Dietary Soy Intake and Breast Cancer Risk

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Purpose/Objectives: To conduct a metasynthesis of the literature on human studies of the relationship between dietary soy intake and breast cancer risk.

Data Sources: Publications in English reporting human studies were searched with the terms *soy* and *breast cancer*, using Ovid®, PubMed, and EBSCO databases. Only human studies investigating the relationship of soy intake to breast cancer development in women published from January 1997 through June 2008 were included in the review.

Data Synthesis: A total of 364 publications were located; 18 of the studies met the inclusion criteria and 18 additional studies were located through other publications identified in the search. Because four articles reported on the same two studies, a total of 34 studies were included in the review.

Conclusions: The naturally occurring dietary intake of soy food or its components appears safe for women without breast cancer; however, the safety of high supplements of soy or its components is less certain.

Implications for Nursing: Nurses should become more knowledgeable about soy foods and supplements and include soy intake in dietary assessments. Nurses caring for women at high risk for or with a history of breast cancer should confer with dietitians on current practice recommendations. Women with health issues should avoid initiating high intake of soy dietary supplements until the possible effects are better understood.

About one in eight women born in the United States today is at risk for receiving a breast cancer diagnosis during his or her lifetime. In 2009, an estimated 192,370 women will be diagnosed with and 40,170 will die from breast cancer (National Cancer Institute [NCI], 2009). The risk for developing invasive breast cancer increases as women age, with about 66% aged 55 years or older at diagnosis (American Cancer Society [ACS], 2009). Age-related breast cancer risks, however, do not reflect an individual woman's risks, which may be greater or smaller depending on a number of factors. In addition to older age and female gender, being of Caucasian race, having inherited certain genetic mutations, having a family or personal history of breast cancer, having more dense breast tissue, having begun menstrual periods before the age of 12 years or menopause after the age of 55 years, radiation treatment to the chest area early in life, and prior treatment (mothers and daughters) with diethylstilbestrol are considered nonmodifiable risk factors. Modifiable risk factors include having not had children or having had the first pregnancy after the age of 30 years, having no history of breastfeeding, being overweight or obese, having a lack of exercise, recent use of birth control pills, postmenopausal hormone therapy, and alcohol use (ACS). The pressing need to discover some means to decrease the risk of breast cancer development has led scientists to examine soy foods as possible prevention strategies.

Soy Isoflavones, Sources, and Effects

Soy Isoflavones

Soybeans, also referred to as soy or soya, are plants of Asian originthat produce beans used in a variety of food products (Biology Online, 2005). Soybeans and soy products are a major source of phytoestrogen, an estrogen-like substance (MedlinePlus, 2008) also referred to as plant estrogen. Isoflavones, one class of phytoestrogens, are structurally similar to mammalian estrogens, have estrogenic properties, and are potential anticarcinogens (Peeters, Keinan-Boker, van der Schouw, & Grobbee, 2003). Isoflavones also are considered a subclass of flavonoids, a large family of compounds synthesized by plants and thought to have potential antioxidant properties (Linus Pauling Institute, 2008). Antioxidants are substances that protect cells from damage caused by free radicals produced by oxidation during normal metabolism, thought to play a role in cancer development (NCI, 2004). The most common dietary isoflavones are genistein, daidzein, and glycitein (Linus Pauling Institute), sometimes also referred to as isoflavonoids (Kelly, Nelson, Waring, Joannou, & Reeder, 1993). The major metabolite of daidzein is equol, a nonsteroidal estrogen produced in the intestines (Medicinenet.com, 2004). Only about 33% of the population from Western cultures are capable of producing equol based on the findings of urinary excretion studies (Setchell, Brown, & Lydeking-Olsen, 2002). Because equol has greater estrogenic activity than daidzein or other metabolites, differences

in its production may account for some of the variation in cancer association reported among different racial or ethnic populations (Linus Pauling Institute). Another daidzein metabolite, O-demethylangolensin, also is thought to be formed in the intestines (Adlercreutz, 1995) and has variable urinary excretion rates possibly related to individual variability in the metabolism of dietary isoflavones (Kelly et al.).

Soy Dietary Sources

Soybeans are the main dietary source of isoflavones. Foods made from soybeans in the traditional Asian diet include tofu, miso, natto, tempeh, and edamame. Foods made from soybeans eaten in Western countries include soy milk, soy cheese, soy yogurt, and soy meat substitutes. Soy isoflavone supplements and extracts are available as dietary supplements, although their actual isoflavone content is not standardized and may vary (Linus Pauling Institute, 2008). Higdon (2007) identified some common foods made from soybeans, their serving sizes, and respective isoflavone content (see Table 1). An estimated upper limit for isoflavone intake is 100 mg per day, or the approximate amount in three servings of traditional soy foods (Messina, 2008).

Soy Estrogenic and Nonestrogenic Effects

Soy isoflavones and their metabolites exert weak estrogenic activity by binding to estrogen receptor sites on cells, mimicking estrogen in some types of tissue, and blocking estrogen effects in others (Wang, 2002). Soy isoflavones also can act independently of estrogen receptors, including inhibition of enzymes involved in estrogen metabolism and cell proliferation as well as antioxidant activities (Barnes et al., 2000). Consequently, possible relationships between dietary soy intake and the development of hormone-associated cancers, including breast cancer, remain a current focus of research interest.

Table 1. Isoflavone Content of Selected Soy Foods

Food	Serving	Total Isoflavones (mg)	Daidzein (mg)	Genistein (mg)
Tofu	3 ounces	20	8	12
Miso	1/2 cup	59	22	34
Tempeh	3 ounces	37	15	21
Edamame	1/2 cup	12	6	6
Soy milk	1 cup	30	12	17
Soy cheese, mozzarella	1 ounce	2	0.3	1
Tofu yogurt	1/2 cup	21	7	12
Soy meat substitute				
Hot dog	1 dog	11	3	6
Sausage	3 links	3	0.6	2

Note. From *An Evidence-Based Approach to Dietary Phytochemicals* (p. 132), by J. Higdon, 2007, New York: Thieme Medical. Copyright 2007 by Thieme Medical. Adapted with permission.

Clinical Evidence of Dietary Soy and Breast Cancer Development

Literature Review

The current review was guided by experts in the process of reviewing and synthesizing literature (Cooper, 1998; Stock, 1994). A search was conducted for publications in English reporting human studies using the terms *soy* and *breast cancer* with Ovid®, PubMed, and EBSCO databases, including CINAHL® and Academic Search Elite.

Only human studies that investigated the relationships between dietary soy intake and breast cancer development in women published from January 1997 through June 2008 were selected as representative of a period of intense investigation of this topic. The intervention studies selected were analyzed, summarized, and synthesized to answer three questions on the relationship between dietary soy intake and breast cancer development in women: what are the characteristics of research studies over the past decade, what do current research findings say about the relationship of soy intake to the development of breast cancer, and what general conclusions can be drawn from these findings?

Using the search terms of *soy* and *breast cancer*, 305 articles were located from OVID, 105 from PubMed, and 114 from EBSCO. After deletion of duplicates, 364 studies remained. Eighteen studies were human studies published from January 1997 through June 2008 that investigated the relationship of soy with breast cancer development in women. Eighteen additional studies were located through publications identified in the search. A total of 36 published studies were included in this review. Because four articles reported on the same two studies, 34 actual studies were reviewed (see Table 2). The 346 excluded publications included 31 literature reviews or meta-analyses related to soy intake and breast cancer risk and 61 general articles (e.g., commentaries, issues, informational, research briefs). The other excluded articles addressed topics that were related to soy intake, breast, or other cancers but were not the focus of this review. They included mammographic density or benign breast disease (n = 15); menopausal symptom management (n = 16); tamoxifen, breast cancer treatment, or survival (n = 19); cognition (n = 1); diabetes (n = 1); biochemical, genetic, cellular, or endocrine effects (n = 113); nutrition or nutrition interventions (n = 55); prostate cancer (n = 6); general cancer prevention (n = 8); dermatologic uses (n = 2); and mouse, rat, or other animal studies (n = 18).

Selected Study Characteristics

Design: The 34 studies selected included cohort and case-control studies. Six had a

cohort design, including three prospective cohort studies. Twenty-eight had a case-control design, including 1 familial matched, 11 nested, 6 hospital-based, and 17 population-based case-control studies.

Race or ethnicity: The populations from which the study samples were derived represented 12 countries and multiple races and ethnicities. Study populations were: Chinese (n = 6); Japanese (n = 6); British (n = 3); Dutch (n = 3); Australian (n = 2); Canadian (n = 2); Filipino (n = 2); German (n = 2); American and predominantly Caucasian (n = 1); Asian American, including Chinese and Japanese, and non-Asian American such as African American, Latino, and Caucasian (n = 1); American and Canadian, predominantly Caucasian (n = 1); South Asian residing in England (n = 1); French (n = 1); Italian (n = 1); Greek (n = 1); and South Korean (n = 1).

Menopausal status: Four of the studies addressed breast cancer risk in premenopausal women only, two in postmenopausal women only, and the remainder addressed breast cancer risk in women from premenopausal through postmenopausal status.

Dietary soy forms: The forms of dietary soy intake included soy foods (total, fermented, and unfermented), soybeans (fresh and dried), soy proteins, tofu (soybean curd), and tofu-containing foods (particularly miso soup and natto), phytoestrogens (traditional and nontraditional soy foods, soy-enriched flour, and soy protein-enriched canned foods), isoflavones, and the specific isoflavones daidzen and genistein.

Dietary soy intake assessment: Assessment of dietary soy intake varied among the studies. A food frequency questionnaire was used in 17 studies, administered either by self-report or by an interviewer. Structured or semistructured interviews or a food diary were used in 11 studies. A nutrient database or food composition table, including U.S. Department of Agriculture and Taiwanese databases, was used in nine studies to determine dietary soy intake.

Dietary soy measures: Direct measures of dietary soy intake included times eaten per day or week, soy proteins in grams per week, tofu in times per week or year, phytoestrogens in micrograms per day, isoflavones in milligrams per day or milligrams per week, and daidzen and genistein in micrograms or milligrams per day. Indirect measures of dietary soy intake included serum and urine levels of total isoflavonoid (isoflavones) and of a variety of specific isoflavonoids (isoflavones) including daidzen, genistein, glycitein, equol, and O-desmethyangolensin. Serum isoflavonoid (isoflavone) levels were reported in nanograms per milliliter, and urine isoflavonoid (isoflavone) levels in nanomols per milligram of urinary creatinine, or micrograms per millimol of urinary creatinine. Serum isoflavone levels were reported in micrograms per milliliter, and daidzen and genistein in nanograms per milliliter.

Findings of Reduced Breast Cancer Risk

Eighteen studies suggested some reduction in breast cancer risk associated with the dietary intake of soy or its components or the plasma levels or urinary excretion of isoflavone metabolites.

Premenopausal: Higher dietary intake of tofu and isoflavones (Hirose et al., 2005; Hirose, Takezaki, Hamajima, Miura, & Tajima, 2003; Witte et al., 1997), and specifically the isoflavones daidzein and genistein (Linseisen, Piller, Hermann, & Chang-Claude, 2004), were associated with a reduced risk of premenopausal breast cancer.

Postmenopausal: Higher urinary excretion of the specific isoflavone diadzein was found in postmenopausal women without breast cancer compared to patients with breast cancer, indirectly suggesting a protective association between higher dietary isoflavone intake and breast cancer (Murkies et al., 2000).

Premenopausal through postmenopausal: Higher dietary soy food intake has been associated with decreased breast cancer risk in pre- and postmenopausal women (Dai et al., 2001; Shu et al., 2001; Wu, Yu, Tseng, Hankin, & Pike, 2003) with a stronger risk reduction for hormone-responsive types of breast cancer (Dai et al.; Shu et al.), although Lee et al. (2005) found a reduced risk only in women aged 40 years or older.

Specific to the type of soy food, a higher dietary intake of miso soup has been associated with reduced breast cancer risk (Yamamoto, Sobue, Kobayashi, Sasaki, & Tsugane, 2003) as has a higher intake of yellow or black soybeans (Do, Lee, Jung, & Lee, 2007; Do, Lee, Kim, Jung & Lee, 2007). Lastly, specific to the age at which soy was consumed, a higher dietary phytoestrogen and soy food intake by adolescents (Thanos, Cotterchio, Boucher, Kreiger, & Thompson, 2006; Wu et al., 2002) and a higher intake by adult women (Wu et al., 2002) was associated with reduced breast cancer risk.

Two studies found that a higher dietary intake of isoflavones and, more specifically, the isoflavones daidzein and genistein, has been associated with reduced breast cancer risk (Dos Santos Silva et al., 2004; Yamamoto et al., 2003). Higher serum plasma levels of the isoflavone genistein have been associated with reduced breast cancer risk in two studies (Iwasaki et al., 2008; Lampe et al., 2007; Verheus et al., 2007), indirectly suggesting a protective association between a higher dietary isoflavone intake and breast cancer. Higher urinary excretion rates of total isoflavonoids (isoflavones), the specific isoflavone glycitein (Zheng et al., 1999), and the daidzein metabolite equol (Ingram, Sanders, Kolybaba, & Lopez, 1997) have all been associated with reduced breast cancer risks, again indirectly suggesting a protective association between higher dietary isoflavone intake and breast cancer. Specific to the age at which isoflavones were consumed, a higher dietary intake of isoflavones during adolescence has been associated with reduced breast cancer risk (Thanos et al., 2006).

Table 2. Studies Investigating the Relationship Between Dietary Soy Intake and Breast Cancer Risk in Women

Study	Design	Sample	Soy Type	Findings
Bosetti et al., 2005	Case control; hospital-based	Italian: pre- and postmenopausal cases (n = 2,569) and controls (n = 2,588)	Dietary isoflavones	No significant association was found between dietary isoflavone intake and breast cancer risk.
Boucher et al., 2008	Case control; population-based	Canadian: pre- and postmenopausal cases (n = 372) and controls (n = 356)	Infant soy formula	Exclusive soy feeding from 0–4 months of age was associated with a 58% reduction in breast cancer risk (odds ratio [OR] = 0.42, 95% confidence interval [CI] = 0.18–1.9) and, from 5–12 months of age, with a 41% reduction in breast cancer risk (OR = 0.59, 95% CI = 0.18–0.9).
Cui et al., 2007	Case control; population-based	Chinese: pre- and postmenopausal cases (n = 1,459) and controls (n = 1,556)	Vegetable-soy or meat-sweet dietary patterns	No association was found between dietary patterns and breast cancer risk.
Dai et al., 2001; Shu et al., 2001	Case control; population-based	Chinese: pre- and postmenopausal cases (n = 1,459) and controls (n = 1,556)	Dietary soy protein and isoflavones	Highest compared to lowest soy intake was associated with a 34% reduction in breast cancer risk (OR = 0.66, 95% CI = 0.46–0.95, p for trend = 0.28) and a 56% reduction in estrogen and progesterone receptor site-positive breast cancer risk (OR = 0.44, 95% CI = 0.25–0.78, p for trend = 0.05).
den Tonkelaar et al., 2001	Case control; population-based	Dutch (Caucasian): postmenopausal cases (n = 88) and controls (n = 268)	Urine genistein	No significant association was found for the highest compared to the lowest urinary genistein excretion and breast cancer risk.
Do, Lee, Kim, et al., 2007; Do, Lee, Jung, et al., 2007	Case control; hospital-based	South Korean: pre- and postmenopausal cases (n = 359) and controls (n = 708)	Soy food grams	No association was found between total soy intake and breast cancer risk in pre- or postmenopausal women. Higher compared to lower intake of yellow or black soybeans was associated with an approximate 33% risk reduction for breast cancer (OR = 0.67, 95% CI = 0.45–0.91, p for trend < 0.02).
Dos Santos Silva et al., 2004	Case control; population-based	South Asian women in England: pre- and postmenopausal cases (n = 240) and controls (n = 477)	Dietary isoflavones	Highest compared to lowest dietary isoflavone intake was associated with a 42% reduction in breast cancer risk (OR = 0.58, 95% CI = 0.33–1, p for trend = 0.08).
Grace et al., 2004	Case control; population-based	United Kingdom: pre- and postmenopausal cases (n = 333) and controls (n = 114)	Dietary phytoestrogens and serum isoflavones (daidzein, genistein glycitein, and their metabolites O-desmethylangolensin and equol)	Higher compared to lower serum daidzen, serum equol, and urine equol were associated with a 22%, 45%, and 34% increase in breast cancer risk (adjusted odds ratio [AOR] = 1.22, 1.005–1.481; p = 0.044; AOR = 1.455, 1.051–2.017; p = 0.024; AOR = 1.344, 1.063–1.699; p = 0.013, respectively).
Hirose et al., 2003	Case control	Japanese: pre- and postmenopausal cases (n = 2,385) and controls (n = 9,013)	Tofu	Higher compared to lower tofu intake was associated with a 16% reduction in breast cancer risk in premenopausal women only (OR = 0.84, 95% CI = 0.67–1.04, p for trend = 0.02).
Hirose et al., 2005	Case control; hospital-based	Japanese: pre- and postmenopausal cases (n = 167) and controls (n = 854)	Soybean products, including tofu and dietary isoflavones	Highest compared to lowest tofu and isoflavone intake was associated with a 51% and 56% reduction in premenopausal breast cancer risk (AOR = 0.49, 95% CI = 0.25–0.95, p for trend = 0.03; AOR = 0.44, 95% CI = 0.22–0.89, p for trend = 0.02).

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Table 2. Studies Investigating the Relationship Between Dietary Soy Intake and Breast Cancer Risk in Women *(Continued)*

Study	Design	Sample	Soy Type	Findings
Horn-Ross et al., 2001	Case control; population-based	Non-Asian American (African American, Latino, and Caucasian): cases (n = 1,272) and controls (n = 1,610)	Dietary phytoestrogens (traditional and nontraditional soy foods)	No significant association was found for the highest compared to the lowest phytoestrogen intake and breast cancer risk for pre- or postmenopausal women, ethnic group, or phytoestrogen type.
Horn-Ross et al., 2002	Prospective cohort	111,526 Caucasian American women: breast cancer cases (n = 711)	Dietary phytoestrogen and genistein	No significant association was found for phytoestrogen or genistein intake and breast cancer risk.
Ingram & Sanders, 1997	Case control; hospital-based	Australian: pre- and postmenopausal cases (n = 144) and controls (n = 144)	Dietary isoflavones (daidzein, genistein, and equol)	Highest equol urinary excretion compared to lowest was associated with a 73% reduction in breast cancer risk (AOR = 0.27, 95% CI = 0.1–0.69, p for trend = 0.009)
Iwasaki et al., 2008	Case control; population-based	Japanese: pre- and postmenopausal cases (n = 144) and controls (n = 288)	Dietary genistein, daidzein, and isoflavones (genistein plus daidzein); serum genistein and daidzein	Highest compared to lowest plasma genistein levels were associated with a 66% reduction in breast cancer risk (AOR = 0.34, 95% CI = 0.16–0.74, p for trend = 0.02).
Keinan-Boker et al., 2004	Case control; population-based	Dutch: pre- and postmenopausal cases (n = 280) and controls (n = 15,555)	Phytoestrogens	No significant association was found between phytoestrogen intake and breast cancer risk.
Key et al., 1999	Prospective cohort	Japanese: pre- and postmenopausal women (N = 11,067)	Soy food	No significant association was found between soy intake and breast cancer risk.
Lampe et al., 2007	Case control; population-based	Chinese: pre- and postmenopausal cases (n = 196) and controls (n = 1,002)	Plasma genistein and daidzein	Highest compared to lowest plasma genistein levels were associated with a 74% reduction in breast cancer risk (OR = 0.26, 95% CI = 0.13–0.5, p for trend < 0.0001).
Lee et al., 2005	Case control	Chinese: pre- and postmenopausal cases (n = 250) and controls (n = 219)	Soy rich foods	Higher compared to lower soy intake was associated with a 50% reduction in breast cancer risk in women older than 40 years only (OR = 0.5, 95% CI = 0.3–1).
Linseisen et al., 2004	Case control; population-based	German: premenopausal cases (n = 278) and controls (n = 666)	Dietary daidzein and genistein	Higher compared to lower genistein intake was associated with a 53% reduction in estrogen and progesterone receptor-positive breast cancer risk (OR = 0.47, 95% CI = 0.29–0.74, p for trend = 0.002).
Murkies et al., 2000	Case control; hospital-based	Australian: postmenopausal cases (n = 18) and controls (n = 20)	Urine daidzein and genistein	Controls had significantly higher urinary excretion levels of daidzein than breast cancer cases (p = 0.03).
Nishio et al., 2007	Prospective cohort	30,454 Japanese women: breast cancer cases (n = 145)	Soy foods	No significant association was found between soy food intake and breast cancer risk.
Peterson et al., 2003	Case control	Greek: pre- and postmenopausal cases (n = 820) and controls (n = 1,548)	Dietary flavonoids	No significant association was found between higher compared to lower dietary isoflavone intake and breast cancer risk.
Piller et al., 2006	Case control; population-based	German: premenopausal cases (n = 220) and controls (n = 237)	Dietary and plasma genistein	No significant association was found between plasma genistein concentration and premenopausal breast cancer risk.

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Table 2. Studies Investigating the Relationship Between Dietary Soy Intake and Breast Cancer Risk in Women *(Continued)*

Study	Design	Sample	Soy Type	Findings
Shannon et al., 2005	Case control	Shanghai Chinese: pre- and postmenopausal cases (n = 378) and controls (n = 1,070)	Soy food (total unfermented and fermented)	No significant association was found between soy intake and breast cancer risk.
Thanos et al., 2006	Case control; population-based	Canadian: pre- and postmenopausal cases (n = 3,024) and controls (n = 3,420)	Soy foods and dietary isoflavones	Higher adolescent phytoestrogen and isoflavone intake was associated with a 29% and 19% reduction in breast cancer risk (AOR = 0.71, 95% CI = 0.62–0.82, p for trend < 0.0001; AOR = 0.81, 95% CI = 0.71–0.94, p for trend < 0.01, respectively).
Touillaud et al., 2006	Prospective cohort	26,868 French premenopausal women: breast cancer cases (n = 402)	Dietary isoflavones	No significant association was found between isoflavone intake and premenopausal invasive breast cancer.
Travis et al., 2008	Prospective cohort	37,643 British women: breast cancer cases (n = 585)	Dietary isoflavones	No significant association was found between isoflavone intake and breast cancer risk in pre- or postmenopausal women.
Verheus et al., 2007	Case control; population-based	Dutch: pre- and postmenopausal cases (n = 383) and controls (n = 383)	Plasma isoflavones (daidzein, genistein, glycitein, O-desmethylangolensin, and equol)	Highest compared to lowest plasma genistein levels were associated with a 32% reduction in breast cancer risk (OR = 0.68, 95% CI = 0.47–0.98, p for trend = 0.07).
Ward et al., 2008	Case control; population-based	1,189 British pre- and postmenopausal women: breast cancer cases (n = 237)	Serum and urine phytoestrogens (daidzein, genistein glycitein, O-desmethylangolensin, and equol)	Higher compared to lower total urinary isoflavone levels were associated with an 8% increase in breast cancer risk (OR = 1.08, 95% CI = 1–1.16, p = 0.055); higher compared to lower urinary equol levels were associated with a 7% increase in estrogen receptor site-positive breast cancer risk (OR = 1.07, 95% CI = 1.01–1.12, p = 0.013).
Witte et al., 1997	Case control; familial-matched, population-based	American and Canadian Caucasian: premenopausal cases (n = 140) and controls (n = 222)	Tofu and soybeans	Higher compared to lower dietary soy intake was associated with a 50% reduction of premenopausal bilateral breast cancer risk (AOR = 0.5, 98% CI = 0.2–1.1).
Wu et al., 2002	Case control; Population-based	Asian American (Chinese, Japanese, and Filipino): pre- and postmenopausal cases (n = 501) and controls (n = 594)	Dietary soy and isoflavones	High adult and adolescent soy intake compared to low was associated with a 47% reduction in breast cancer risk (OR = 0.53, 95% CI = 0.36–0.78, p for trend = 0.001); high adolescent and low adult soy intake was associated with a 23% reduction in breast cancer risk (OR = 0.77, 95% CI = 0.51–1.16, p for trend = 0.001).
Wu et al., 2003	Case control; population-based	Asian American: pre- and postmenopausal cases (n = 501) and controls (n = 594)	Dietary isoflavones	High compared to low soy intake during both adolescence and adulthood was associated with a 60% reduction in breast cancer risk (OR = 0.4, 95% CI = 0.24–0.66).
Yamamoto et al., 2003	Prospective cohort	21,852 Japanese women: breast cancer cases (n = 179)	Soy, miso soup, and dietary isoflavones	Highest compared to lowest miso soup and dietary isoflavone intake was associated with a 40% and 54% reduction in breast cancer risk (adjusted risk ratio [ARR] = 0.6, 95% CI = 0.34–1.1, p for trend = 0.042; ARR = 0.46, 95% CI = 0.25–0.84, p for trend = 0.043, respectively).
Zheng et al., 1999	Case control; population-based	Chinese: pre- and postmenopausal cases (n = 60) and controls (n = 60)	Urine daidzen, genistein, glycitein, O-desmethyangolensin, and equol	Higher compared to lower urinary excretion of phenols plus total isoflavonoids and glycitein was associated with an 86% reduction in breast cancer risk (AOR = 0.14, 95% CI = 0.02–0.88; AOR = 0.14, 95% CI = 0.03–0.79).

Findings of No Breast Cancer Risk Reduction

Twelve studies (13 articles) reported no significant overall reduction of breast cancer risks associated with a higher dietary intake of one or more forms of soy or its components (Bosetti et al., 2005; Cui et al., 2007; Do, Lee, Jung, et al., 2007; Do, Lee, Kim, et al., 2007; Horn-Ross et al., 2001, 2002; Keinan-Boker, van der Schouw, Grobbee, & Peeters, 2004; Key et al., 1999; Nishio et al., 2007; Peterson et al., 2003; Shannon et al., 2005; Touillaud, Thiebaut, Niravong, Boutron-Ruault, & Clavel-Chapelon, 2006; Travis et al., 2008). No significant association was found between plasma genistein levels and breast cancer risks (Piller, Chang-Claude, & Linseisen, 2006), indirectly suggesting no difference in breast cancer risk related to dietary isoflavone intake. Nor was a significant association between urinary genistein levels and breast cancer risks found (den Tonkelaar et al., 2001), again indirectly suggesting no difference in breast cancer risk related to dietary isoflavone intake.

Findings of Increased Breast Cancer Risk

Two studies reported an association between exposure to isoflavones and increased breast cancer risk. Serum levels of the specific isoflavone diadzein and of its metabolite equol in serum (Grace et al., 2004) and urine (Grace et al.; Ward et al., 2008) were significantly associated with an increased risk of developing breast cancer. Additionally, urine equol was significantly associated with estrogen receptor site-positive breast cancer risk in premenopausal and perimenopausal women only (Ward et al.).

Findings by Nationality

North American: Two studies of Caucasian Americans and non-Asian Americans found no significant relationship between dietary phytoestrogens or phytoestrogens and genistein and breast cancer risks (Horn-Ross et al., 2001, 2002). Two studies of Asian Americans found decreased breast cancer risks associated with higher dietary soy or isoflavone intake (Wu et al., 2002, 2003). One study of Caucasian Americans and Canadians found decreased breast cancer risks associated with increased dietary tofu intake (Witte et al., 1997), and two studies of Canadians found decreased breast cancer risks associated with infant soy formula use or higher dietary isoflavone intake (Boucher et al., 2008; Thanos et al., 2006).

European: One British study reported no relationship with breast cancer risk (Travis et al., 2008), two reported contradictory increased breast cancer risks for dietary isoflavone intake and urinary equol excretion (Grace et al., 2004; Ward et al., 2008), and one of South Asians living in England reported a decreased breast cancer risk associated with higher dietary isoflavone intake (Dos Santos Silva et al., 2004). One French study found decreased breast cancer risks and higher dietary isoflavone intake (Touillaud et al., 2006). Two German studies found no relationship between dietary genistein intake or plasma genistein levels and breast cancer risks (Linseisen et al., 2004; Piller et al., 2006). Two Dutch studies found no relationship between dietary phytoestrogen intake or urinary genistein excretion and breast cancer risks (den Tonkelaar et al., 2001; Keinan-Bokar et al., 2004), although one study found decreased breast cancer risks associated with higher plasma genistein levels (Verheus et al., 2007). One Italian (Bosetti et al., 2005) and one Greek study (Peterson et al., 2003) found no relationship between dietary phytoestrogen or isoflavone intake and breast cancer risks.

Asian: One South Korean study (two journal articles) found no relationship between dietary soy intake and breast cancer risks (Do, Lee, Kim, et al., 2007; Do, Lee, Jung, et al., 2007). Two Chinese studies found no relationship between dietary vegetable-soy patterns or soy intake (Cui et al., 2007; Shannon et al., 2005), although four Chinese studies (five journal articles) found decreased breast cancer risks associated with higher dietary soy or isoflavone intake and higher plasma genistein levels (Dai et al., 2001; Shu et al., 2001; Lampe et al., 2007; Lee et al., 2005; Zheng et al., 1999). Two Japanese studies found no relationship between dietary soy, phytoestrogen, or genistein intake (Nishio et al., 2007), although four Japanese studies found decreased breast cancer risks associated with dietary tofu, miso soup or isoflavone intake, and higher plasma genistein levels (Hirose et al., 2003; 2005; Iwasaki et al., 2008; Yamamoto et al., 2003).

Lastly, two Australian studies found decreased breast cancer risks associated with urinary daidzein and equal excretion levels. The ethnicity of participants were not described (Ingram & Sanders, 1997; Murkies et al., 2000).

In summary, the sample nationality most consistently reporting a decrease in the risk for developing breast cancer was Chinese, and it should be noted that Asian Americans and South Asians living in England also reported decreased breast cancer risks.

Limitations

Limitations to these studies are related to difficulties in accurate quantification of soy intake and inadequate knowledge of the bioavailability, interactions, dose response, and metabolism and excretion of soy and isoflavones. Unmeasured sources of soy intake and unidentified bioactive substances also may have confounded the findings. Because different forms, methods, and measures of soy were used in the studies, only general conclusions can be offered.

Conclusions

This review of studies on the dietary intake of soy or soy products suggests a protective or no relationship to breast cancer risk in women, although two studies suggest an associated increased risk for breast cancer development. Clearly, nurses should become more knowledgeable of

What is soy?
- Soy refers to soybeans, an Asian plant used in many foods.
- Soy is a major source of plant estrogens (phytoestrogens).
- Isoflavones are one type of plant estrogen, and include daidzein and genistein.

What foods commonly contain soy?
- Soy is most common in Asian diets as tofu, miso, natto, tempeh, and edamame. Some foods gaining in popularity in Western culture include tofu yogurt, soy milk, cheese, and meat substitutes. Foods also may be fortified with soy.

How might dietary soy be related to the risk of breast cancer?
- Soy or its components might block estrogen and exert a protective effect.
- Soy or its components might act like estrogen and stimulate the growth of some types of cancer.
- Soy or its components may act as antioxidants, and protect cells from damage which may lead to cancer development.

What have researchers learned about dietary soy intake and related breast cancer risk?
- About 50% of studies found a protective effect for breast cancer.
- About 50% of studies found no protective effect for breast cancer.
- Two studies have found an increased risk of breast cancer.
- The age at which soy is eaten may influence breast cancer risk.
- Soy intake may actually represent a healthy lifestyle overall.

Recommendations for women regarding soy intake and breast cancer development:
- Dietary soy supplements and medications are not considered "drugs" and are not regulated by the U.S. Food and Drug Administration.
- Consuming foods which naturally contain soy is probably safer than consuming foods fortified with concentrated amounts of soy additives.
- The safety of consuming dietary supplements or medications with high doses of soy or soy components (isoflavones, daidzein, or genistein) is unknown and is questionable for women who have had or are at high risk of developing breast cancer.

Figure 1. What Patients Should Know About Soy and Breast Cancer Risk

Note. Based on information from Linus Pauling Institute, 2008; MedlinePlus, 2008; Messina, 2008.

soy foods and products that are less familiar in Western culture and more familiar with alternative therapies such as soy-based supplements. Questions on the intake of soy foods and over-the-counter soy-based products should be included when obtaining patient nutrition histories. Nurses caring for women who are not at a high risk for developing breast cancer may include general information about the possible breast cancer-protective properties of routine dietary soy intake in client education (see Figure 1), although no certain recommendations can be made based on the current state of the science. In the meantime, nurses caring for women at high risk for developing breast cancer or those with a previous diagnosis should collaborate closely with dieticians regarding the most current practice recommendations and closely monitor emerging scientific releases regarding dietary soy. Women at high risk for developing breast cancer or who have breast cancer histories should be told to avoid initiating high dietary intake or supplementation with soy or its components until their possible cancer-related interactions are better understood.

Future research recommendations should include the study of dietary soy intake and breast cancer risks in particular age groups as well as racial or ethnic groups, such as African American and Hispanic women. Given the complexity of the possible soy-breast cancer relationship, an interdisciplinary approach and uniformity of methods will strengthen future research findings. Consistent and comprehensive assessment of both soy food and component intake, as well as urinary excretion of these substances, is essential.

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Digital Object Identifier: 10.1188/09.ONF.531-539

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