soy products, foods that naturally contain soy with no or little additives (e.g., tofu, soy milk) are safer than products that have large doses of a single soy compound or substances other than soy.
- Most soy supplements contain a high concentration of a single soy compound, such as isoflavones tablets and soy protein isolate. However, many good nutrients such as fiber have been removed and are not available for those who take only supplements.
- Supplements should never replace a healthy diet.
- Read nutrition labels carefully. Many soy products are high in fat or sugar and contain monosodium glutamate (MSG) and/or other substances to mask the flavor of soy.
- Soy products sold in health food stores are considered food, not medication, and therefore do not require FDA approval.
- Be aware of the languages that are used in commercials. Distinguish the difference between "isoflavones *are* good for your health" and "isoflavones *may be* good for your health."
- There is no shortcut for good health. Diet, exercise, and healthy lifestyle behaviors always should go together.

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microflora caused by the use of antibiotics or bowel diseases and a slower gastrointestinal transit time that can be induced by stress (Ingram, Sanders, Kolybaba, & Lopez, 1997; Murkies et al., 2000). Another example is a diet that is high in fat or carbohydrates or contains large portions of meat, which may increase the excretion of isoflavones. Lu et al. also determined that excretion of isoflavones is much greater during the follicular phase of the menstrual cycle compared to the luteal phase in healthy premenopausal women. Some people, for unknown reasons, are not able to produce or excrete large amounts of soy isoflavones (Adlercreutz & Mazur, 1997; Elkind-Hirsch, 2001; Glisson et al., 1999).

Estrogen Agonist Versus Estrogen Antagonist Effects

Soy isoflavones can produce either an estrogen agonist (estrogenic) or estrogen antagonist (antiestrogenic) effect depending on gender, menopausal status, and concentration of estrogen or isoflavones in the body of an individual (Adlercreutz, 1990; Adlercreutz & Mazur, 1997; Carusi, 2000; Greenwood et al., 2000; Murkies et al., 2000; Quella et al., 2000; Vincent & Fitzpatrick, 2000). Soy isoflavones may act like antiestrogens in high-estrogenic environments or estrogens in low-estrogenic environments. They also are known commonly by their similar structure to estrogen produced by women (17b-estradiol) (see Figure 1) and may exert their estrogenic effect only in selected tissues in the human body.

Estrogen agonist: Isoflavones are the most potent class of plant-form estrogens that first were recognized to have estrogenic effects as early as 1926 (Davis, Murkies, & Wilcox, 1998). Genistein is recognized as the main isomer with estrogen agonist properties (Messina & Loprinzi, 2001). Because of their similar chemical structure, soy isoflavones have estrogen-receptor affinities that allow them to compete with estrogen. Isoflavones also are more soluble and easier to break down into small molecules, which further increases their affinity to estrogen receptors. Furthermore, the fact that isoflavones have estrogenic properties that are 100–100,000 times weaker than 17b-estradiol enables them to produce mild estrogenic effects in both animals and human beings (Fitzpatrick, 1999; Harborne et al., 1999; Messina & Loprinzi). Even though they are mild, if digested in certain quantities, these estrogenic effects may account for a reduction in early symptoms and long-term effects of menopause (Baron-Faust, 1995; Cerrato, 1998).

Estrogen antagonist: Although soy isoflavones are most well known for their estrogenic properties, antiestrogenic effects in breast tissues have been reported (Folman & Pope, 1966). Many in vivo studies, mainly with mice, subsequently were conducted that confirmed the earlier results (Adlercreutz & Mazur, 1997; Folman & Pope, 1969; Messina & Loprinzi, 2001). In contrast, Welshons, Murphy, Koch, Calaf, and Jordan (1987) did not find that soy isoflavones had any estrogen antagonist effects in an in vitro study using human breast cancer cells. Some researchersed suggest that soy isoflavones may act as an estrogen antagonist mainly in women who normally produce a great deal of estrogen (Eden, 2000; Messina, Messina, et al., 1994). Premenopausal women have higher estrogen levels in their serum compared to postmenopausal women. Therefore, researchers have hypothesized that the estrogen antagonist effect of soy may occur predominantly in premenopausal women (Adlercreutz, 1990; Adlercreutz & Mazur; Carusi, 2000; Quella et al., 2000).

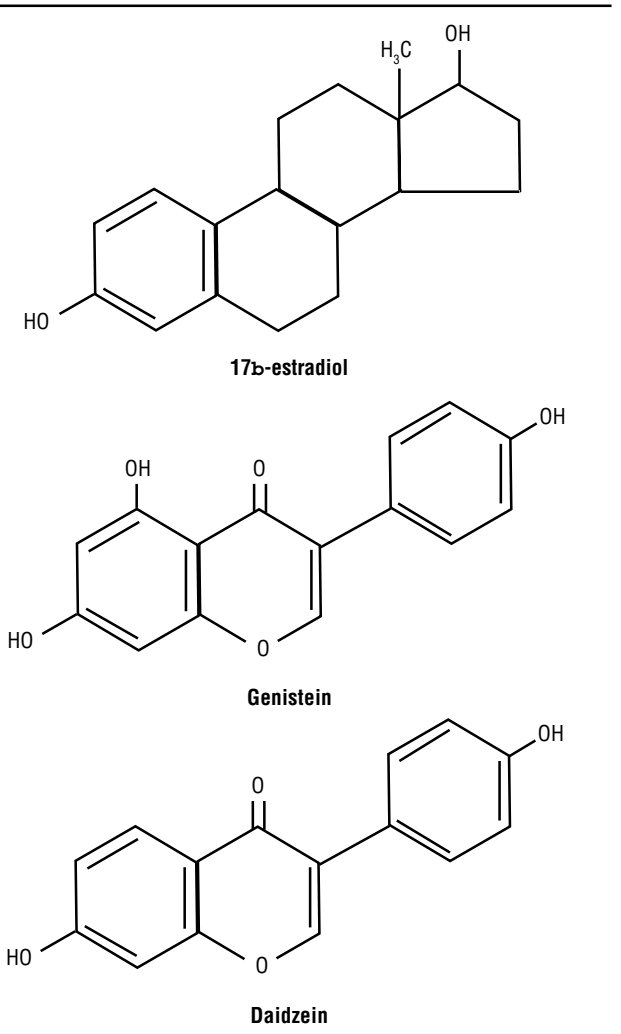

Figure 1. Chemical Structures of Estrogen (17b-Estradiol) and Two Soy Isoflavones: Genistein and Daidzein

Soy isoflavones have been known to have this dual effect of estrogen agonist and estrogen antagonist for more than 40 years (Seibel, 1999). This unique characteristic makes the mechanism of action and clinical implications of soy isoflavones complex and controversial, especially for breast cancer survivors.

Clinical Evidence of Soy Isoflavones

Soy and soy isoflavones have been studied since the mid 1980s and more extensively since 1990. Scientists have been trying to determine whether soy isoflavones contribute to the low incidence of breast cancer in Asian women; specifically, they have attempted to discover whether soy isoflavones prevent breast cancer. The second major research focus has been the evaluation of soy in the relief of menopausal symptoms.

Epidemiologic data suggest that Japanese women not only have a lower risk of breast cancer but also have a better survival rate from breast cancer than Western women. Moreover, Japanese women generally have fewer menopausal symptoms than women in Western countries (Carusi, 2000; Chung, Yip, Lam, Chang, & Haines, 1996; Lock, 1991). These benefits,

however, do not appear in Japanese offspring born in Western countries or those who have high consumption of a westernized diet (Messina, Messina, et al., 1994). All of these observations strongly suggest that estrogen may be a factor explaining the discrepancies in risk of breast cancer and prevalence of menopausal symptoms between Asian and Western women.

Relationship of Soy Isoflavones and Risk of Breast Cancer

The unique geographic variability of breast cancer around the world and the low rate of breast cancer in Asian compared to Western countries prompted exploration of the intake of soy isoflavones and their possible cancer prevention effect. Five case-controlled studies conducted in Australia, the United States, Singapore, and China have been reported (see Table 1). These studies examined the relationship between the intake of soy isoflavones and breast cancer. Data on diet, level of intake of isoflavones, and their metabolites in serum and urine were collected and analyzed. Four of the five studies recruited women with breast cancer who were matched with controls without breast cancer. In premenopausal women with breast cancer, two studies reported that high soy isoflavones may be associated with a lower incidence of breast cancer, but one study failed to confirm this relationship. In postmenopausal women with breast cancer, the data are more contradictory with two studies supporting a relationship between isoflavones and breast cancer risk and two studies failing to demonstrate such a relationship.

A study conducted by Lu et al. (2000) evaluated 10 healthy premenopausal women who consumed a soy diet that contained 113–207 mg per day of isoflavones. Estrogen and progesterone levels were significantly lower in those on the soy diet, but no difference was found between the luteinizing

Table 1. Breast Cancer and Soy: Summary of Five Studies

Study	Design	Sample	Purpose of Study	Data Collection	Results
Lee et al., 1991	Case controlled, longitudinal, retrospective	200 Chinese women from Singapore with breast cancer were matched with 420 women from same cultural background who did not have breast cancer.	To analyze the relationship between diet and the risk of breast cancer	Food frequency questionnaire: 90 common food items to track the food consumption in the past year	In premenopausal women, a positive relationship was found between the risk of breast cancer and the intake of red meat and animal proteins and an inverse relationship was found between the risk of breast cancer and the intake of polyunsaturated fatty acids, beta-carotene, soy proteins, and total soy products. However, in postmenopausal women, a statistically significant relationship did not exist among these dietary variables and risk of breast cancer.
Yuan et al., 1995	Case controlled	834 women from Shanghai and Tianjin with breast cancer were matched with 834 women from the same communities by sex and age.	To determine a relationship between diet and breast cancer	Food frequency questionnaires: 63 common food items in Shanghai and 68 common food items in Tianjin	A large intake of soy protein high in isoflavones was not related to breast cancer in Shanghai and Tianjin. A diet high in pork and low in vegetables, however, increased the risk of breast cancer. The analysis of nutrient factors further suggests that crude fiber, beta-carotene, and vitamin C strongly display cancer preventive effects, but soy protein high in isoflavones does not.
Ingram et al., 1997	Case controlled	144 pairs of Australian women: newly diagnosed breast cancer matched by age and living area in control group	To investigate the relationship between phytoestrogens and breast cancer	Food frequency questionnaires and three consecutive 24-hour urine collections to measure the excretion of phytoestrogen	Increasing excretion of isoflavone equol and lignan enterolactone was associated with a reduced risk of breast cancer in pre- and postmenopausal women.
Lu et al., 2000	Longitudinal	10 healthy premenopausal American women	To determine whether a soy diet decreases circulating levels of estrogen and gonadotropins	Black's Health Habit History Questionnaire and serum and urine samples for isoflavones	Premenopausal women who consumed a diet high in isoflavones had high urinary excretion of genistein and daidzein, and low levels of estrogen and progesterone without affecting the level of gonadotropins throughout the menstrual cycle.
Murkies et al., 2000	Case controlled	18 postmenopausal women newly diagnosed with breast cancer were matched with 20 postmenopausal women without breast cancer from the same region in Australia.	To examine the relationship between the intake of isoflavones and the risk of breast cancer	Interview, self-administered food frequency questionnaire, and serum and urine samples for isoflavones	Postmenopausal women with breast cancer had a significantly lower urinary excretion of daidzein and a trend of lower urinary excretion of genistein. Therefore, low urinary daidzein and genistein may be associated with breast cancer in postmenopausal women.

hormone and follicle-stimulating hormone during the month of the soy diet compared to levels in the preceding month when women ingested a regular diet. Because high levels of estrogen correlate with a higher risk of breast cancer and progesterone may enhance the proliferation of breast cells, Lu et al. suggested that a soy diet high in isoflavones may provide a preventive effect against breast cancer for women who consume a soy diet for an extended period of time.

These studies demonstrate that a high intake of soy food will lead to a high level of excretion of isoflavones in serum and urine, but the data fail to conclusively support a positive relationship between a high level of isoflavones and a lower risk of breast cancer. Factors that may explain some of the differences among the studies include different rates of metabolism and excretion of isoflavones, food interactions, and a predominance of retrospective study designs. Nonetheless, the relationship between soy and breast cancer risk has not yet been established, but it is not disproven.

Effectiveness of Soy for Menopausal Symptoms

The potential of soy isoflavones as an HRT alternative for women with menopausal symptoms has been explored. Several studies have examined whether soy isoflavones can alleviate early menopausal symptoms in healthy women (see Table 2).

The results of the research on reduction of menopausal symptoms from soy isoflavones are mixed. Several studies have reported that soy isoflavones effectively reduced hot flashes, although the difference in percent reduction of hot flashes between the soy and placebo groups was not statistically significant (Brzezinski et al., 1997; Burke et al., 2003; Dalais et al., 1998; Murkies, Lombard, & Strauss, 1995; St. Germain, Peterson, Robinson, & Alekel, 2001; Washburn, Burke, Morgan, & Anthony, 1999). In all studies, a consistent placebo effect was found, which is predictable from previous research (Berga, 2000; Vincent & Fitzpatrick, 2000). In contrast, a few studies have reported a statistically significant reduction in hot flash frequency for the soy intervention (Albertazzi et al., 1998; Faure, Chantre, & Mares, 2002; Han, Soares, Haidar, de Lima, & Baracat, 2002; Scambia et al., 2000; Upmalis et al., 2000) and a significant difference for reduction in severity of vasomotor symptoms (Scambia et al.; Upmalis et al.; Washburn et al.). Of interest, Albertazzi et al. (1999) reported that women who took the soy protein isolate had a higher level of isoflavones in serum and urine, but these levels were not correlated with the reduction of hot flash frequency. According to the data, Albertazzi et al. (1999) suggested that unknown phytoestrogens may exist in soy that can improve hot flashes. The wide variation in individual serum and urinary excretion of isoflavones makes them unreliable indicators for measuring hot flashes. Finally, the variation in the bioavailability of isoflavones within each individual (i.e., gastrointestinal flora and interaction with other food components) limits the level of experimental control and interpretation of findings (Albertazzi et al., 1998; Elkind-Hirsch, 2001; Greenwood et al., 2000). In summary, soy is associated with a low side-effect profile and may provide modest relief from hot flash frequency or severity. However, interpretation of the conflicting research findings for practice application is challenged further by differences in the products used, doses, and measurement of menopausal symptoms (Kronenberg & Fugh-Berman, 2002).

Menopausal Symptoms in Breast Cancer Survivors

HRT generally is contraindicated in breast cancer survivors; therefore, alternatives to manage menopausal symptoms are needed for this population. Two studies have been reported that evaluated the effect of soy on menopausal symptoms in women with breast cancer (see Table 3).

In a trial conducted by Quella et al. (2000), soy tablets (approximately 150 mg of soy isoflavones per day) were provided to women with breast cancer and compared to placebo. The four-week intervention included a crossover to the other arm for four additional weeks. Soy was not more effective than placebo in relieving hot flashes. Van Patten et al. (2002) conducted a similar study in women with breast cancer. Those women were randomized by a soy beverage for 12 weeks versus a placebo beverage. Interestingly, the placebo groups in this trial, as well as those in the Quella et al. study, had equivalent or slightly superior outcomes with reduction in hot flashes. In contrast to several studies of women without breast cancer that suggest soy's benefit for reducing hot flashes, both of these studies failed to demonstrate a benefit of using soy isoflavones in treating menopausal symptoms.

Soy Products: Consumption and Safety

An estimated 123.5 million Americans have used natural products for a variety of reasons such as weight loss, sexual function improvement, and cancer prevention (Doyle, 2002; Spake, 2001). Soy products represent a large percentage of consumed natural products. According to Hasler (2002) and data presented by Chapman (1998) in the *Third Annual Soyfoods Symposium Proceedings,* soy-based functional food products reached $175.1 million in 1997 and will reach $6.9 billion by 2005. The daily consumption of soy isoflavones varies significantly across cultures and countries. The estimated consumption of soy isoflavones ranges from 20–200 mg per day in Japan (Bascom, 2002; Elkind-Hirsch, 2001; Messina & Loprinzi, 2001; Upmalis et al., 2000), compared to 20–150 mg per day in other Asian populations (Elkind-Hirsch) and less than 1–5 mg per day in individuals who consume a traditional Western diet (Babaknia, 2001; Hasler & Finn, 1998). However, the consumption of soy products has increased significantly in the United States. For example, regular soy milk users in the United States have increased from 14% in 2002 to 17% in 2003 (United Soybean Board, 2003).

Many soy products on the market are considered as a category of functional food, which is defined as "manufactured foods for which scientifically valid claims can be made" (Doyle, 2002, p. 273; Spake, 2001). Since the FDA's 1998 announcement that soy protein could decrease cholesterol, many different forms of soy products emerged and were marketed. Soy protein, which is high in isoflavones, can be added to drinks or baking goods. Concentrated soy isoflavone tablets and capsules also are available commercially. Healthcare providers should be aware that many products have not been tested and have been promoted by commercial business as healthy food products. The ingredients of many products sold in Western countries are either highly concentrated soy isoflavones or a single chemical compound. The safety of those products, however, is unknown. For example, extracted soy isoflavones are worrisome because people not only lose the

Table 2. Studies Investigating the Relationship Between Soy Isoflavones and Menopausal Symptoms in Healthy Women

Study	Design and Length of Study	Sample	Purpose of Study	Soy Product Used	Data Collection	Results
Murkies et al., 1995	Randomized, double-blind, outpatient clinical trial conducted over 12 weeks	58 healthy postmenopausal Australian women with severe hot flashes	To test the hypothesis that soy flour (more potent phytoestrogen) would decrease hot flashes, improve vaginal cell maturation, and improve lipids more than the less potent phytoestrogen wheat flour	45 g of either soy or wheat flour was added to the women's regular diet for 12 weeks.	Baseline studies were conducted for two weeks to document the number of hot flashes and usual diet; women then were randomly assigned to either a soy or wheat flour diet for 12 weeks.	Hot flash symptoms decreased significantly in both groups (40% in soy group and 25% in wheat group), with more rapid and more relief in the soy group, but the differences between the two groups were not statistically significant ($p = 0.82$). Vaginal cell maturation remained unchanged.
Brzezinski et al., 1997	Randomized, outpatient study conducted over 12 weeks	145 menopausal Israeli women who were experiencing hot flashes	To investigate the effect of a phytoestrogen-rich diet on menopausal symptoms, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), and phytoestrogens	A phytoestrogen-rich diet (tofu, soy drink, miso, and flex seed) in the intervention group ($n = 78$) was compared to a normal diet in the control group.	Body height, weight, menopausal symptoms assessment, and serum for estradiol, LH, FSH, SHBG, and phytoestrogens	The phytoestrogen-rich diet increased serum levels of phytoestrogens and SHBG significantly in the experimental group, but they remained unchanged in the control group. The total score for menopausal symptoms was reduced in both groups but did not reach statistical significance. However, hot flashes and vaginal dryness were reduced in the phytoestrogen-rich diet group ($p = 0.004$ and $p = 0.005$).
Albertazzi et al., 1998	Randomized, double-blind, multicenter (two sites), placebo-controlled, outpatient trial conducted over 12 weeks	104 postmenopausal Italian women with ≥ 7 moderate to severe hot flashes per day during at least the prior two weeks	To determine whether daily intake of soy protein isolate powder alleviates hot flashes in postmenopausal women	Soy protein isolate 60 g (contains 40 g of protein and 76 mg of soy isoflavones) or placebo (casein) 60 g (contains 40 g of protein only)	Diaries to record the severity of menopausal symptoms and any bleeding during the study period	Daily consumption of soy protein isolate reduced frequency of daily hot flashes by 45% in the soy group compared to a 30% reduction in the placebo group ($p < 0.01$).
Dalais et al., 1998	Randomized, double-blind, placebo-controlled, crossover, outpatient trial conducted in Australia over 24 weeks	52 postmenopausal women with a hot flash rate ≥ 14 per week	To test the hypothesis that increasing dietary intake of phytoestrogens reduces the health impact of menopause	A high-phytoestrogen diet (i.e., breads either made by 45 g per day of soy grits or 45 g per day of linseed kibble) and low-phytoestrogen diet (i.e., bread made by 45 g per day of wheat kibble); the soy diet provided isoflavones 52.64 ± 8.68 mg per day; treatment was for 12 weeks followed by a four-week rest and then crossover treatment for another 12 weeks.	Urinary phytoestrogen concentrations, hot flash rate, vaginal smears, bone mineral density, and bone mineral content for two 12-week periods	High-phytoestrogen groups had urinary excretion of phytoestrogen 10–30 times higher compared to the low-phytoestrogen diet group ($p < 0.01$). The hot flash rate declined 41% in the linseed group ($p < 0.009$) and 51% in the wheat group ($p < 0.001$), but only declined 22% in the soy group, which did not reach statistical significance.

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Table 2. Studies Investigating the Relationship Between Soy Isoflavones and Menopausal Symptoms in Healthy Women *(Continued)*

Study	Design and Length of Study	Sample	Purpose of Study	Soy Product Used	Data Collection	Results
Albertazzi et al., 1999	Randomized, double-blind, multicenter (two sites), placebo-controlled, outpatient trial conducted over 12 weeks	104 postmenopausal Italian women with severe hot flashes (≥ 7 moderate to severe hot flashes per day during at least the prior two weeks)	To assess the relationship between phytoestrogen level in the blood and urine and postmenopausal symptoms	Soy protein isolate 60 g (contains 40 g of protein and 76 mg of soy isoflavones) or placebo (casein) 60 g (contains 40 g of protein only)	Hot flashes daily diary, lateral vaginal wall cytology, and blood and urine samples	Women in the experimental group had higher levels of isoflavones in their blood and urine. However, the high level of isoflavones did not correlate with a decrease in hot flashes.
Washburn et al., 1999	Randomized, double-blind, single-center, crossover, placebo-controlled, outpatient trial conducted in the United States over three six-week periods	51 nonhypertensive, nonhypercholesterolemic, perimenopausal women with at least one hot flash or night sweat per day	To determine whether daily intake of phytoestrogens in a precise amount affects chronic disease risk and menopausal symptoms in perimenopausal women	20 g soy protein supplement containing 34 mg of phytoestrogens consumed either once or twice per day or 20 g placebo (carbohydrate supplement) containing no phytoestrogens	Body weight, height, blood pressure, lipids, lipoproteins, clinical chemistry, frequency and severity of menopausal symptoms, and quality of life; the studies were repeated in six-week intervals before each instance that women were reassigned to another group.	Total cholesterol declined significantly in both soy groups ($p < 0.01$); low-density lipoprotein (LDL) declined significantly in the once-daily ($p < 0.05$) and twice-daily ($p < 0.01$) groups.
Scambia et al., 2000	Randomized, double-blind, placebo-controlled, outpatient trial conducted in Italy over 12 weeks	39 postmenopausal women with echographic endometrial thickness of less than 4.5 mm, negative x-ray mammography, and a metabolic and biochemical index within the normal range	To examine the effect of soy extract and placebo when given alone or in combination with conjugated equine estrogen on early-climacteric symptoms in postmenopausal women	400 mg soy extract (50 mg soy isoflavones) versus placebo for 10 weeks; conjugated equine estrogen 0.625 mg per day was administered to both groups (weeks 6–10).	Plasma concentrations of daidzein, genistein, cholesterol, triglycerides, high-density lipoproteins, LDL, FSH, LH, growth hormone, parathormone, osteocalcin, and prolactin, vasomotor symptoms, vaginal cytology, endometrial thickness, and pulsatility index of the uterine artery	A statistically significant reduction was found only in hot flash frequency ($p < 0.01$) and severity ($p < 0.001$) in the soy extract group. No other changes were associated with soy administration.
Upmalis et al., 2000	Randomized, double-blind, multicenter (15 sites), placebo-controlled, outpatient, parallel trial conducted over 12 weeks	177 healthy postmenopausal American women with five or more hot flashes per day	To examine the safety and efficacy of an oral isoflavone extract in alleviating hot flashes in postmenopausal women	Two soy isoflavone extract tablets daily at bedtime (50 mg total of genistein and daidzein) compared to placebo	Daily diary card, FSH levels, SHBG, serum osteocalcin, urinary N-telopeptides, vaginal pH, maturation index, menopausal-related quality of life, vital signs, hematology, chemistry, urinalysis, and transvaginal ultrasonography	The number and severity of hot flashes decreased in both groups ($p < 0.05$). However, the soy extract group had a statistically significant reduction in hot flash severity compared to the placebo group ($p = 0.01$) and a reduction in the frequency of hot flashes over the first six weeks ($p = 0.03$). No significant change was found in any of the other outcome variables.

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Table 2. Studies Investigating the Relationship Between Soy Isoflavones and Menopausal Symptoms in Healthy Women *(Continued)*

Study	Design and Length of Study	Sample	Purpose of Study	Soy Product Used	Data Collection	Results
St. Germain et al., 2001	Randomized, double-blind, placebo-controlled, outpatient trial conducted in the United States over 24 weeks	69 nonsmoking perimenopausal women with at least 10 hot flashes and/or night sweats per week	To investigate whether intake of an isoflavone-rich (80.4 mg) soy protein daily for 24 weeks has any effect on menopausal symptoms of perimenopausal women	Isoflavone-rich soy protein isolate (80.4 mg isoflavones), and isoflavone-poor soy protein isolate (4.4 mg isoflavones) versus control (no isoflavones)	Menopausal Diary and Menopausal Index were used to record the frequency, duration, and severity of menopausal symptoms; 24-hour urine samples were collected to measure urinary isoflavone concentrations.	Frequency of hot flashes ($p = 0.0003$) and night sweats ($p = 0.0007$) was statistically significant over time in all groups. Severity of hot flashes was not significantly different for any of the three groups over time.
Faure et al., 2002	Randomized, double-blind, multicenter (two sites), placebo-controlled, outpatient, parallel trial conducted in France over 16 weeks	75 women in natural or surgical menopause suffering from at least seven hot flashes per day	To examine the effect of intake soy isoflavones on hot flashes in menopausal women	Soy extract group compared to placebo group	A menopausal diary was used to record hot flashes and night sweats; women were assessed at baseline and weeks 2, 4, 8, and 16.	The soy extract group had a significant decline in the frequency of hot flashes compared to placebo ($p = 0.01$).
Han et al., 2002	Randomized, double-blind, placebo-controlled trial conducted over four months	80 healthy postmenopausal Brazilian women with hot flashes	To assess the effectiveness of soy isoflavone 100 mg per day for four months in decreasing menopausal symptoms and the influence on cardiovascular risk factors in postmenopausal women	Three soy isoflavone capsules per day (one capsule every eight hours for a total 100 mg per day of genistein, daidzein, and glycitein)	Menopausal symptoms, levels of FSH, LH, 17ъ-estradiol, plasma lipids, lipoproteins, body mass index, blood pressure, blood glucose, and transvaginal sonography	Menopausal symptoms decreased in both groups but were significantly lower in the soy isoflavone group ($p < 0.01$). Total cholesterol and LDL decreased significantly in the experimental compared to the placebo group ($p < 0.001$). Serum estrogen levels were higher in the experimental group, but no differences were found in FSH, LH, or endometrial thickness between experimental and placebo groups.
Burke et al., 2003	Randomized, double-blind, study-controlled, outpatient clinical trial conducted over 24 months	241 healthy American women with vasomotor symptoms at least once a day	To examine the effect of the intake of different amounts of isoflavones on vasomotor symptoms in peri- and postmenopausal women	25 g soy protein beverages containing 4 mg, 42 mg, and 58 mg per day of isoflavones	Symptom diaries were assessed on months 3, 6, 12, 18, and 24 for the number and severity of hot flashes and night sweats.	In all three groups, the number of vasomotor symptoms were reduced significantly during the follow-up period ($p < 0.0001$), but no significant difference was found at 24 months ($p = 0.1$). Among three groups, symptom severity reduced over time ($p < 0.0001$), but no significant difference existed at 24 months ($p = 0.37$).

Table 3. Relationship of Soy Isoflavones and Menopausal Symptoms in Women With Breast Cancer

Study	Design and Length of Study	Sample	Purpose of Study	Soy Product Used	Data Collection	Results
Quella et al., 2000	Randomized, double-blind, placebo-controlled, crossover clinical trial conducted over nine weeks	177 American breast cancer survivors with frequent (at least 14 times per week) and severe (to an extent that warrants intervention) hot flashes	To determine whether soy isoflavones could alleviate hot flashes in women with breast cancer (n = 87 in the soy-placebo group and n = 88 in the placebo-soy group)	Three soy tablets per day (total 150 mg of soy isoflavones)	A questionnaire booklet to record the pattern of hot flashes and any side effects that might be caused by the study medication	Hot flashes were reduced in both groups. For women who received soy, 44% reported a reduction of less than 25%, 21% reported a 25%–50% reduction, and 35% reported a reduction of more than 50%. For women who received placebo, the respective reduction rate was 40%, 22%, and 38% (p = 0.78). The results suggest that soy isoflavones are not superior to a placebo.
Van Patten et al., 2002	Randomized, double-blind, placebo-controlled, outpatient clinical trial conducted over 12 weeks	123 Canadian women with early-stage breast cancer with a hot flash score (frequency x intensity) of ≥ 10 per week.	To evaluate the effectiveness and acceptability of a soy beverage in treating hot flashes in postmenopausal women with breast cancer compared to placebo; to test the hypothesis that soy beverages can reduce 33% mean weekly hot flash score of ≥ 10 for women in the study group; soy beverages group (n = 59) was compared to rice beverage group (n = 64).	Soy beverage 250 ml twice a day (45 mg soy isoflavones) versus rice beverage as placebo	Baseline studies were conducted for four weeks to document the frequency and severity of hot flashes. Then, women were required to continuously record their hot flashes for 12 weeks. In the last week of the study, the participants' perceived rate of the effect of the beverage, acceptability, and a guess of which beverage they used were recorded.	The soy group had a 30% reduction in hot flashes compared to 40% in placebo group. The results suggest that the placebo provided the same or better relief of hot flashes in women with breast cancer. In addition, the soy group had more frequent and severe gastrointestinal side effects than the placebo group and had a higher dropout rate because of this reason.

possible benefit of other ingredients in soy such as fiber but also expose themselves to the possibility of overdose (Messina & Loprinzi, 2001).

Genetically modified soy products also are functional foods that commonly are sold in the United States. Bioengineers use a method of adding in or removing genes from soy DNA to create a new breed of plant. Genetically modified soy is different from conventional soy in its genes, which may alter its nutritional value. The land used to grow genetically modified soy in the United States has risen from 6 million acres in 1996 to more than 58 million acres in 2001. Most soybeans currently produced in the United States are genetically modified (O'Shea, 2001). Because genetically modified soy products are not required to be labeled (Keeler & Lappe, 2001), consumers cannot determine whether a soy product contains genetically modified soy. Although these soy products are generally considered safe, whether DNA alteration by artificial means can cause any harm in the future is unknown.

The complex food process is another problem related to some soy products. To mask the unpleasant flavor of soy, artificial flavors such as monosodium glutamate (MSG) commonly are added to soy products (Fallon & Enig, 2000). Many soy products also are high in fat, oil, sodium, and sugar to attract consumers of different age groups. Energizing bars and soy nuts, for example, are available commercially and promoted as healthy snacks for young age groups. High consumption of those products, however, may not be healthy because of other harmful ingredients.

Soy isoflavone products are readily available, but their processing raises concerns about their safety. Healthcare professionals must be aware of the risks and benefits. For healthcare providers in oncology, the use of soy isoflavones in women with breast cancer remains controversial (Messina, 2000) because soy isoflavones may have estrogen-like properties. Whether isoflavones exert estrogenic effects in women who already have high estrogen levels is unclear. If the effect of soy isoflavones depends on the estrogen environment, then isoflavones may act as an estrogen agonist in a low-estrogenic environment, which is common in postmenopausal women with breast cancer, regardless of their estrogen-receptor status.

Conclusion

Soy is perceived as a healthy lifestyle choice in the United States, but it also has potential as a complementary therapy for women to prevent breast cancer and as an alternative treatment to alleviate menopausal symptoms. For breast cancer survivors, however, the use of soy isoflavones to promote their health remains controversial. Most physicians are reluctant to recommend soy isoflavones to women for several reasons: Efficacy and safety dosage have not been established, the potential effect as an estrogen agonist still is a concern in

breast cancer survivors, and only scant scientific data exist about this population. More data are necessary at the cellular level to determine the effect of soy isoflavones in normal breast tissues and breast cancer cells. More clinical trials need to be conducted on a longitudinal basis to evaluate the safe dosage, effectiveness, and side-effect profile in midlife women, including breast cancer survivors. There is no shortcut to good health. Nurses are key informants to the public about the available evidence in adapting safe and effective lifestyle behaviors. Printed materials, such as the Patient Education Fact Sheet provided, can be used to enhance patients' knowledge about soy. Advanced practiced nurses should not only provide updated information to the public but also interpret research results carefully.

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For more information . . .

- Susan G. Komen Breast Cancer Foundation
  www.komen.org
- Y-ME National Breast Cancer Organization
  www.y-me.org
- National Breast Cancer Coalition
  www.natlbcc.org

Links can be found at www.ons.org.