Randomized Trial of Black Cohosh for the Treatment of Hot Flashes Among Women With a History of Breast Cancer

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Purpose: **Most breast cancer survivors experience hot flashes; many use complementary or alternative remedies for these symptoms. We undertook a randomized clinical trial of black cohosh, a widely used herbal remedy for menopausal symptoms, among breast cancer patients.**

Patients and Methods: **Patients diagnosed with breast cancer who had completed their primary treatment were randomly assigned to black cohosh or placebo, stratified on tamoxifen use. At enrollment, patients completed a questionnaire about demographic factors and menopausal symptoms. Before starting to take the pills and at 30 and 60 days, they completed a 4-day hot flash diary. At the final visit, they completed another menopausal symptom questionnaire. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured in a subset of patients at the first and final visits.**

Results: **Of 85 patients (59 on tamoxifen, 26 not on tamoxifen) enrolled in the study, 42 were assigned to treatment and 43 were assigned to placebo; 69 completed all three hot flash diaries. Both treatment and placebo groups reported declines in number and intensity of hot flashes; the differences between the groups were not statistically significant. Both groups also reported improvements in menopausal symptoms that were, for the most part, not significantly different. Changes in blood levels of FSH and LH also did not differ in the two groups.**

Conclusion: **Black cohosh was not significantly more efficacious than placebo against most menopausal symptoms, including number and intensity of hot flashes. Our study illustrates the feasibility and value of standard clinical trial methodology in assessing the efficacy and safety of herbal agents.**

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LIKE OTHERS in the United States,[1] increasing numbers of cancer patients are using complementary and alternative medicine to supplement their medical treatment or to enhance their overall health and well-being. Among 305 breast cancer patients surveyed at our institution, 37% percent reported that, subsequent to their breast cancer diagnosis, they had used one or more oral medications not prescribed by their physician.[2,3] Other recent studies have reported frequencies of use ranging from 28% to as high as 91%.[3,4]

The largest segment of the cancer survivor community consists of breast cancer patients.[5] Nearly two-thirds of such patients report experiencing hot flashes, and the majority are reluctant to use, or have physicians who discourage them from using, estrogen replacement.[6] As increasing numbers of women take tamoxifen to prevent or treat breast cancer, more and more of them will experience menopausal symptoms for which conventional therapy cannot be used.[7] Medications other than estrogen that have been used to control such symptoms among breast cancer survivors include megesterol, clonidine, ergotamine tartrate (Bellergal-S; Sandoz Pharmaceuticals, East Hanover, NJ), vitamin E, venlafaxine, and phytoestrogens.[8-15] Of these treatments, megesterol acetate[9,15] and venlafaxine[9,15] and, to a lesser extent, vitamin E[9,15] and clonidine[9,15] have shown efficacy in well-controlled clinical trials.

Black cohosh (*Cimicifuga racemosa*),[16] a plant native to the eastern United States and Canada, was originally used by American Indians as a remedy for menstrual, menopausal, and other conditions. In Europe, particularly in Germany, extracts of the rootstock of black cohosh have been used for more than 50 years to treat climacteric symptoms.[16] In 1989, German Commission E, which regulates the use of herbal products, issued a positive monograph about black cohosh root extracts.[17] A commercially

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prepared extract was found to be more efficacious than placebo and similar to conventional hormone replacement therapy in relieving menopausal symptoms in women without a history of breast cancer.[16] Black cohosh extract was also not found to be associated with changes in hormonal or vaginal cytological parameters[16] or endometrium thickness.[18]

In the United States, many women with breast cancer take various black cohosh products, often with other over-the-counter remedies of unknown efficacy and safety. We undertook a randomized clinical trial to assess the efficacy, side effects, and safety of black cohosh among breast cancer survivors.

PATIENTS AND METHODS

Study Participants

Study participants were women over age 18, previously treated for breast cancer at the Columbia-Presbyterian Medical Center or one of its affiliates, who reported experiencing hot flashes daily. To be eligible, women had to have completed primary therapy, including chemotherapy and radiation therapy, at least 2 months before entering the trial. Patients were ineligible if they were using hormonal replacement therapy for hot flashes, were pregnant, had major psychiatric illness, or were known to have recurrent or metastatic breast cancer.

Study Design

Study design was a two-arm randomization, double masked and placebo controlled, to assess the effect of black cohosh on the frequency and intensity of hot flashes. We used one randomization list developed using the RanCode Plus program (IDV Datenanalyse und Versychoplanung, Gauting, Germany). The randomization list was numbered from one to 160: we stratified on tamoxifen/no tamoxifen use by using numbers one to 80 for users and 81 to 160 for nonusers. Study participants received their treatment assignment in the order of recruitment, with a 50% probability of assignment to either group. Women were permitted to use nonhormonal medications while participating in the study but were instructed not to initiate new therapy for hot flashes. Informed consent was obtained from all participants. We planned to enroll 80 women within 12 months.

The black cohosh and placebo were supplied by the manufacturer; each study participant's supply consisted of 130 tablets encased in cellophane bubble sheets in a single box. Participants were instructed to take one tablet twice daily with meals for 60 days. They were also asked to record the number of hot flashes and the intensity of each, scored as 1 = mild, 2 = moderate, and 3 = severe, for 3 days before starting to take any study pills, then again on days 27 to 30, and on days 57 to 60. Before starting and at the completion of the study, study participants completed a detailed menopausal symptom index and a visual analog scale rating of overall health and well-being. The subjects were asked to report any adverse events to the primary investigators, and the trial was to be discontinued if more than two women experienced a recurrence (expected incidence of more than two recurrences over the 12-month trial period) or a serious adverse event. The first 41 study participants were also asked to supply a blood specimen at the first and last study visits.

Analyses of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were performed on the first 37 and 18 women, respectively, who supplied specimens at both the start and end of the participation. Serum was assayed for these gonadotropins using microparticle enzyme immunoassay. This method has good validity and reliability.[19]

Compliance was monitored by pill counts at the final visit (all study medication packets were returned for counting) and by telephone calls halfway through and at the end of the participants' time on study. The callers asked about any relevant events since previous contact and reminded the study participants to take their pills, to complete their hot flash diaries, and to keep their final appointments.

Statistical Analysis

Sample size was chosen for 90% power to detect a 30% difference between groups in mean numbers of hot flashes, with a SD of 4.0. All analyses were stratified by tamoxifen use. The primary efficacy end point was mean numbers of hot flashes at 57 to 60 days. An analysis of covariance of mean numbers of hot flashes was conducted for treatment versus placebo, stratifying on tamoxifen use, with the baseline number of hot flashes as a covariate. In addition, we compared treatments using nonparametric Wilcoxon tests on the change in number of hot flashes from baseline to 60 days, stratifying by tamoxifen use. We also compared means at baseline and at 30 days for the two groups, as well as changes from baseline at 30 and 60 days. Study participants rated the intensity of their hot flashes on a 1 to 3 scale, and we compared the two groups' mean intensity of hot flashes in their three reports. We also developed an overall score of hot flash activity calculated as the product of number and intensity of hot flashes at each time point, similar to those used in other studies.[12,20]

The safety end points were changes in mean levels of FSH and LH at the start and end of study participation associated with treatment. Additional analyses were performed using data from the menopausal symptom index and visual analog scale ratings of overall health and well-being.

Missing data were handled by including all available data in the primary analyses in an intent-to-treat fashion. To assess possible bias, data were also analyzed by including only complete cases and by a last value carried forward approach. The results were consistent across these approaches.

RESULTS

We enrolled 85 study participants, of whom 59 were using tamoxifen and 26 were not. The 85 participants were randomly assigned to treatment (n = 42) or placebo (n = 43). Table 1 lists the demographic and clinical characteristics of the study participants, stratified by treatment assignment and tamoxifen use. The overall treatment group was significantly less educated ($P = .02$) than the placebo group. It also was older and included more racial and ethnic minorities, fewer full-time employed workers, more women who were currently married, and more mothers of more than two children than the placebo group, but these differences were not significant. The groups did not differ significantly in height or weight at baseline. Of the 85 who enrolled and responded to the baseline questionnaire, nine chose not to participate in the rest of the study. The remaining 76 subjects completed hot flash diaries at baseline; of these, 70 completed hot flash diaries at the study midpoint, and 69

Table 1. Demographic and Clinical Characteristics of Study Participants at Baseline, Stratified on Treatment Assignment and Tamoxifen Use

Characteristic	No. of Patients			
	Tamoxifen Use		No Tamoxifen Use	
	Treatment (n = 29)	Placebo (n = 30)	Treatment (n = 13)	Placebo (n = 13)
Age				
< 50 years	3	12	4	3
50-54 years	8	8	4	3
55-59 years	7	7	3	4
60– years	11	3	2	3
Race/ethnicity				
African-American	0	1	4	0
Asian/Pacific Islander	1	0	0	1
European-American	23	26	7	11
Hispanic	5	3	2	1
Years of education				
≤ 12	9	6	8	2
13-16	13	11	3	4
> 16	7	13	2	7
Employment status				
Employed full-time outside home	10	15	7	4
Homemaker	4	4	4	0
Other/unknown	15	11	2	9
Marital status				
Married	20	16	10	10
Divorced/separated	1	6	2	2
Widowed	5	3	0	0
Never married	3	5	1	1
Number of children				
0	6	8	6	4
1-2	15	17	3	6
> 2	8	4	4	3
Mean height in inches ± SD	63.0 ± 3.4	64.5 ± 3.6	64.8 ± 2.0	63.9 ± 3.8
Mean weight in pounds ± SD	149.7 ± 36.6	166.4 ± 32.6	164.1 ± 36.0	137.5 ± 35.7

also completed diaries at 57 to 60 days. One of the 69 left the first two days of the last hot flash diary blank and was therefore excluded from the hot flash analyses involving the last diary. Seven were found not to be compliant with the study protocol by pill count at the end of the study but were included in the intent-to-treat analysis.

Table 2 lists averages and ranges for numbers and intensities of hot flashes for the 76 study participants who supplied usable 4-day hot flash diary data at baseline, stratified on treatment assignment and tamoxifen use. Among the 68 study participants who provided usable hot flash diary data for all three time points, 24 were in the treatment/tamoxifen group, 26 were in the placebo/tamoxifen group, nine were in the treatment/no tamoxifen group, and 10 were in the placebo/no tamoxifen group.

Figures 1 and 2 show the medians, quartiles, and ranges for hot flash number and for the index of overall hot flash activity. In the course of the study, the average reported numbers of hot flashes declined in both groups; the overall decline in means from baseline to completion of the study was about 27%. However, the differences between treatment groups at the end of the study were not significant ($P = .86$ via analysis of covariance adjusting for baseline number and for tamoxifen use; $P = .44$ via stratified

Table 2. Hot Flash Number and Intensity Reported in the Baseline 4-Day Diaries, by Group

	Tamoxifen Use		No Tamoxifen Use	
	Treatment (n = 26)	Placebo (n = 28)	Treatment (n = 12)	Placebo (n = 10)
Number				
Mean	27.9	31.6	26.7	29.8
Median	24.5	27.5	22.5	21.0
Range	7-66	9-81	5-71	3-87
Intensity				
Mean	1.94	2.06	1.97	1.74
Median	2.01	2.01	1.94	1.69
Range	0.83-3.00	0.98-2.95	1.25-3.00	0.88-2.60

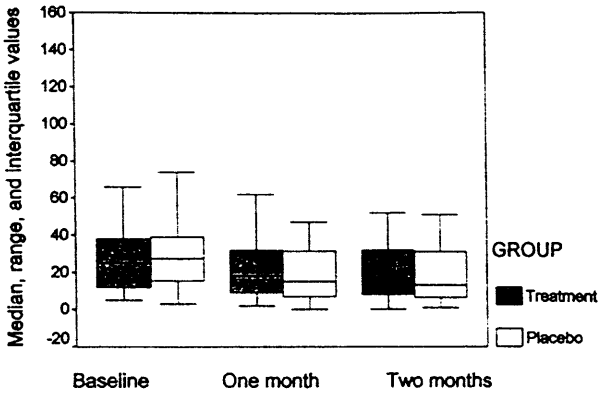

Fig 1. Number of hot flashes by group and time point.

Table 3. FSH and LH Levels at Baseline and Completion of Trial by Treatment Assignment and Tamoxifen Use

Treatment/ Placebo	Tamoxifen/No Tamoxifen	No. of Patients	Baseline (mean ± SD)	Completion (mean ± SD)
FSH				
Treatment	Tamoxifen	12	42.9 ± 32.9	40.8 ± 25.6
Placebo	Tamoxifen	16	33.5 ± 27.1	34.8 ± 19.2
Treatment	No tamoxifen	4	75.9 ± 29.9	76.2 ± 34.6
Placebo	No tamoxifen	1	94.4 ± 0	103.2 ± 0
LH				
Treatment	Tamoxifen	5	23.5 ± 11.8	26.9 ± 9.5
Placebo	Tamoxifen	7	24.7 ± 26.9	24.6 ± 20.0
Treatment	No tamoxifen	4	52.6 ± 7.0	49.7 ± 11.4
Placebo	No tamoxifen	2	28.3 ± 35.6	43.8 ± 24.3

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Wilcoxon test in difference from baseline to completion). At the midpoint of study participation, the tamoxifen and no tamoxifen groups differed (data not shown), but the treatment and no treatment groups did not.

In hot flash intensity, both groups experienced a decline during the first month of study participation. The differences between groups in intensity at the end of the study were not significant. For the overall hot flash activity score (Fig 2), the differences between the treatment and placebo groups adjusted for tamoxifen were not statistically significant.

We also analyzed changes in menopausal symptoms and in a global rating of health and well-being on a zero to 100 scale in the treatment and placebo groups. The global rating did not change significantly during the study period. The menopausal symptoms were heart palpitations, excessive sweating, headaches, poor sleep, depression, and irritability or nervousness. Both the treatment and placebo groups reported improvements in these symptoms during the study period; for none of the symptoms except sweating did the treatment group report significantly greater improvement than the placebo group ($P = .04$ by stratified Wilcoxon test).

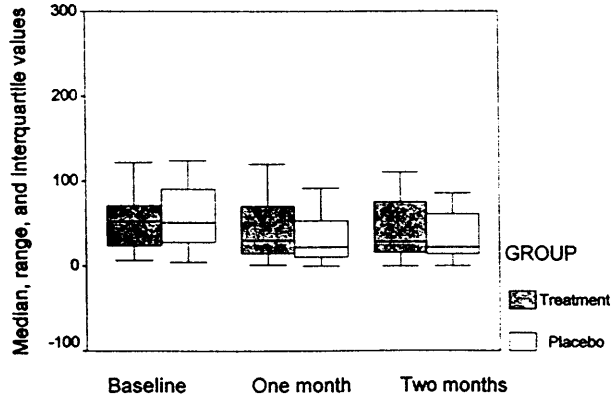

Fig 2. Hot flash activity by group and time point.

A comparison of FSH and LH levels at baseline and completion of study participation for a subset of study participants is listed in Table 3. The changes in FSH levels were very small and not significant in any group. However, the two tamoxifen groups had lower FSH levels than the two no-tamoxifen groups at both baseline and completion. Changes in LH levels were also small, except for the increase in the placebo/no tamoxifen subjects, and are not statistically significant.

Three serious adverse events occurred: one in the placebo/tamoxifen group and two in the treatment/tamoxifen group. Ten minor events also occurred: six in the treatment/tamoxifen group, two in the placebo/tamoxifen group, and two in the treatment/no tamoxifen group (Table 4).

Sixteen women dropped out of the trial: nine dropped out early (without completing the first hot flash diary), and seven dropped out late (without completing the final hot flash diary). Table 5 lists the treatment assignments and reported reasons for the dropouts. The study completers did not differ significantly from the dropouts in age, race/ethnicity, marital status, or menopausal status.

DISCUSSION

We initiated this trial because hot flashes have an adverse effect on breast cancer survivors' quality of life, and a number of breast cancer patients reported that using black cohosh relieved these symptoms. Both the treatment group and the placebo group experienced a benefit in terms of reduced number and reduced intensity of hot flashes. Both the treatment and placebo groups, whether using tamoxifen or not, reported a reduction in the intensity of hot flashes at

Table 4. Adverse Events During the Trial by Treatment Assignment and Tamoxifen Use

Adverse Event	Tamoxifen/No Tamoxifen	Treatment/ Placebo	Serious/ Minor
Hysterectomy	Tamoxifen	Treatment	Serious
Breast cancer recurrence	Tamoxifen	Treatment	Serious
Appendectomy	Tamoxifen	Placebo	Serious
Constipation	Tamoxifen	Treatment	Minor
Swollen finger	Tamoxifen	Placebo	Minor
Arrhythmia	No tamoxifen	Treatment	Minor
Weight gain	Tamoxifen	Treatment	Minor
Endometrial hyperplasia	Tamoxifen	Treatment	Minor
Dilatation and curettage	Tamoxifen	Treatment	Minor
Cramping	No tamoxifen	Treatment	Minor
Indigestion	Tamoxifen	Treatment	Minor
Vaginal bleeding	Tamoxifen	Treatment	Minor
Rash on abdomen	Tamoxifen	Placebo	Minor

the midpoint of the study. Although the treatment/no tamoxifen group experienced a continued decline in hot flash intensity throughout the study, this group included only nine study participants, and the difference between the treatment/no tamoxifen group and the other groups was not statistically significant.

The mean reduction in number of hot flashes was about 27% overall. The effect in the placebo groups was comparable with that observed in other studies.[20] Evidence from other studies suggests that women who have hot flashes tend to underreport them.[21,22] The feeling of security that results from taking a medication believed to control hot flashes may reinforce this tendency.

Of the seven menopausal symptoms we assessed, sweating was the only symptom for which the difference in improvement reported by the treatment and placebo groups at the end of the study was statistically significant. This finding may be caused by chance, but unlike, for example, nervousness or headaches, sweating is directly related to the perception of heat and is also what many women find most unpleasant about hot flashes (F. Kronenberg, personal communication, December 2000).

Table 5. Dropouts During the Trial by Treatment Assignment and Reason

Timing/Reasons	No. of Patients	
	Treatment	Placebo
Early		
Adverse event	1	0
Forgot pills while traveling	0	1
Unknown	3	4
Total early dropouts	4	5
Late		
Adverse event	2	1
Forgot pills while traveling	1	0
Unknown	2	1
Total late dropouts	5	2
Total dropouts	9	7

Our concerns about the safety of agents used by breast cancer patients motivated us to conduct the FSH and LH analyses. We reasoned that if an over-the-counter product were efficacious in alleviating menopausal symptoms, its benefits might be attributable to mechanisms that would make it no more acceptable for breast cancer patients than conventional hormone replacement therapy. However, we were willing to try black cohosh because in healthy women it had no documented estrogenic effects,[18] contraindications, or interactions.[17] We observed no significant changes in hormone levels by treatment group during study participation but found that at both baseline and completion, tamoxifen users had significantly lower FSH and LH levels than nonusers. These findings are not unexpected;[23-30] we stratified on tamoxifen use in the study design because of the reported effects of tamoxifen on hormone levels and menopausal symptoms.[31,32] (Tamoxifen use was not associated with hot flash number or intensity in our study, probably because to be eligible, all participants had to report daily hot flashes.)

A limitation of this study is that participation lasted only two months. We feared that study participants might drop out if they did not experience a benefit within that period of time. In fact, the dropout rate (16 of 85 or 18.8%) was relatively high. The early dropout rate may have been caused in part by our consent process, in which we noted the safety issues raised by treatments for hot flashes in the setting of breast cancer; the late dropout rate may reflect lack of benefit. In other studies of nonhormonal treatments, study participation has generally been shorter and estrogenicity has not been assessed. One recently reported study of venlafaxine also had a double-blinded randomized design but treated women for only 4 weeks.[15] Other studies of treatments for hot flashes in breast cancer patients have had a cross-over design in which women received treatment and placebo for about one month each.[8,10,12,20] It is possible that when used for a longer period of time, black cohosh may show greater efficacy relative to placebo, although our data show no strong indication of such a trend. Many women use black cohosh at higher doses than those used in this study or in combination with other agents intended to suppress menopausal symptoms; our study was not designed to compare dose levels or to assess interactions.

Of the three serious adverse events that occurred during study participation, hysterectomy may have been caused by tamoxifen, and the patient whose cancer recurred had had an increase in carcinoembryonic antigen that had not been reported to the referring physician when the patient entered

the study. Most of the study participants who experienced minor adverse events were in the treatment group; almost all were taking tamoxifen. The adverse events did not appear to be related to treatment. All but four of the women who experienced adverse events completed their trial participation.

In short, for breast cancer survivors, our data provide little evidence of either harm or benefit from using black cohosh to control hot flashes, although a reduction in sweating may be important to patients. More intensive studies of the effects of black cohosh, other botanicals, and other products sold over the counter and used by cancer patients are clearly needed. Such products cannot be assumed to be biologically inert, and some have been shown to be estrogenic.[33,34] In this study, we have collected information about black cohosh that is not available about most other over-the-counter agents used by breast cancer patients to control hot flashes.

This study demonstrates the value and feasibility of conducting randomized clinical trials of herbal agents.[35] Recent reviews have suggested that randomized trials are not necessarily more informative than observational studies.[36,37] However, the placebo effects in our study were significant; without a control group, we might easily have attributed all the improvement in menopausal symptoms to black cohosh. Herbal remedies in standardized formulations of high pharmaceutical quality (World Health Organization standard: Good Manufacturing Practices) are well suited for randomized, double-blind trials. Because so many people, including patients with life-threatening diseases and those taking other medications, use complementary and alternative medicine, the research community has a responsibility to assess their efficacy and safety in these patient populations; in the case of herbal agents, a ready-made methodology is available for such assessments.

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