Effect of Soy Phytoestrogens on Hot Flashes in Postmenopausal Women With Breast Cancer: A Randomized, Controlled Clinical Trial

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Purpose: **Vasomotor symptoms, such as hot flashes and night sweats, in breast cancer survivors are often worsened by chemotherapy and tamoxifen, and/or the discontinuation of hormone replacement therapy at diagnosis. This study evaluated the acceptability and effectiveness of a soy beverage containing phytoestrogens as a treatment for hot flashes in postmenopausal women with breast cancer.**

Methods: **A randomized, placebo-controlled, double-blind clinical trial was conducted in postmenopausal women with moderate hot flashes who were previously treated for early-stage breast cancer. Women were stratified for tamoxifen use and randomized to a soy beverage (n = 59) containing 90 mg of isoflavones or to a placebo rice beverage (n = 64). Women recorded the number and severity of hot flashes daily with a daily menopause diary for 4 weeks at baseline and for 12 weeks while consuming 500 mL of a soy or placebo beverage.**

Results: **There were no significant differences between the soy and placebo groups in the number of hot flashes or hot flash scores. However, presumably because of a strong placebo effect, both groups had significant reductions in hot flashes. Mild gastrointestinal side effects were experienced by both groups but occurred with greater frequency and severity with soy. The mean serum genistein concentration at 6 weeks was significantly higher in women who consumed soy (0.61 ± 0.43 μmol/L) compared with placebo (0.43 ± 0.37 μmol/L) (P = .02). Overall acceptability and compliance were high and similar in both groups.**

Conclusion: **The soy beverage did not alleviate hot flashes in women with breast cancer any more than did a placebo. Future research into other compounds is recommended to identify safe and effective therapies for hot flashes in breast cancer survivors.**

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VASOMOTOR SYMPTOMS (VMS) such as hot flashes and night sweats can negatively affect women's quality of life, particularly in women who have also undergone treatment for breast cancer.[1-3] In women with breast cancer, VMS may be caused by premature menopause caused by chemotherapy, or may be worsened by tamoxifen,[3,4] and/or the abrupt discontinuation of hormone replacement therapy (HRT) at diagnosis. Furthermore, the use of HRT to treat VMS remains controversial because of concern that it may stimulate cancer growth.[5]

A number of alternatives to HRT, largely with limited efficacy, have been tested in women with breast cancer.[6-12] Complementary therapies for VMS are popular and widely available, but rigorous data evaluating their safety and efficacy are lacking.[10] Soy foods containing phytoestrogens (or isoflavones) exhibit both weak estrogenic and antiestrogenic effects[13] and therefore have been hypothesized as a treatment for VMS. Preliminary evidence in healthy women suggests that phytoestrogens can alter serum hormones,[14] lengthen the menstrual cycle,[14,15] reduce hot flashes,[16-20] and improve vaginal dryness.[19] At the time of study planning, however, there were limited published studies examining the effect of soy on hot flashes, and none included women with breast cancer. Thus, a randomized, placebo-controlled, double-blind clinical trial was conducted to evaluate the acceptability and effectiveness of a soy beverage in treating hot flashes in symptomatic postmenopausal women with treated breast cancer.

METHODS

Study volunteers were solicited through the media, British Columbia Cancer Agency outpatient breast cancer clinics, support groups, and physicians' offices in British Columbia, Canada. Women were eligible if they had breast cancer, had more than 4 months since completion of cancer treatment (with the exception that tamoxifen use was allowed), were menopausal (≥ 12 months of amenorrhea), and had not used HRT for ≥ 4 months. Eligible subjects had to be experiencing troublesome hot flashes, defined as a score (frequency × intensity) of ≥ 10/wk. This criterion was selected because it was considered to be clinically meaningful, and there was concern that changes in hot flashes would be difficult to detect with lower baseline scores. Women taking comple-

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mentary therapies and prescription medications, including tamoxifen, were eligible if there had been no change in therapy for ≥ 4 months. Exclusion criteria were based primarily on factors that modify estrogen or phytoestrogen metabolism or that had the potential to require medical intervention during the study. Therefore, women were excluded if they were smokers, were using antibiotics, or had inflammatory bowel disease, liver impairment (gamma-glutamyltransferase and alkaline phosphatase of > 1.5 times normal), or recurrent breast cancer. Women with an allergy to or who regularly consumed soy foods were also excluded, and all participants were instructed to avoid soy-based foods and soy supplements during the study.

Eligible participants attended a recruitment interview to provide anthropometric and demographic information and medical history and to answer questionnaires on soy intake and the use of medications and complementary therapies. During this visit, women were instructed on completing the validated daily menopause diary.[21] Participants recorded their baseline VMS daily for 4 weeks, and, if eligible, women were enrolled onto the study, stratified for tamoxifen use, and randomized to soy or placebo. Women continued to record their VMS daily for 12 weeks while consuming 250 mL of the study beverage twice per day. On subsequent visits at 4, 8, and 12 weeks of intervention, questionnaires were repeated, and diaries were reviewed for accuracy and missing data. A final study exit questionnaire was administered to obtain the participant's perceived effect of the study beverage on hot flashes, ratings of participation and acceptability, and the subject's guess about which beverage she consumed during the trial.

Blood samples were obtained at baseline for eligibility screening and at 6 weeks of intervention to measure concentrations of the isoflavones genistein and daidzein as a measure of compliance. For the serum isoflavone analysis, blood samples were available from 105 subjects (85%). Blood samples were clotted for 30 minutes and centrifuged at 3,000 rpm for 10 minutes, and serum was stored at −20°C until the completion of the study. Blinded samples were shipped on dry ice to the Department of Food Science and Human Nutrition laboratory at Iowa State University, where they were batch tested in duplicate by using reverse-phase high-performance liquid chromatography with a previously published methodology.[22,23]

Hot flashes were measured with use of a daily menopause diary, which included the self-reported number and average estimated intensity during the day and night, measured with a five-point scale (0 = absent to 4 = very intense). The amount of the study beverage consumed was recorded daily.

The study used a soybean beverage as the treatment and a rice beverage as placebo. The beverage was selected because a reasonable quantity approximated the phytoestrogen content of a traditional Asian diet[13] and contained additional potentially active components lacking in phytoestrogen pills. In addition, because the beverage did not require any preparation and was a naturally occurring, commonly available food, it was believed that compliance would be improved and safety concerns minimized. Both beverages were vanilla flavored, with similar calorie and fat contents; however, the soy was higher in protein and lower in carbohydrate compared with the rice beverage. They were produced in monthly batches, in identical blank 1-L cartons, and were assigned a randomly allocated letter. A blinded sample of each beverage was tested initially for isoflavone content, and the soy beverage was tested every 4 weeks thereafter. Total isoflavone concentration (as glycosides) was measured with high-performance liquid chromatography by the Analytic Services Unit at the University of Guelph.[24] Adverse effects were monitored during study visits or telephone interviews and were classified and graded on a four-point scale according to the National Cancer Institute of Canada common toxicity criteria.[25]

Data analysis was performed with the Statistical Analysis System (SAS; SAS Institute, Cary, NC). The primary outcome variable was the mean 24-hour hot flash score, created by summing the hot flash score (frequency × intensity) during the day and night. The main analysis, with Student's *t* test, was a comparison between groups in the change in the mean 24-hour hot flash score during the 4 weeks of baseline compared with the last 4 weeks of treatment. This analysis was also conducted for the hot flash number and score during the day and night and the hot flash number per 24 hours. Secondary analyses included a comparison between groups of the (1) consumption and acceptability ratings for each beverage, (2) frequency of side effects, (3) responses to the study exit questionnaire, and (4) serum isoflavone concentrations. The average serum isoflavone concentration of the soy beverage was also calculated. All statistical tests were two tailed and used a significance level of alpha = 0.05. Response was evaluated on an intention-to-treat basis.

The a priori hypothesis was that the study subjects would have a one third reduction in their mean weekly hot flash score of ≥ 10. A 33% reduction was based on a level of improvement in hot flashes considered to be clinically meaningful. The sample size calculation, based on pilot data from postmenopausal women with breast cancer, suggested that 54 subjects per group would be required to have an 80% power to detect this difference with an alpha = 0.05. It was also estimated a priori that approximately 20% of subjects would not complete the full study protocol. Therefore, the planned sample size was to recruit approximately 160 subjects.

Diary data for 123 subjects with more than 6 weeks of intervention and fewer than 20% missing values were included in the statistical analysis (set a priori). All but three women completed the 12 weeks of intervention. For these women, their last 4 weeks of data were used as the final 4 weeks of intervention.

Ethical approval was obtained from the University of British Columbia and British Columbia Cancer Agency research ethics review boards. All subjects provided written, informed consent.

RESULTS

As indicated in Fig 1, there were 263 eligible women screened, and of these, 157 were randomized from August 1998 to February 2000. Nine women (6%) became ineligible after randomization, and 25 (16%) dropped out because of time commitment (n = 9), intolerance of the study beverage (n = 10, including seven women in the soy group and three women in the placebo group), or other reasons (n = 6). The remaining 123 women completed the study by June 2000, including 59 randomized to soy and 64 to placebo.

Subject baseline characteristics and breast cancer treatment history are listed in Tables 1 and 2, respectively. These were similar between groups, as were the mean baseline serum concentrations of follicle-stimulating hormone, gamma-glutamyltransferase, and alkaline phosphatase (data not shown).

As indicated in Tables 3 and 4, none of the hot flash reductions were significantly different between groups. Both groups had significant reductions in the number of hot

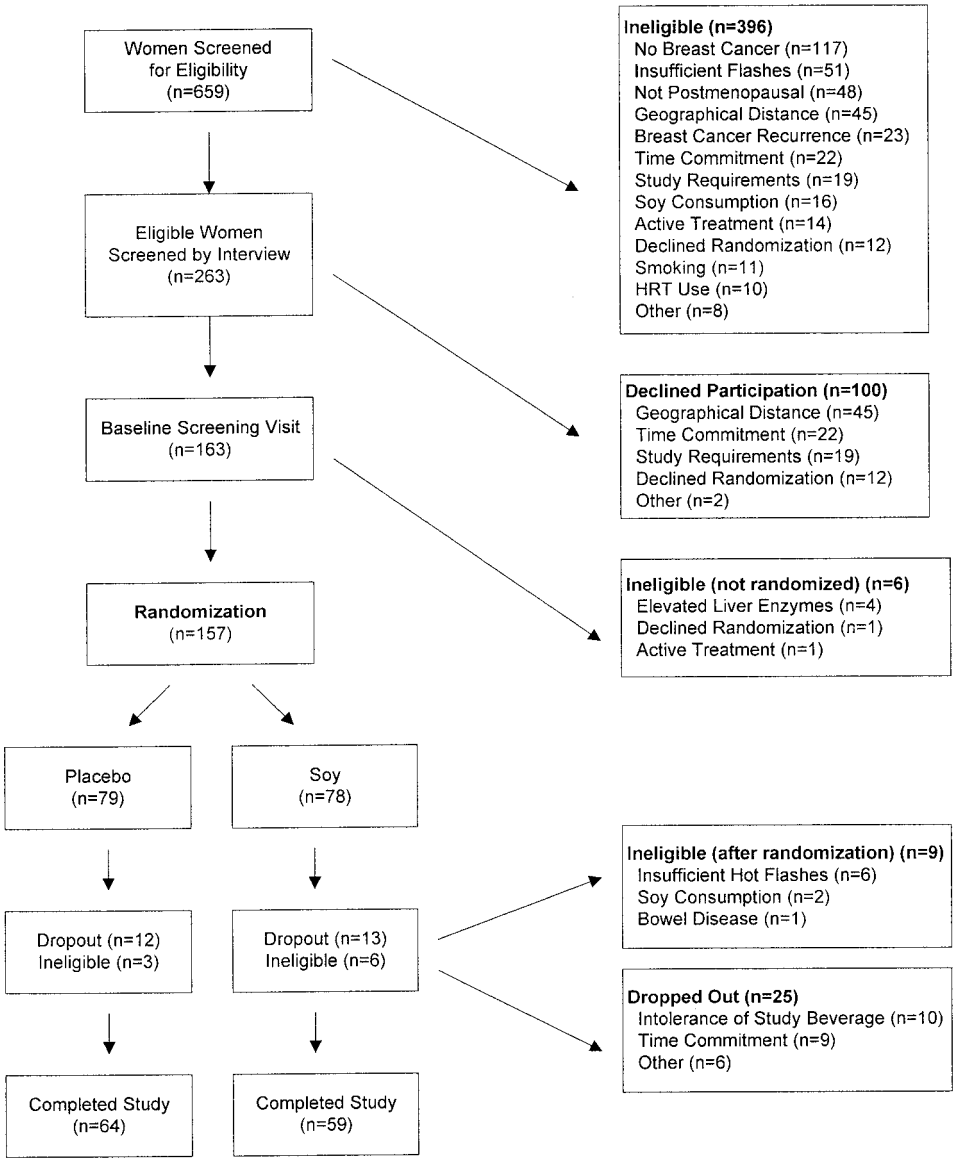

Fig 1. Recruitment of women with breast cancer in a clinical trial to evaluate the effect of soy on hot flashes.

flashes during the day, night, and 24 hours and in their respective hot flash scores from baseline to the final 4 weeks of treatment. Overall, there was a 5.4 (30%) reduction in the 24-hour hot flash score with soy and a 7.5 (40%) reduction with placebo. Figure 2 indicates the mean change per week in the hot flash score (± SEM) during 4 weeks of baseline and 12 weeks of treatment with either soy or placebo (total of 16 weeks).

Table 5 lists the most common adverse effects. The soy group had more frequent and severe gastrointestinal (GI) side effects, and more women in the soy group dropped out of the study for this reason. Weight gain ≥ 5% of body weight (grade 1 toxicity) was uncommon and occurred equally in both groups. Vaginal spotting was reported by four women consuming soy (including one woman taking tamoxifen) and in one woman consuming the placebo beverage. All of these participants were referred for investigation and completed the trial.

On the study exit questionnaire, a large number of women in both the soy and placebo groups, respectively, perceived a marginal decrease in hot flash number in the day (54% *v* 58%) and night (48% *v* 56%) and in severity in the day

Table 1. Baseline Characteristics of Women With a History of Breast Cancer*

Baseline Characteristic	Soy (n = 59)	Placebo (n = 64)
Age at study entry, years	55.5 ± 6.3	54.9 ± 6.5
No. of years since menopause	8.9 ± 9.7	7.6 ± 7.0
No. of years since diagnosis	3.6 ± 3.8	5.1 ± 4.8
Previous hysterectomy ± oophorectomy	23 (39%)	28 (44%)
Previous use of HRT†	26 (44%)	21 (33%)
Height, cm	164.0 ± 5.9	163.5 ± 7.0
Weight, kg	71.7 ± 12.1	71.6 ± 13.1
Body mass index, kg/m^2	26.8 ± 4.5	26.6 ± 4.2‡
No. of hot flashes in 24 hours	7.1 ± 4.3	7.4 ± 6.4
Hot flash score in 24 hours§	18.0 ± 13.9	18.9 ± 18.9

*Data are mean ± SD or number (%).
†Hormone replacement therapy including estrogen, progesterone, or both.
‡One missing value, n = 63.
§Hot flash score = [hot flash frequency × intensity for day] + [hot flash frequency × intensity for night] for 24 hours.

Table 2. Baseline Breast Cancer Characteristics and Treatments

Variable	Soy (n = 59)		Placebo (n = 64)	
	No.	%	No.	%
Stage of cancer at diagnosis				
In situ	8	14	6	9
I	20	34	22	34
II	25	42	26	41
III	2	3	2	3
Unknown	4	7	8	13
Estrogen receptor status				
Positive	41	70	41	64
Negative	9	15	8	13
Unknown	9	15	15	23
Previous treatment				
Surgery	59	100	64	100
Adjuvant chemotherapy	26	44	29	45
Adjuvant radiation therapy	45	76	45	70
Tamoxifen	9	15	6	9
Current tamoxifen use	20	34	18	28

(50% *v* 56%) and night (52% *v* 55%). The overall acceptability ratings were 1.9 and 2.0 out of 5 for the soy and placebo groups, respectively (1 = highest rating). At study completion, only half of the women in the soy and placebo groups (48% *v* 52%, respectively) could correctly identify which beverage they were consuming.

Most women in both groups had no missing diary data. Sixteen women (13%) had ≥ 1 day of missing data, with an average of 6 days. Compliance in consuming the study beverage was similar for both groups. Overall, women consumed 95% of the quantity of beverage set in the protocol.

Use of complementary therapies and prescription medications during the study was common in both groups. With the exception of vitamin E and evening primrose oil, agents with proposed claims for the treatment of VMS were rarely used. Black cohosh, wild yam, and red clover were each used by three or fewer women in either group, and flaxseed and selective serotonin reuptake inhibitors were each used by a maximum of six women. Use of vitamin E and evening primrose oil were more common but were used in comparable proportions in both groups.

The average isoflavone concentration of the soy beverage was 45 ± 13 mg/250 mL, and isoflavones were undetectable in the rice beverage. Thus, 90 mg of isoflavones was consumed daily for women assigned to the soy beverage. The serum concentration of genistein (0.61 ± 0.43 μmol/L *v* 0.43 ± 0.37 μmol/L; $P = .02$), but not of daidzein (0.29 ± 0.85 μmol/L *v* 0.20 ± 0.64 μmol/L; $P = .56$), was significantly higher at 6 weeks of intervention in women who consumed soy (n = 51) compared with placebo (n = 54), respectively.

DISCUSSION

This randomized, placebo-controlled, double-blind clinical trial does not support the use of a soy beverage containing phytoestrogens as a treatment for hot flashes in

Table 3. Mean Hot Flash Number and Score (per week) at Baseline and the Final 4 Weeks of Treatment in Postmenopausal Women With a History of Breast Cancer*

Variable	Soy (n = 59)		Placebo (n = 64)	
	Baseline (4 weeks)	Final 4 Weeks of Treatment	Baseline (4 weeks)	Final 4 Weeks of Treatment
Day				
No. of hot flashes	4.7 ± 3.4	3.5 ± 3.2	5.2 ± 5.6	3.4 ± 2.7
Hot flash score†	11.7 ± 9.8	8.3 ± 9.6	13.1 ± 16.2	7.8 ± 7.8
Night				
No. of hot flashes	2.4 ± 1.4	1.9 ± 1.4	2.3 ± 1.5	1.6 ± 1.6
Hot flash score†	6.4 ± 5.4	4.3 ± 4.7	5.9 ± 5.0	3.7 ± 5.0
24 Hours				
No. of hot flashes	7.1 ± 4.3	5.3 ± 4.1	7.4 ± 6.4	4.9 ± 3.9
Hot flash score†	18.0 ± 13.9	12.6 ± 13.4	18.9 ± 18.9	11.4 ± 11.3

*Differences between groups were not statistically significant.
†Intensity × frequency of hot flashes.

Table 4. Difference in Mean (%) Hot Flashes From Baseline to the Final 4 Weeks of Treatment in Postmenopausal Women With a History of Breast Cancer*

Variable	Soy (n = 59)		Placebo (n = 64)	
	Mean	%	Mean	%
Day				
No. of hot flashes	−1.2	26	−1.8	35
Hot flash score†	−3.4	29	−5.3	40
Night				
No. of hot flashes	−0.5	21	−0.7	30
Hot flash score†	−2.1	33	−2.2	37
24 Hours				
No. of hot flashes	−1.8	25	−2.5	34
Hot flash score†	−5.4	30	−7.5	40

*Differences between groups were not statistically significant.
†Intensity × frequency of hot flashes.

Table 5. Frequency of Adverse Effects (%) Reported by Women With a History of Breast Cancer Who Consumed Either a Soy or Placebo Beverage

Adverse Effect*	Soy (n = 59)		Placebo (n = 64)	
	No. of Women	%	No. of Women	%
Gastrointestinal				
Abdominal bloating	10	17	5	8
Abdominal gas/flatulence	6	10	0	0
Constipation	2	3	2	3
Gastritis	2	3	1	2
Diarrhea (or loose stools)	3	5	6	9
Nausea	2	3	0	0
Vomiting	1	2	0	0
Heartburn	2	3	0	0
Any gastrointestinal effect†	28	47	14	22
Weight gain, ≥ 5% UBW	5	8	4	6
Vaginal spotting	4	7	1	2
Other‡	3	5	2	3

Abbreviations: UBW, usual body weight.
*More than one adverse effect may be reported for each participant.
†In addition, 10 participants dropped out from intolerance of the study beverage (seven soy, three placebo).
‡Includes leg cramps (n = 2), fluid retention (n = 2), and headache (n = 1).

breast cancer survivors. These results concur with other studies[26-29] that also demonstrated a reduction in hot flashes with both soy and placebo but that did not find a statistically significant difference between groups. Previous studies that have claimed a positive effect of soy on hot flashes have had important limitations in that they have been small[17,20] or not blinded[19] or have found only a minimal reduction in hot flashes[16] or a nonsignificant trend toward a benefit.[18,20]

The only other study including breast cancer survivors also reported a nonsignificant reduction in hot flashes, with a trend for greater improvement in the placebo group.[29] The majority of women in that study were taking tamoxifen (68%). In this study, the number of women taking tamoxifen was relatively small, and thus a separate analysis of the interaction between tamoxifen and phytoestrogens was not performed.

In this study, the phytoestrogen dose was similar to that of other studies in which dose was reported.[16-18,20,27-29] The higher levels of serum genistein in women who consumed soy compared with placebo suggests adherence to the study protocol. However, both groups demonstrated high interindividual variability in serum concentrations, and there was no difference in daidzein levels between groups. Overall, compliance (measured also by a daily diary) and acceptability of the study beverages were high, and most women indicated that they would participate in a similar trial.

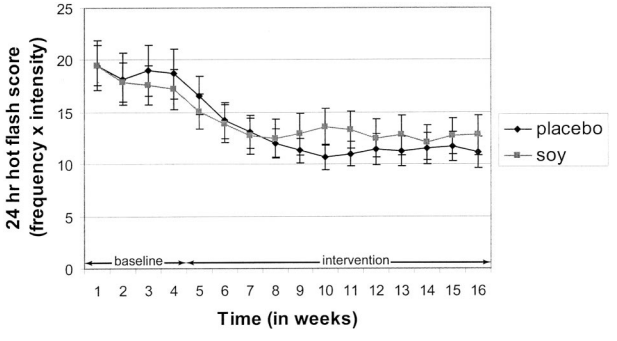

Fig 2. Mean change in hot flashes in postmenopausal women with breast cancer. Weeks 1 to 4 are baseline; weeks 5 to 16 are intervention with soy or placebo. Error bars represent SEM. Reductions in hot flash number and scores were not statistically significant between groups.

Conflicting findings of existing studies may be explained by differences in subject characteristics such as menopausal status, reproductive history, hormone use, severity of symptoms, and the variation of phytoestrogens in human metabolism.[13] Study findings may also be affected by the variability in the phytoestrogen content of foods[13] and difficulties in the measurement of VMS because of considerable variation within and between women.

The improvement in hot flashes in the placebo group reported in clinical trials has been considerable—in the range[16,18-20,26-28] of 25% to 51%. A comparable placebo effect was demonstrated in this study and occurred despite effective blinding. Regardless, a placebo effect with any therapy for hot flashes may be caused by the variability and spontaneous improvement that occurs over time[28] or may simply be a result of monitoring and expectation, particularly in highly motivated women. Positive interaction with a research assistant may also improve symptoms.[30]

The most frequently reported side effects were GI related and caused some women (seven in the soy group and three in the placebo group) to drop out of the study early,

generally within 1 month. Although greater GI side effects are common,[16,19,29] not all studies have reported them with soy compared with placebo,[17,29] and several studies reported none.[17,26-28] Previous treatment with chemotherapy and tamoxifen may explain the weight gain[31] that occurred in women in this trial, but not in other studies with equivalent caloric content and duration.[17] Given the negative findings of this study, the occurrence of vaginal spotting may be related to endogenous estrogen and tamoxifen use rather than to the estrogenic activity of phytoestrogens.

The effects of hormone withdrawal, present[16,18] or unknown[20] in other studies, are unlikely to explain these findings because at least 4 months had elapsed since the discontinuation of HRT and either starting or stopping tamoxifen. Seasonal effects are also unlikely to have had an important effect, because the study intervention occurred over a period longer than 1 year. Finally, the relatively short duration of the study is not seen as an important limitation, because a recent controlled trial of longer duration (24 weeks) also reported negative findings.[28]

A potential limitation of this study was the considerable interindividual and intraindividual variation in VMS. Although randomization reduced the between-group variability, it is possible that a small reduction in hot flashes could have been obscured. Another concern could be the monitored but uncontrolled use of complementary therapies. However, the use complementary therapies was similarly distributed between groups, and therapies that were used by more than just a few women have had limited efficacy in relieving hot flashes.[11,32,33]

Overall, women are interested in alternatives to traditional HRT to treat hot flashes and night sweats. The efficacy of a number of agents tested in breast cancer survivors, however, has been variable, leaving VMS inadequately or untreated in many women. At present, there is insufficient evidence to qualify soy or phytoestrogens as a viable alternative to HRT to treat hot flashes. Although this study demonstrates the feasibility of the use of scientific methods in evaluating alternative therapies, further study is required into safe and effective treatments for VMS and the long-term safety of phytoestrogens in breast cancer survivors.

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REFERENCES

1. Finck G, Barton DL, Loprinzi CL, et al: Definitions of hot flashes in breast cancer survivors. J Pain Symptom Manage 16:327-333, 1998

2. Carpenter JS, Andrykowski MA, Cordova M, et al: Hot flashes in postmenopausal women treated for breast carcinoma: Prevalence, severity, correlates, management, and relation to quality of life. Cancer 82:1682-1691, 1998

3. Canney PA, Hatton QF: The prevalence of VMS in patients treated for breast cancer. Clin Oncol 6:297-299, 1994

4. Love RR, Cameron L, Connell BL, et al: Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Intern Med 151:1842-1847, 1991

5. Schairer C, Lubin J, Troisi R, et al: Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 283:485-491, 2000

6. Quella SK, Loprinzi CL, Sloan JA, et al: Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. Cancer 82:1784-1788, 1998

7. Loprinzi CL, Pisansky TM, Fonseca R, et al: Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. J Clin Oncol 16:2377-2381, 1998

8. Goldenberg RM, Loprinzi CL, O'Fallon JR, et al: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. J Clin Oncol 12:155-158, 1994

9. Stearns V, Isaacs C, Rowland J, et al: A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. Ann Oncol 11:17-22, 2000

10. Castiel M: Management of VMS in the cancer patient. Oncology 13:1363-1383, 1999

11. Barton DL, Loprinzi CL, Quella SK, et al: Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 16:495-500, 1998

12. Pandya KJ, Raubertas RF, Flynn PJ, et al: Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: A University of Rochester Cancer Centre Community Clinical Oncology Program study. Ann Intern Med 132:788-793, 2000

13. Tham DM, Gardner CD, Haskell WL: Potential health benefits of dietary phytoestrogens: A review of the clinical, epidemiological, and mechanistic evidence. J Clin Endocrinol Metab 83: 2223-2235, 1998

14. Cassidy A, Bingham S, Setchell KDR: Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr 60:333-340, 1994

15. Lu LJW, Anderson KE, Grady JJ, et al: Effects of soya consumption for one month on steroid hormones in premenopausal women: Implications for breast cancer risk reduction. Cancer Epidemiol Biomarkers Prev 5:63-70, 1996

16. Albertazzi P, Pansini F, Bonaccorsi G, et al: The effect of dietary soy supplementation on hot flashes. Obstet Gynecol 91:6-11, 1998

17. Washburn S, Burke GL, Morgan T, et al: Effect of soy protein supplementation on serum lipoproteins, blood pressure, and VMS in perimenopausal women. Menopause 6:7-13, 1999

18. Umpalis DH, Lobo R, Bradley L, et al: Vasomotor symptom relief of soy isoflavone extract tablets in postmenopausal women: A multicenter, double-blind, randomized, placebo-controlled study. Menopause 7:236-242, 2000

19. Brzezinski A, Adlercreutz H, Shaoul R, et al: Short-term effects of phytoestrogen-rich diet on postmenopausal women. Menopause 4:89-94, 1997

20. Scambia G, Mango D, Signorile PG, et al: Clinical effects of a standardized soy extract in postmenopausal women: A pilot study. Menopause 7:105-110, 2000

21. Prior JC, Alojado N, McKay DW, et al: No adverse effects of medroxyprogesterone treatment without estrogen in postmenopausal women: Double-blind, placebo-controlled, crossover trial. Obstet Gynecol 83:24-28, 1994

22. Zhang Y, Wang G-J, Song TT, et al: Urinary disposition of the soybean isoflavones daidzein, genistein and glycitein differs among humans with moderate fecal isoflavone degradation activity. J Nutr 129: 957-962, 1999 (published erratum appears in J Nutr 131:147-148, 2001)

23. Xu X, Wang H-J, Murphy PA, et al: Daidzein is a more bioavailable soymilk isoflavone than is genistein in adult women. J Nutr 124:825-832, 1994

24. Wang H-J, Murphy P: Isoflavone composition of American and Japanese soybeans in Iowa: Effect of variety, crop, year and location. J Agric Food Chem 42:1674-1677, 1994

25. Common Toxicity Criteria (version 2.0). Bethesda, MD, National Institutes of Health, National Cancer Institute, 1998

26. Murkies AL, Lombard C, Strauss BJG, et al: Dietary flour supplementation decreases postmenopausal hot flashes: Effect of soy and wheat. Maturitas 21:189-195, 1995

27. Dalais FS, Rice GE, Wahlqvist ML, et al: Effects of dietary phytoestrogens in postmenopausal women. Climacteric 1:124-129, 1998

28. St Germain A, Peterson CT, Robinson JG, et al: Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. Menopause 8:17-26, 2001

29. Quella SK, Loprinzi CL, Barton DL, et al: Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. J Clin Oncol 18:1068-1074, 2000

30. Ganz PA, Greendale GA, Petersen L, et al: Managing menopausal symptoms in breast cancer survivors: Results of a randomized controlled trial. J Natl Cancer Inst 92:1054-1064, 2000

31. Demark-Wahnefried W, Peterson BL, Winer EP, et al: Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 19:2381-2389, 2001

32. Chenoy R, Hussain S, Tayob Y, et al: Effect of gamolenic acid from evening primrose oil on menopausal hot flushing. BMJ 308:501-503, 1994

33. Jacobson JS, Troxel AB, Evans J, et al: Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 19:2739-2745, 2001