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Implications of Phytoestrogen Intake for Breast Cancer

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ABSTRACT Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol. Interest in phytoestrogens has been fueled by epidemiologic data that suggest a decreased risk of breast cancer in women from countries with high phytoestrogen consumption. Women with a history of breast cancer may seek out these "natural" hormones in the belief that they are safe or perhaps even protective against recurrence. Interpretation of research studies regarding phytoestrogen intake and breast cancer risk is hampered by differences in dietary measurement, lack of standardization of supplemental sources, differences in metabolism amongst individuals, and the retrospective nature of much of the research in this area. Data regarding the role of phytoestrogens in breast cancer prevention is conflicting, but suggest early exposure in childhood or early adolescence may be protective. In several placebo-controlled randomized trials among breast cancer survivors, soy has not been found to decrease menopausal symptoms. There is very little human data on the role of phytoestrogens in preventing breast cancer recurrence, but the few studies conducted do not support a protective role. There is in vivo animal data suggesting the phytoestrogen genistein may interfere with the inhibitive effects of tamoxifen on breast cancer cell growth. (*CA Cancer J Clin 2007;57:260–277.*) *© American Cancer Society, Inc., 2007.*

INTRODUCTION

Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol.[1,2] Interest in phytoestrogens, particularly soy, has been fueled by epidemiologic studies that have suggested low incidence of breast cancer in countries with high soy intake, and this has been followed by in vitro and in vivo animal research suggesting a potential role for phytoestrogens in preventing breast cancer development.[1,3,4] Dietary changes present one of the few socially acceptable modifiable risk factors for breast cancer, the second leading cause of cancer deaths in women.[5] Hence, even a modest protective role of phytoestrogens could have important implications for public health. In addition to its potential role in preventing breast cancer, there has been much interest in using phytoestrogens for menopausal symptoms among breast cancer survivors. Women diagnosed with breast cancer report more menopausal symptoms than women who undergo menopause naturally,[6–8] yet they are generally advised not to use hormone therapy (HT) [9] because of concerns that HT may increase risk of recurrence.[10,11] Women often seek out complementary and alternative (CAM) therapies in place of HT for menopausal symptoms, particularly phytoestrogens, in the belief they are more "natural."[12,13]

There have been concerns that phytoestrogens, through their estrogenic properties, may increase the risk of recurrence or stimulate the growth of existing tumors.[14] Despite significant research in the area, the role of phytoestrogens in breast cancer remains controversial. Given the prevalence of CAM therapy use among breast cancer survivors[15] and research that suggests women with breast cancer consider soy products safe,[16] there is a need to clarify what is known and not known about the risks and benefits of phytoestrogens. Such information is important in enabling patients to make informed decisions about their care.

The purpose of this article is to provide a basic overview of phytoestrogen classification, source, and metabolism and to summarize current evidence regarding the most pressing clinical questions patients and providers may have about phytoestrogens and breast cancer. We review the available evidence regarding (1) the relationship between phytoestrogens and primary prevention of breast cancer; (2) the use of phytoestrogens to treat menopausal symptoms in breast cancer survivors; (3) the association between phytoestrogen use and the risk of breast cancer recurrence; and (4) interactions between phytoestrogens and tamoxifen. While not exhaustive, these are issues commonly encountered in clinical practice. Because soy and soy supplements are the most widely used and studied sources of phytoestrogens both worldwide and in the United States,[4] our main focus is on soy, although we also include data on lignans, which are another significant source of phytoestrogens in the US diet.[17,18]

PHYTOESTROGEN CLASSIFICATION AND METABOLISM

Phytoestrogens are a broad group of plant-derived compounds with the presence of a phenolic ring that allows them to bind to the estrogen receptor (ER), mimicking the effects of estrogen.[19] There are 2 major classes of phytoestrogens: the lignans and isoflavones. The coumestans and stilbenes represent 2 additional classes, but are less abundant in the diet and less well-studied.[19,20]

Lignans exist in many plants, where they form the building blocks for plant cell walls.[4] They are found in the woody portions of plants, the seed coat of seeds, and the bran layer in grains.[17] Flaxseed is by far the greatest single dietary source of lignans, but whole grains, vegetables, and tea are also significant sources and more typically ingested in the American diet.[21] Isoflavones are the most common form of phytoestrogens and are found in a variety of plants, the greatest dietary source being soy.[4,22,23] Although other legumes such as chick peas and green peas contain isoflavones as well, levels are at least 2 orders of magnitude below soy.[24] The amount of phytoestrogen in plants and foods varies considerably based on location of crop, time of harvest and crop conditions, processing, and preparation.[2,14] For example, isoflavone content in soyabeans can be decreased by more than half simply by boiling.[24]

The metabolism of lignans is quite complex. Once ingested, they are biotransformed by the action of intestinal microflora and converted to hormone-like compounds with weak estrogenic activity.[3,20,25] The main plant lignans are matairesinol and secoisolariciresinol, which are converted to the mammalian lignans enterodiol (EDL) and enterolactone (ENL), respectively, on passage through the gut and subsequent metabolism by gut microflora. Enterodiol can be further metabolized to ENL.[17] The main lignan found in blood and urine is ENL, and urinary ENL has been used as a marker for lignan intake.[17]

Isoflavones have a similarly complex metabolism. The 2 main isoflavones, genistein and daidzein, are present in soy primarily as β-D-glycosides, genistin, and dadzin.[19] Glycosidic bonds are hydrolyzed by glucosidases of the intestinal bacteria in the intestinal wall to produce aglycons.[26,27] The aglycons are further metabolized to glucuronide conjugates in the intestine and liver.[19,28] Daidzein may be metabolized to equol or to O-desmethylangolensin (O-DMA) and genistein to p-ethyl phenol. The major isoflavones that can be detected in the blood and urine are daidzein, genistein, equol, and O-DMA.[4,17,19] The aglycone form of isoflavones is biologically active.[29]

There is a great deal of individual variability in the metabolism of phytoestrogens.[1,17,30–35] Individual differences in gut microflora, use of antimicrobials, intestinal transit time, and genetic polymorphisms all likely contribute to this great variability.[14,17,19] For instance, the lignans are metabolized into ENL and EDL via gut bacteria, yet not all individuals are capable of metabolizing lignans into these metabolites. Similarly, only 30% to 50% of adults excrete equol (a metabolite of daidzein).[31,34,35] The foods ingested with phytoestrogens can affect their bioavailability, as well. Fiber intake has been shown to correlate positively with serum and urinary levels of phytoestrogen attained in women.[36,23] There is also much variability in the phytoestrogen content of dietary supplements. Setchell et al[37] analyzed 33 phytoestrogen supplements to determine whether their actual phytoestrogen content matched that of the manufacturers' claims and found considerable differences between claimed and actual content. Such differences in phytoestrogen metabolism, bioavailability, and content of supplements may account for some of the inconsistent findings of the effects of phytoestrogens in humans.[1,38]

Soy is the major source of phytoestrogens in most populations and is widely available in the

United States. Approximately 30% of individuals in the United States report using soy products at least monthly.[39] Despite this, intake of phytoestrogens remains low in the United States (.15 to 3.0 mg/day)[40,41] in comparison with East and Southeast Asian countries (20 to 50 mg/day).[42,43] Many foods available in the American diet contain a wide variety of hidden sources of processed soy (soy protein isolate, soy concentrate) often used as inexpensive fillers in processed foods.[18] Although the amounts are small, the widespread practice and frequent consumption in US diets of processed foods make them a significant source of the total phytoestrogen intake in US women. For example, Horn-Ross et al[41] found that just over 20% of US women's genistein and daidzen actually comes from doughnut consumption. Table 1 provides values of phytoestrogen contents of selected foods from a North American diet, as adapted from Thompson et al.[44]

ESTROGENIC ACTIVITY OF PHYTOESTROGENS

Estrogens have diverse effects throughout the body, attributable in part to their ability to modulate transcription of target genes in a variety of organs.[45,46] Phytoestrogens are only weakly estrogenic, having 1/10,000 (daidzein) to 1/100

TABLE **1** Phytoestrogen Content of Foods as Consumed (Wet Weight) per Serving (μg)

Food Item (100 g Serving)	DAI	GEN	MAT	SECO	Total ISO	Total PE
Soy products						
Soy milk (8.5 oz)	2,312.3	4,649.1	0.5	14.4	7,390.0	7,422.5
Tofu (1/4 cup)	2,988.0	5,456.1	0.3	5.8	8,677.9	8,688.0
Veggie burger (1/4 cup)	133.8	322.3	0.2	3.1	480.2	484.7
Legumes						
Hummus (1/4 cup)	0.5	5.7	9.5	1.5	8.3	605.8
Nuts and oil seeds						
Almonds (1/4 cup)	0.8	5.3	0.1	26.0	6.7	48.5
Cashews (1/4 cup)	0.5	3.5	0.1	12.8	7.5	41.5
Flaxseed (1/4 cup)	25.0	74.5	65.9	161,388.4	138.2	163,133.6
Sesame seed (1/4 cup)	0.9	0.7	41.8	2.5	3.6	2,722.8
Vegetables						
Alfalfa sprout (1/4 cup)	0.2	0.8	0.0	0.2	39.4	44.1
Broccoli (1/4 cup)	N/D	0.0	0.0	1.2	0.0	18.8
Carrots, raw (1/4 cup)	0.0	0.0	0.0	1.4	0.1	2.2
Garlic (1 tbsp)	0.9	2.4	0.8	7.2	3.5	102.6
Olives (1/4 cup)	0.5	0.7	0.0	11.9	2.4	15.4
Sweet potatoes (1/4 cup)	0.1	0.1	6.3	1.6	0.2	13.9
Tomatoes (1/4 cup)	0.0	0.1	0.0	0.5	0.2	3.9
Winter squash (1/4 cup)	0.0	0.1	0.0	4.7	0.1	39.8
Fruit						
Dried apricots (1/4 cup)	2.4	7.3	0.2	54.6	14.7	164.4
Dried dates (1/4 cup)	0.4	1.0	0.1	32.9	1.6	102.1
Cereals and breads						
Bread, multi (1 slice)	0.4	1.9	0.6	2,194.4	5.8	2,207.4
Bread, white (1 slice)	0.1	0.2	0.0	0.5	0.6	1.9
Cereal, high-fiber (1/4 cup)	0.3	0.3	0.1	3.8	0.9	9.5
Cereal, regular (1/4 cup)	0.1	0.3	0.2	1.2	0.9	2.8
Doughnuts (1 whole)	569.6	961.5	0.1	10.6	1,551.0	1,568.1
Wine, red (6 oz)	2.7	4.5	0.1	61.8	29.1	94.8
Tea, black (8.5 oz)	1.1	0.1	0.2	9.4	1.5	21.7
Tea, green (8.5 oz)	0.9	0.4	0.4	25.4	1.7	31.6

DAI = daidzein.
GEN = genistein.
MAT = matairesinol.
SECO = secoisolariciresinol.
ISO = isoflavone.
PE = phytoestrogen.
N/D = nondetectable.
Adapted from Thompson LU, Boucher BA, Liu Z, et al[44] with permission from *Nutrition and Cancer*.

(coumestrol),[47–49] the activity per mole compared with 17β estradiol. Despite this weak activity, concentrations of phytoestrogens in the body are 100 to 1,000-fold higher than peak levels of endogenous estradiol in premenopausal women.[1,50,51] In fact, the isoflavone metabolites genistein and daidzein have been shown to exert estrogenic effects even greater than endogenous estradiol at high concentrations in vitro, though these are outside the range of concentrations typically found in humans.[45,52–54]

It is difficult to ascertain the estrogenic activity of phytoestrogens in vivo because in addition to the marked interindividual variability in metabolism and, hence, serum levels obtained, the hormonal milieu of the individual consuming the phytoestrogen likely impacts its effects.[14,55] Another important issue to consider in these studies is the dose of phytoestrogen administered to the animals and how this might affect its actions. De Lemos performed a systematic review of the literature on the effects of genistein on breast cancer cell growth and concluded that at low (<10 μmol/L) physiologically relevant levels, genistein stimulates estrogen receptor positive (ER+) tumors, while at higher (>10 μmol/L) concentrations, genistein appears to be inhibitory. This has been attributed to the estrogenic properties of genistein being predominant at low levels, while at higher levels, other anticancer actions of phytoestrogens predominate.[56] It is important to note, however, that plasma phytoestrogen levels of over 10 μmol/L are difficult to achieve with dietary intake.[29]

The estrogenic activity of phytoestrogens may also depend on their affinity for particular ERs in the body. Phytoestrogens appear to preferentially bind to the ERβ and have sometimes been classified as selective ER modulators (SERMS).[14,57,58] ERβ may play a protective role in breast cancer development by inhibiting mammary cell growth, as well as inhibiting the stimulatory effects of ERα.[57,59] Phytoestrogens have also been shown to inhibit aromatase[60,61] (which converts androstenedione and testosterone to estradiol), the target for aromatase inhibitors, which are used to treat postmenopausal breast cancer.

NONHORMONAL ACTIONS OF PHYTOESTROGENS

Phytoestrogens also have antitumor activities that are independent of their estrogenic activity.[1,19] Dietary phytoestrogens have been shown to inhibit proliferation of hormone-independent breast cell lines.[62–64] This has been postulated to occur via a number of mechanisms, including inhibition or downregulation of protein tyrosine kinases (PTK), which are involved in growth signaling pathways.[1,65,66] Genistein has been shown to inhibit PTK, particularly the autophosphorylation and activation of epidermal growth factor receptor, which is important in regulating apoptosis and cell proliferation.[67] Pharmacologic doses of genistein inhibit the PTK-dependent transcription of c-fos and subsequent cellular proliferation in estrogen receptor negative (ER-) human breast cancer cell lines.[68] Other potential mechanisms that have been reported in vitro include phytoestrogen stimulation of the immune system, antioxidant activity, and inhibitory effects on angiogenesis.[1,3,4,17,19,69]

BREAST CANCER PREVENTION

Interest in phytoestrogens' effects on breast cancer stemmed from correlational epidemiologic studies indicating the incidence rates of breast cancer are lower in countries that report high consumption of soy foods.[70–72] In addition, rates of breast cancer among immigrants from countries of high phytoestrogen intake to countries of low intake increase as length of time in the host country increases,[70,73,74] suggesting lifestyle changes, including dietary changes in phytoestrogen intake, may play a role. Although intriguing, other dietary or lifestyle changes that occur with immigration to a new country could contribute to these findings.

STUDIES EXAMINING PHYTOESTROGENS AND BREAST CANCER INCIDENCE

Many case-control studies have been conducted exploring the role of phytoestrogens in breast cancer risk (see Table 2). Although most case-control studies have indicated some protective effect of soy,[75–79,82,83] findings have been inconsistent, and some have failed to show any relationship between phytoestrogen intake and breast cancer development.[40,80,81] There has been some evidence that the menopausal status of a woman may modulate the effects of soy.

TABLE **2** Case-control Studies Examining Phytoestrogen Intake and Breast Cancer Risk

Author, Year, and Country of Study	Method of Obtaining Phytoestrogen Intake	Patient Characteristics	Cases/Controls	Results	Comments
Dai Q, Shu XO, Jin F, et al,[75] 1996 to 1998, China (Shanghai)	Interviewer administered FFQ; usual dietary intake; comprehensive soy intake	Premenopausal and postmenopausal women aged 25 to 64 years	1,459 cases cancer registry; 1,556 population-based controls	Reduced breast cancer risk for women in highest decile total soy intake versus lowest decile (OR, 0.66 [0.46 to 0.95]; *P* for trend = 0.02)	Extensive information on total soy intake; capture 90% of soy intake
Shu XO, Jin F, Dai Q, et al,[76] 1990 to 1993, China (Shanghai)	Interviewer administered FFQ; usual dietary intake in adolescence (aged 1 to 15 years); also asked mothers their daughters' soy intake in a subgroup of women; comprehensive measurement of soy intake	Premenopausal and postmenopausal women aged 25 to 64 years	1,459 cases cancer registry; 1,556 population-based controls	Reduced risk of breast cancer in upper quartile of soy intake during adolescence compared with lowest quartile (OR, 0.75 [0.57 to 0.93]) in premenopausal and postmenopausal women	Extensive information on soy; results unchanged when stratified by usual adult soy intake; low correlation between maternal and study subjects estimates of intake (0.29 cases; 0.30 controls)
Lee HP, Gourley L, Duffy SW, et al,[77] 1986 to 1988, Singapore (Chinese)	Interviewer using FFQ (soya protein); diet previous year	Premenopausal and postmenopausal Chinese women living in Singapore aged 28 to 83 years	200 cases; 420 hospital-based controls	Reduced breast cancer risk with increased soya protein intake in highest tertile versus lowest (OR, 0.30 [0.1 to 0.6]); association only seen in premenopausal women	Small numbers
Hirose K, Tajima K, Hamajima N, et al,[78] 1988 to 1992, Japan	Self-administered FFQ of dietary habits (diet period not specified); bean curd consumption frequency/week	Premenopausal and postmenopausal women >18 years (upper limit not specified)	1,186 cases outpatient; 21,295 hospital outpatient controls	Reduced risk of breast cancer with bean curd consumption >3 servings/week versus <3 servings/week (OR, 0.81 [0.65 to 0.99]) in premenopausal women	
Wu AH, Ziegler RG, Horn-Ross PL, et al,[79] 1983 to 1987, United States (Americans of Chinese, Japanese, and Filipino descent)	FFQ usual adult diet; fresh, dried, deep-fried tofu, miso, and natto	Premenopausal and postmenopausal women aged 30 to 55 years	597 cases cancer registry; 966 population-based controls	Reduced risk of breast cancer for each additional serving of soy/week (OR, 0.85 [0.74 to 0.99])	Number of postmenopausal women was small; effect mostly seen in Asian immigrants, not US-born
Yuan JM, Wang QS, Ross RK, et al,[80] 1984 to 1985, China (Shanghai, Tianjin)	Interviewer administered FFQ; usual adult diet	Premenopausal and postmenopausal women (Shanghai, aged 20 to 69 years; Tianjin, aged 20 to 55 years)	834 cases population-based cancer registry; 834 community controls	No association of breast cancer risk with soy protein or soy as % total protein; repeated analysis for premenopausal and postmenopausal women the same	Food rationing likely made recall excellent
Zheng W, Dai Q, Custer LJ, et al,[81] 1996 to 1997, China (Shanghai breast cancer study)	Urinary excretion of isoflavinoids daidzein, genistein, glycitein, equol, and O-DMA (HPLC analysis)	Premenopausal and postmenopausal women aged 25 to 64 years	60 cases population-based cancer registry; 60 cases from general population	Trend for decreasing breast cancer odds with increasing isoflavone intake, but not statistically significant	No difference in soy intake between cases and controls, suggesting individual metabolism may be important
Ingram D, Sanders K, Kolybaba M, Lopez D,[82] 1992 to 1994, Australia	Urinary excretion of phytoestrogens daidzein, genistein, equol, enterodiol, and enterolactone	Premenopausal and postmenopausal women aged 30 to 84 years	144 hospital-based outpatient clinic; 144 controls electoral roll	Increasing equol and enterolactone levels in urine associated with reduced breast cancer risk, but NS (*P* = 0.13). Similar trends for premenopausal and postmenopausal analysis	Measurement soon after diagnosis could affect gut transit
Murkies A, Dalais FS, Briganti EM, et al,[83] 2000, Australia (Melbourne)	24-hour urinary isoflavones, including genistein and daidzein	Postmenopausal women only; age range not stated; mean age 59.3 years	18 cases from outpatient medical center; 20 cases from mammography	Daidzein excretion significantly lower in cases (*P* = 0.03); genistein excretion lower in cases, but NS (*P* = 0.08)	

TABLE **2** Case-control Studies Examining Phytoestrogen Intake and Breast Cancer Risk (continued)

Author, Year, and Country of Study	Method of Obtaining Phytoestrogen Intake	Patient Characteristics	Cases/Controls	Results	Comments
Horn-Ross PL, John EM, Lee M, et al,[40] 1995 to 1998, United States (California, non-Asian women)	Interviewer administered FFQ; diet in previous year to diagnosis of 7 phytoestrogen compounds (not named)	Premenopausal and postmenopausal women aged 35 to 79 years	1,326 population-based cases from cancer registry; 1,657 random-digit dialing matched on age and ethnicity	No association; no change with analysis by menopausal status, individual phytoestrogens, or ethnic groups	
Wu AH, Wan P, Hankin J, et al,[84] 1995 to 1998, United States (Chinese, Japanese, and Filipino women in Los Angeles County)	Interviewer administered diet questionnaire that assessed adult soy intake the year prior to diagnosis and adolescent intake (aged 12 to 18 years)	Premenopausal and postmenopausal women aged 25 to 74 years	501 cases, population-based cancer registry; 594 neighborhood controls matched for ethnicity and age	Risk of breast cancer was decreased with increasing quartiles of soy intake as adult (OR, 0.85 [0.59, 1.24]; OR, 0.80 [0.54, 1.20]; OR, 0.61 [0.39 to 0.97]; *P* = 0.04 for trend) and as an adolescent (OR, 0.73 [0.47 to 1.14]; OR, 0.62 [0.42, 0.92]; OR, 0.65 [0.38 to 1.10]; *P* = 0.04 for trend); high soy consumers during adolescence and adulthood had lowest risk (OR, 0.53 [0.36 to 0.78]); results for premenopausal and postmenopausal women were in the same direction, but statistically significant for postmenopausal women	
Linseisen J, Piller R, Hermann S, Chang-Claude J,[85] 1992 to 1995, Germany	Self-administered FFQ; usual intake in previous year; assessed isoflav-enoids and lignans	Premenopausal only (defined as age < 50 years at diagnosis)	278 cases, population-based; 666 controls matched by age and study region	Reduced risk of breast cancer in highest versus lowest quartiles of daidzein and genistein (OR, 0.63 [95% CI 0.40 to 0.95]; OR, 0.47 [95% CI 0.29 to 0.74, respectively]); intake of enterodiol and enterolactone were also inversely associated with breast cancer risk (OR, 0.61 [95% CI 0.39 to 0.98] and 0.57 [95% CI 0.35 to 0.92], respectively)	No effect for total phyto-estrogen intake
Thanos J, Cotterchio M, Boucher BA, et al,[86] 2002 to 2003, Canada	Self-administered FFQ; intake between age 10 to 15 years; assessed lignans and isoflavones	Premenopausal and postmenopausal; population-based; women aged 25 to 74 years	3,024 cases; 3,420 controls matched via random digit dialing matched on age	Decreased breast cancer risk associated with increasing isoflavone, lignan, and total phytoestrogen intake in adolescence; compared with lowest quartile (OR, 0.91 [95% CI 0.79 to 1.04]; OR, 0.85 [95% CI 0.75 to 0.98]; and OR, 0.71 [95% CI 0.63 to 0.82] for quartiles 2, 3, and 4, respectively; *P* for trend = <0.01)	
McCann SE, Kulkarni S, Trevisan M, et al,[87] 1996 to 2001, United States (New York State, Western New York exposures and breast cancer study)	FFQ from previous 12 to 24 months prior to interview; assessed lignans, isolariciresinol, and metairesinol	Premenopausal and postmenopausal women aged <65 years	1,166 cases; population-based 2,105 controls matched on age, race, and county residence	Decreased risk of ER- breast cancer with increasing lignan intake (OR, 0.68 [95% CI 0.36 to 1.26]; OR, 0.62 [95% CI 0.33 to 1.18]; OR, 0.48 [95% CI 0.25 to 0.95] compared with lowest quartile; *P* for trend = 0.03, but only among premenopausal women)	No relation-ship for ER+ tumors, nor for post-menopausal
Piller R, Chang-Claude J, Linseisen J,[88] 1992 to 1995, Germany	Plasma enterolactone and genistein	Premenopausal women aged ≤50 years	220 premenopausal population-based cases; 220 age-matched controls	Decreased risk of premenopausal breast cancer with increasing plasma enterolactone (OR, 0.42 [95% CI 0.20 to 0.90]; OR, 0.35 [95% CI 0.17 to 0.85] for the upper 2 quartiles of intake [lowest as ref]; *P* = 0.007 for trend)	

FFQ = food frequency questionnaire.
HPLC = high performance liquid chromatography.
OR = odds ratio.
NS = not significant.
CI = confidence interval.
ER+ = estrogen receptor positive.
ER- = estrogen receptor negative.

Case-control studies have generally found more evidence for a protective role in premenopausal women versus postmenopausal. This lends support to a current hypothesis that phytoestrogens' effects are dependent on the hormonal status of the woman, with stimulatory effects in low-estrogen environments, while in high-estrogen states, they may block the effects of estrogen.[89,90]

In contrast, most prospective cohort studies (Table 3) have failed to show any relationship between soy intake and breast cancer risk.[91–93,96] One prospective cohort study among premenopausal and postmenopausal Japanese women aged 40 to 59 years that specifically asked about miso soup, soybeans, tofu, and natto did suggest a protective effect of increasing quartiles of isoflavone intake.[94] Another prospective cohort study with premenopausal and postmenopausal women aged 45 to 75 years from the United Kingdom found an *increased* risk of breast cancer with increasing urinary and serum isoflavone levels in this population, although intake was quite low (<1 mg/day).[95] A recent meta-analysis[97] of cohort and case-control studies examining soy intake and breast cancer risk found that high versus low soy intake was associated with a small reduced breast cancer risk (odds ratio [OR] 95%, confidence interval [CI] 0.75 to 0.99). In this meta-analysis, the protective effect of soy consumption on breast cancer risk appeared to be stronger among premenopausal women. However, the researchers noted a high degree of heterogeneity among studies and lack of a dose-response relationship between soy and breast cancer risk. In addition, the methods of measuring and categorizing soy were different among the studies. The classification of high versus low soy intake in the meta-analysis was based on the cutpoints chosen by the authors of each study and, hence, was not standardized. In addition, the populations studied were different and, hence, food sources of phytoestrogen differed. Such methodological differences among studies make it difficult to pool results and interpret findings.

While there are fewer studies examining the effect of lignans, the other major source of phytoestrogens in the US diet,[41] on breast cancer development, most studies have suggested a protective role of high lignan intake[85,96,98,99] or in those who have higher serum or urinary levels of the main lignan metabolites, ENL and EDL.[82,88,100,101] However, a few studies have failed to show a relationship between lignan biomarkers and breast cancer.[92,95,102] Nearly all studies were conducted in non-Western populations. One prospective cohort study among premenopausal and postmenopausal women in the United States indicated an increased risk of breast cancer associated with higher dietary lignan intake,[93] but lignan intake was relatively low in this population.

The epidemiologic studies exploring phytoestrogen intake and breast cancer risk are subject to a number of methodological limitations. All the retrospective case-control studies are subject to important biases. Recall bias after a cancer diagnosis is a major concern, but there may also be changes in dietary habits after a diagnosis, colonic transit changes related to stress, or antibiotic use (which alters colonic bacteria) associated with treatment and complications of a cancer diagnosis. For non-Asian populations, intake may be too low to differentiate meaningful exposure levels among individuals, and in populations of high consumers of phytoestrogens, uniformly high intakes may present similar problems. Measurement of phytoestrogens, either by food frequency questionnaire or by urinary excretion, is imprecise, as well.

PHYTOESTROGENS AND MARKERS OF BREAST CANCER RISK

It is generally accepted that higher lifetime estrogen exposure is associated with increased breast cancer risk.[103–105] Some researchers have examined the relationship between phytoestrogens and endogenous hormone levels. Concentrations of 17β-estradiol are approximately 40% lower in Asian women compared with their Caucasian counterparts,[51,106] but whether this is due to high phytoestrogen intake is not clear. While some studies have shown that phytoestrogen intake is associated with decreased estradiol levels[107–111] or estrogen metabolites,[112] many have failed to show any association.[113–115] In a substudy of the European Prospective Investigation into Cancer and Nutrition study, investigators examined the relationship between the major phytoestrogens (as measured by urine, TABLE **3** Cohort Studies Examining Phytoestrogen Intake and Breast Cancer Risk

Study	Method of Obtaining Soy	Patient Characteristics	Number of Study Cases/Participants	Results	Comments
Key TJ, Sharp GB, Appleby PN, et al,[91] nested case control, 1969 to 1993, Japan, women from Radiation Effects Research Foundation's Life Span Study	Mailed questionnaire of dietary consumption of 19 foods, including miso soup, tofu	Throughout life span, individuals living in Nagasaki or Hiroshima	427/43,759	No association; repeated analysis for premenopausal and postmenopausal the same	Women with radiation exposure; limits generalizability
den Tonkelaar I, Keinan-Boker L, Veer PV, et al,[92] nested case control, 1977 to 1985, Netherlands, selected from cohort of women in a population-based breast cancer screening program	Urinary enterolactone and genistein	Postmenopausal women; aged 50 to 64 years	88/268 from total population of 14,697	No significant association; test for trend NS	Women selected from a breast cancer screening program; limits generalizability
Horn-Ross PL, Hoggatt KJ, West DW, et al,[93] 1995 to 1997, California teacher's study	Self-administered block FFQ; intake year prior to baseline; phytoestrogen content estimated from responses	Premenopausal and postmenopausal, aged 21 to 103 years	711/111,526	No association between phytoestrogen consumption and breast cancer risk	Participants from one state only; limits generalizability
Yamamoto S, Sobue T, Kobayashi M, et al,[94] 1990 to 1999, Japan, The Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular diseases	Self-administered FFQ that specifically asked about habitual miso soup and "soybeans, tofu, deep-fried tofu, and natto"	Premenopausal and postmenopausal, aged 40 to 59 years	179/21,852	Decreased risk of breast cancer with increasing quartile of isoflavone intake and miso soup; no relationship with soy foods	Stronger association in postmenopausal women; miso soup and soya food accounted for 80% of isoflavone intake
Grace PB, Taylor JI, Low YL, et al,[95] nested case-control study, 1993 to 2001, United Kingdom, Norfolk cohort of the European prospective investigation into cancer and nutrition	Urinary daidzein, genistein, glycitein, equol, enterodiol, and enterolactone	Premenopausal and postmenopausal; aged 45 to 75 years	114/13,070	Urinary and serum isoflavone levels were associated with increased risk of breast cancer, statistically significant for equol and daidzein; for a doubling of level, log2 (OR, 1.34 [95% CI 1.06 to 1.70]) for urine equol; (1.46 [95% CI 1.05 to 2.02]) serum equol; and (1.22 [95% CI 1.01 to 1.48]) for serum daidzein	Dietary intake of isoflavones was low
Keinan-Boker L, van Der Schouw YT, Grobbee DE, Peeters PH,[96] 1993 to 2001, Netherlands, Dutch cohort of the European prospective investigation into cancer and nutrition	Self-administered FFQ; previous year	Premenopausal and postmenopausal women; aged 49 to 70 years	280/15,555	No relationship between isoflavone and lignans and breast cancer risk; test for trend negative	Dietary intake was low

FFQ = food frequency questionnaire.
OR = odds ratio.
NS = not significant.
CI = confidence interval.

serum, and diet), genetic variants involved in estrogen metabolism, and plasma estradiol and sex hormone-binding globulin.[108] They found that the decreased levels of estradiol they observed in women consuming phytoestrogens were almost completely due to women with a particular gene polymorphism. The authors suggest that the effects of dietary phytoestrogens may be very pronounced in a small group of women, which might explain some of the contradictory findings among studies.

The effects of soy or isoflavones on breast cell proliferation and mammographic density have also been explored. Soy supplementation has been shown to increase breast cell proliferation and hyperplasia on biopsy of healthy breast tissue in premenopausal women,[116,117] a concerning finding suggesting soy might increase breast cancer risk. In contrast, self-reported soy intake among premenopausal and postmenopausal women in Singapore was associated with reduced mammographic density.[118] Among a postmenopausal US population,[119] the ability to produce O-DMA (a metabolite of daidzein) was also associated with reduced breast density. However, 2 randomized trials conducted in premenopausal women in the United States, one using soy isoflavone supplements[120] and another using dietary soy,[121] failed to have any effect on mammographic density. The results of one study might shed some light on these discrepancies. In a prospective nested case-control study of premenopausal women living in Hawaii and Los Angeles, adult soy intake was associated with increased breast density, but childhood intake was negatively associated with adult mammographic density.[122] Again, interpretation is difficult, as each study used different methodologies, and sources of soy were different. Measuring markers of breast cancer risk, rather than actual breast cancer outcomes, is an additional limitation of available data. Yet, given the large expense, numbers of women required, and time needed to conduct a randomized controlled trial (RCT) to show a difference in breast cancer risk with soy intake, studying intermediary outcomes has been more feasible. Ongoing National Cancer Institute-funded prospective Phase II studies should help elucidate the effects of soy supplementation on breast mammographic density in premenopausal women (NCT00204490) and the effect of genistein on breast cell epithelium in high-risk women (NCT00290758).

PHYTOESTROGENS AND MENOPAUSAL SYMPTOMS

Breast cancer treatment, including chemotherapy and/or hormonal therapy, may induce or accelerate ovarian failure.[123–125] Breast cancer survivors who experience chemotherapy-related ovarian failure report high levels of menopausal symptoms.[7,123,124,126] The results of the HABITS (Hormone therapy after breast cancer—is it safe?) trial suggested an increased risk of recurrence in women who use exogenous HT,[10] and hence, women with breast cancer are generally advised to avoid exogenous HT. A history of breast cancer remains a black-box warning on hormonal agents, even treatments with low systemic exposure to estrogen such as estradiol vaginal rings. Although other medications, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), clonidine, and gabapentin, have been shown to significantly reduce the frequency and intensity of hot flashes,[127,128] soy supplementation may be an attractive dietary alternative for women who have had breast cancer and have been advised against the use of HT. Dietary supplements and dietary changes are often viewed as "natural," and in fact, breast cancer survivors report high use of CAM.[129] In a telephone survey of breast cancer survivors, over 10% were increasing the amount of soy in their diet[16] to treat menopausal symptoms. This is concerning given the lack of data to support soy as a treatment for these symptoms.

Four randomized placebo-controlled trials have been conducted investigating the use of isoflavones to treat menopausal symptoms in breast cancer survivors (see Table 4).[130–133] None of the 4 studies of women who received oral isoflavone supplementation showed any significant treatment effect on hot flash symptoms. All studies used soy tablets and reported isoflavone content, except one[132] that used a soy drink with isoflavone added. Methods of measuring hot flashes varied across studies, and no study included supplementation for longer than 12 weeks. These disappointing results are in agreement with 2 recent reviews of CAM therapies for menopausal symptoms, both of which found little evidence

TABLE **4** RCT Using Phytoestrogens to Treat Menopausal Symptoms in Breast Cancer Survivors

Isoflavone Studies						
Author, Year	**Isoflavone Content**	**Study Inclusion Criteria**	**Length of Trial**	**Outcomes Measure**	**Results**	**Comments**
MacGregor CA, Canney PA, Patterson G, et al,[130] 2004	35 mg/day	Aged >18 years; histologically confirmed pre-existing breast cancer; menopausal score >1; concomitant or preceding adjuvant therapy allowed	12 weeks	EORTC QL: Q-C30 questionnaire, Breast Cancer Module BR23, and menopausal scale	No difference	No significant difference in global quality of life scores
Nikander E, Kilkkinen A, Metsa-Heikkila M, et al,[131] 2003	114 mg/day	Postmenopausal women who had been treated for breast cancer; no residual disease; incapacitating hot flashes, night sweats, and sleeplessness; FSH >30 U/L	3 months	Kupperman Index and 10-cm-long visual analogue scale	No difference	Blood samples were taken after an overnight fast on the first day and on the last day of treatment
Van Patten CL, Olivotto IA, Chambers GK, et al,[132] 2002	90 mg/day	4 months post-treatment: no HT for 4 months; stratified by tamoxifen; 59 soy beverage, 63 controls	12 weeks	Daily menopause diary, number of hot flashes on 5-point scale; converted to 24-hour score	No difference	Genistein serum levels were higher, but not daidzein; GI side effects; compliance high
Quella SK, Loprinzi CL, Barton DL, et al,[133] 2002, 118 RCT	150 mg/day	Women aged >18 years; >4 months post-treatment: 14 hot flashes/week; tamoxifen allowed; 177 women soy	4 weeks	Hot flash frequency and intensity via question-naire; converted to weekly hot flash scores	No difference	Self-reported compliance high
Black Cohosh Studies						
Author, Year	**Date**	**Study Inclusion Criteria**	**Length of Trial**	**Outcomes Measure**	**Results**	**Comments**
Pockaj BA, Gallagher JG, Loprinzi CL, et al,[134] 2006	20 mg tablet	History of breast cancer or increased risk of breast cancer; tamoxifen allowed	9 weeks	Weekly symptom experience dairy, Greene Climacteric Scale	No difference	Black cohosh well tolerated
Jacobson JS, Troxel AB, Evans J, et al,[135] 2001	Not given	Women aged >18 years; experience hot flashes daily; no HT; tamoxifen allowed; 42 black cohosh, 42 placebo	60 days	Number and intensity of hot flashes baseline and at 30 and 60 days	No difference	Compliance by pill counts, telephone survey, high

RCT = randomized controlled trial.
FSH = follicle-stimulating hormone.
HT = hormone therapy.
GI = gastrointestinal.

that phytoestrogens are an effective treatment of menopausal symptoms in women without a history of breast cancer.[136,137] Two RCTs of black cohosh (a phytoherb sometimes classified as a phytoestrogen) also failed to provide significant benefit with regard to menopausal symptom management in women with breast cancer.[134,135]

PHYTOESTROGENS AND BREAST CANCER SURVIVORS

Recurrence

There has been great interest by clinicians and breast cancer survivors in the potential for phytoestrogens to reduce the risk of breast cancer recurrence. Unfortunately, almost all data to guide patients and clinicians are from observational epidemiologic studies or based on in vitro and animal models. In a population-based case-control study in China (a follow up of the Shanghai Breast Cancer Study) designed to explore risk factors associated with breast cancer, soy intake before cancer diagnosis was unrelated to disease-free breast cancer survival. A subgroup analysis to determine whether postdiagnosis change in soy food consumption altered breast cancer risk found no support for an association,[138] though the study was neither designed nor powered to detect differences in survival related to phytoestrogen intake. One RCT examined the impact of dietary flaxseed on markers of tumor cell growth and proliferation in postmenopausal breast cancer patients. They found 25 g/day of flaxseed reduced cell proliferation, increased apoptosis, and reduced c-erbB2 expression of human breast cancer cells in biopsy tissue between time of diagnosis and time of definitive breast surgery.[139] However, no RCTs have specifically studied whether phytoestrogen supplementation reduces the risk of breast cancer recurrence.

ANIMAL MODELS

Many studies have explored the role of phytoestrogens in breast cancer using rodent models of breast cancer initiation and growth. Animals genetically bred to develop breast cancer or the use of a chemical carcinogen administered to the animals have both been used to study the effects of phytoestrogens on breast cancer tumorigenesis. Researchers have also used human breast cancer cell lines (mostly MCF-7, which are ER+ breast cancer cells) injected into laboratory animals and then modulated the animal's diet with phytoestrogens. While none of these models captures the complexities of a human model for breast cancer initiation and growth, the last model is probably most applicable to breast cancer survivors' consumption of phytoestrogens and risk of recurrence.

Concerns regarding safety of phytoestrogen consumption have been raised as several studies have indicated phytoestrogens could play a stimulatory role in breast cancer growth.[26,140–145] Allred et al[26] found that diets containing increasing amounts of soy stimulated growth of estrogen-dependent tumors in a dose-dependent manner. The plasma levels of genistein reached in the rats were 2 μmol/L, which is similar to levels measured in women who drink soy-milk. Similarly, Ju et al[89] found that physiologic levels of genistein stimulate MCF-7 breast cancer cells implanted into a novel animal model with low circulating levels of estradiol (which models postmenopausal breast cancer).

However, many studies have indicated an inhibitory effect of soy or isoflavones on transplanted breast cancer cell growth[62,146–150] and metastasis using rodent models.[151] Constantinou et al[62] found that in vitro genistein treatment of MCF-7 breast cancer cells (ER+), as well as MDA-MB-468 cells (ER-), reduced the tumorigenicity of both cell lines in athymic mice. Yan et al[151] examined the effect of soy supplementation on metastasis of the highly metastatic 4526 murine mammary carcinoma cell line implanted into BALB/c mice and found a 26% reduction in metastasis in the soy-fed group. The majority of studies that have found a protective effect of isoflavones have been animal studies involving chemically induced tumors with 7,12-dimethlydenza(a)anthracene (DMBA). The applicability of these findings to breast cancer survivors remains uncertain.

TIMING OF EXPOSURE

Researchers have postulated that timing of dietary estrogenic exposures influences whether the exposure increases or decreases subsequent breast cancer risk.[152,153] For instance, prepubertal exposure to genistein decreases the risk of mammary tumorigenesis in female rats,[149,154,155] while exposure in utero increased risk of tumors developing in the offspring[156] or had no effect.[153] Studies evaluating adult rat exposure to genistein have failed to find a protective effect.[153] Lamartiniere et al demonstrated that exposure of prepubertal rats to genistein before the administration of the carcinogen (DMBA) was protective against mammary cancer.[146,147] In rats treated neonatally with genistein, mammary glands were larger, there were more terminal end buds and terminal ducts, and more proliferative activity in all terminal ductal structures. It appeared that neonatal genistein treatment exerted its chemoprevention by acting directly to enhance maturation of terminal ductal structures and by altering the endocrine system to reduce cell proliferation in the mammary gland. Lamartiniere concluded that prenatal-only exposure to genistein is not sufficient to protect against mammary cancer in the rat model and that genistein exposure must occur prepubertally to exert a chemoprotective effect.[153]

There is some human data from case-control studies to support the hypothesis that timing of phytoestrogen exposure may influence its effects. Shu et al,[76] in a population of Asian women, found that women who consumed higher amounts of tofu between the ages of 13 to 15 years were less likely to develop both premenopausal and postmenopausal breast cancer. Similarly, Wu et al[84] conducted a case-control study in an Asian premenopausal and postmenopausal population living in the United States and found that adolescent exposure to soy was protective against developing breast cancer as an adult. Thanos et al,[86] in a population of Canadian premenopausal and postmenopausal women, found that adolescent intake of both isoflavones and lignans was protective of breast cancer development later in life. Women who consumed high phytoestrogens in both early (adolescent) and later life (adult) actually had the lowest risk of breast cancer.

How such studies should be interpreted for breast cancer survivors is difficult to ascertain. If protective effects are conferred only with prepubertal exposure to phytoestrogens, then there may be no justification for increasing phytoestrogen intake in adult women in Western countries since their prepubertal intake can be expected to be quite low. Increasing soy (with its potential to stimulate growth) may not be prudent. More research is needed to clarify how the timing of phytoestrogen exposure impacts protective effects on breast cancer development and growth.

PROCESSING AND COADMINISTRATION

In addition to timing of the phytoestrogen exposure, processing and agents coadministered with phytoestrogens may impact their actions. Allred et al[157] examined the effect of various soy products on growth of MCF-7 cells transplanted into ovariectomized athymic mice. Products investigated included soy flour and 2 crude extracts of soy (soy molasses and a commercially available mixture of isoflavones and genistein in pure form). The soy flour did not stimulate breast cancer cell growth, while the extracts and pure forms stimulated growth. The researchers commented that soy flour is the more commonly consumed form of soy in Asian countries and concluded that consuming less-processed soy formulations such as soy flour rather than purified forms may be advisable. Saarinen et al[158] has examined the effect of flaxseed on the stimulatory effects of soy protein on MCF-7 breast cancer cells in ovariectomized athymic mice and found that flaxseed appears to eliminate any stimulatory effect of soy on breast cancer growth.

Studies involving ENL, the major lignan, have been fewer, but have indicated growth inhibition of existing breast cancer tumors in animals,[159–164] although in vitro at low doses, ENL has stimulated breast cancer cell growth in at least one study.[165]

LIMITATIONS OF ANIMAL MODELS

While there are many similarities in mammary gland development in rodents and humans (differentiation to form lobules and terminal end-bud structures at puberty; further maturation of breast cells during pregnancy and lactation), there are important limitations of using animal models to predict the effects of isoflavones[14,166] or lignans[167] in humans. For instance, while the gut flora of rats are able to metabolize large quantities of daidzein to equol, only a quarter of women contain the gut flora necessary to metabolize daidzein to equol.[166] In addition, the equol produced is the S-enantiomer in humans and binds preferentially to ERβ. Whether this is the case in rodents is not known yet.[166] In addition, Allred et al[27] have found that soy processing of rodent diets affects the levels of aglycon (bioactive form) genistein produced by the animals, and phytoestrogens added to rodent diets are not standardized in studies. All these issues suggest caution is warranted when extrapolating available animal data to humans.

ADJUVANT HORMONAL TREATMENTS AND PHYTOESTROGENS

Tamoxifen

Although aromatase inhibitors are increasingly being used in early stage breast cancer, tamoxifen remains the first-line hormonal adjuvant therapy for premenopausal women and is one of the first-line hormonal adjuvant treatments recommended by the National Comprehensive Cancer Network for treatment of hormone-positive postmenopausal breast cancer (http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf). Additionally, it is the only Food and Drug Administration–approved medication for the prevention of breast cancer.[168] However, it is associated with high levels of vasomotor symptoms.[16,126,169,170] Concern that breast cancer survivors on tamoxifen may seek out phytoestrogens for the treatment of these symptoms has prompted investigators to explore the role of phytoestrogens in modulating the effects of tamoxifen on breast cancer cell growth. In particular, there has been concern that soy may abrogate inhibition of tumor growth by tamoxifen. Although no studies in humans have been conducted, there have been some in vitro studies[50,171] suggesting genistein interferes with tamoxifen's antiproliferative activity in ER+ breast cancer cell lines. Additionally, in animal models using ovariectomized athymic mice implanted with MCF-7 breast cancer cell lines[89,141] and in MMTV-wt-erbB-2/neu transgenic mice,[142] genistein has been found to interfere with the antiestrogen effects of tamoxifen. However, in Sprague-Dawley rats fed the combination of daidzein and tamoxifen,[172] there was *decreased* tumor burden. Other in vivo animal-feeding studies using miso[173] and flaxseed[159] have shown potentiation of tamoxifen's antitumor effects. These studies are summarized in Table 5.

TABLE **5** Studies Involving Tamoxifen and Phytoestrogens

Author, Year	Cell Line/Animal	ER Status	Phytoestrogen	Results
Zava DT, Duwe G,[50] 1997	MCF-7 T47D; MDA-468	ER+; ER-	Genistein	ER+: at low doses, tamoxifen did not block the stimulatory effects of genistein; ER-: genistein was inhibitory on cell growth
Gotoh T, Yamada K, Ito A, et al,[173] 1998	Sprague-Dawley rats	ER+	Miso diet	Mean tumor size from pretreatment was smaller in miso and tamoxifen group (85%) versus tamoxifen only (141%) versus control (160%)
Schwartz JA, Liu G, Brooks SC,[171] 1998	Transiently infected HeLA cells	ER+	Genistein	Low physiological concentrations of genistein were sufficient to reverse effects of 4-hydroxy-tamoxifen on ERα-responsive reported genes
Shen F, Xue X, Weber G,[174] 1999	MDA-MB-435 breast cell lines	ER+	Genistein	Synergisms in growth inhibition and cytotoxic effects when tamoxifen was added to genistein
Ju YH, Doerge DR, Allred KF, et al,[141] 2002	MCF-7 implanted in ovariectomized athymic mice	ER+	Genistein	Genistein negated the inhibitory effects of tamoxifen; increased expression of estrogen-responsive genes
Liu B, Edgerton S, Yang X, et al,[142] 2005	MCF-7; wt-erbB-2 transgenic mice	ER+	Genistein	Low-dose genistein coadministered with tamoxifen resulted in higher tumor formation than those fed high-dose isoflavone, soy, or milk protein-based diet; low-dose genistein and tamoxifen resulted in growth stimulation of mammary cell lines and MCF-7, while high-dose genistein resulted in inhibition of growth
Constantinou AI, White BE, Tonetti D, et al,[172] 2005	Sprague-Dawley rats given DMBA		Genistein and daidzein	Daidzein and tamoxifen had reduced tumor multiplicity, while genistein and tamoxifen had increased tumor multiplicity as compared with tamoxifen alone

ERα = estrogen receptor alpha.
ER+ = estrogen receptor positive.
ER- = estrogen receptor negative.

Such conflicting data make interpretation difficult. It may be that the level of isoflavone concentration reached is important, as noted earlier. At low levels, genistein acts as a weak estrogen, partially displacing tamoxifen from the ER, while at higher doses, genistein's effects may be estrogen independent and act synergistically with tamoxifen. How the results of these studies should be applied to human breast cancers is still controversial, but the results do raise concerns about the safety of consuming soy products, and some have recommended women with breast cancer who are on tamoxifen not consume soy or consume cautiously,[175,176] while others have suggested women can consume soy products safely.[22]

Whether phytoestrogens might interfere with the inhibitory effects of the aromatase inhibitors is not known. Both isoflavones[177] and lignans[178] have been shown to inhibit aromatase weakly in vivo. One study examined whether formestane's (an aromatase inhibitor) actions on tumor growth were altered by the coadministration of black cohosh. Formestate reduced estrogen levels by 50%, regardless of coadministration with black cohosh, suggesting no interaction between the 2.[179] Clarifying whether phytoestrogen intake might alter the effectiveness of aromatase inhibitors is an important area for further research, given their increasing use.

SUMMARY AND RECOMMENDATIONS

Research suggests that the relationship between phytoestrogens and breast cancer is not straightforward. There is evidence for both a protective role and a stimulatory role in breast cancer cell growth. The nature of the relationship between phytoestrogens and breast cancer likely depends on a number of factors, including the timing of the phytoestrogen exposure, individual differences in metabolism, hormonal milieu, whether phytoestrogens are consumed as food or as supplement, and the growing conditions and processing practices for the plants that contain phytoestrogens.

Both in vitro studies with breast cancer cell lines and in vivo animal studies suggest the timing of exposure to phytoestrogens may be a key component in determining its effects, with animal data consistent with a protective effect of soy prepubertally. Epidemiologic studies in humans support this hypothesis with studies showing adolescent soy exposure appears to be protective, while the studies examining the effects of adult exposure and risk of breast cancer are quite heterogeneous. Heterogeneity across epidemiologic studies of phytoestrogen intake and breast cancer risk is likely related to difficulties in measuring phytoestrogen exposure (especially in Western diets).[97] Caution is warranted in interpreting results of such epidemiologic studies since most were conducted in Asian countries. Genetic differences in phytoestrogen metabolism and estrogen exposure, as well as early life exposure to phytoestrogens, make extrapolation to non-Asian populations questionable.

There is no compelling evidence that phytoestrogens help menopausal symptoms, and given potential concerns for stimulating breast cancer cell growth, it should not be recommended for use to treat these symptoms in this population.

Although not definitive, research suggesting genistein stimulates breast cancer cell growth in in vivo animal models suggests women should be advised against claims that soy is a "safe" estrogen product and informed that some research indicates it could increase risk of recurrence. Women should be informed of the conflicting data in this regard and the lack of good-quality studies (placebo-controlled randomized trials) that directly address this issue. In particular, women on tamoxifen should be cautioned against the use of soy supplements and purified products. While data are insufficient to conclusively say that supplements are less beneficial (or more harmful) than dietary phytoestrogen intake, research suggests that these processed products may have detrimental effects compared with soy flour and tofu (sources most commonly consumed in Asian countries with low incidence of breast cancer). The consumption of high-dose isoflavone supplements by women at high risk or by breast cancer survivors cannot be recommended. Several recent reviews are in agreement with this recommendation.[97,176]

There is less evidence to guide intake of other phytoestrogens, such as lignans, but current research suggests they may play a protective role. Also, lignans do not appear to interfere with tamoxifen's anticancer actions in the same way that isoflavone products might, although again, data are limited.

Several federally funded trials are currently being conducted to try to answer some of the unanswered questions regarding phytoestrogens and breast cancer. These include (1) a randomized placebo-controlled trial of an oral genistein in preventing breast cell proliferation in high-risk women (NCT 00240758); (2) a randomized placebo-controlled trial examining the effect of soy supplement pills on premenopausal breast density (NCT00204490); (3) a dietary intervention with soy meal replacement drinks among breast cancer survivors to assist with weight loss (NCT 00343434); and (4) a Phase II trial to add genistein to the chemotherapy agent gemcitabine in Stage IV breast cancer patients (NCT 00244933).

Consuming naturally occurring soy products such as tofu or soy flour as part of a balanced diet low in saturated fats and high in fruits and vegetables is likely safe and perhaps even beneficial. Emerging evidence suggests that avoiding weight gain after a breast cancer diagnosis may help prevent recurrence.[180] To the extent that phytoestrogens may be found in such a diet, such intake is likely safe, although supplemental intake or augmentation of dietary phytoestrogen sources cannot be recommended at this time.

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