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ORIGINAL REPORT

Randomized, Controlled Trial of Acupuncture for the Treatment of Hot Flashes in Breast Cancer Patients

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ABSTRACT

Purpose
To determine the immediate and long-term effects of true acupuncture versus sham acupuncture on hot flash frequency in women with breast cancer.

Patients and Methods
Seventy-two women with breast cancer experiencing three or more hot flashes per day were randomly assigned to receive either true or sham acupuncture. Interventions were given twice weekly for 4 consecutive weeks. Hot flash frequency was evaluated at baseline, at 6 weeks, and at 6 months after initiation of treatment. Patients initially randomly assigned to the sham group were crossed over to true acupuncture starting at week 7.

Results
The mean number of hot flashes per day was reduced from 8.7 (standard deviation [SD], 3.9) to 6.2 (SD, 4.2) in the true acupuncture group and from 10.0 (SD, 6.1) to 7.6 (SD, 5.7) in the sham group. True acupuncture was associated with 0.8 fewer hot flashes per day than sham at 6 weeks, but the difference did not reach statistical significance (95% CI, −0.7 to 2.4; $P = .3$). When participants in the sham acupuncture group were crossed over to true acupuncture, a further reduction in the frequency of hot flashes was seen. This reduction in hot flash frequency persisted for up to 6 months after the completion of treatment.

Conclusion
Hot flash frequency in breast cancer patients was reduced following acupuncture. However, when compared with sham acupuncture, the reduction by the acupuncture regimen as provided in the current study did not reach statistical significance. We cannot exclude the possibility that a longer and more intense acupuncture intervention could produce a larger reduction of these symptoms.

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INTRODUCTION

A hot flash is a sensation of increased temperature accompanied by peripheral vasodilation and profuse sweating. Feelings of anxiety, palpitations, and sleep disturbance can also occur.[1] Between 50% and 80% of postmenopausal women suffer from hot flashes.[2-5] Hot flashes are associated with treatment for breast cancer due to abrupt menopause or estrogen ablation therapy. Approximately two thirds of breast cancer patients report hot flashes and 60% of these (ie, 40% of all patients) rate their problem as moderately or extremely severe.[6] An increasing number of breast cancer survivors are taking hormonal therapy, and reduction of hot flashes would make a significant impact on their quality of life.

Estrogen replacement therapy was the treatment of choice for menopausal symptoms for decades. However, use of hormones for this purpose declined when hormones were associated with increased risks of breast cancer, coronary artery disease, stroke, and other thromboembolic events.[7,8] Moreover, estrogen replacement therapy is contraindicated in estrogen receptor-positive breast cancer patients. Several pharmacologic agents, including megestrol acetate,[9] clonidine,[10,11] and selective serotonin reuptake inhibitors (SSRIs), reportedly reduce hot flashes in breast cancer patients.[12-15] These agents can cause side effects, and they have low patient acceptance. A systematic review concluded that they are not optimal choices for most women.[16]

Several natural products have also been investigated for the treatment of hot flashes.[17] Randomized trials have failed to find clinically meaningful effects for soy phytoestrogens,[18-25] red clover,[26] or black cohosh.[27-29] Vitamin E, although superior to placebo, produces only a small effect size–an improvement of about one hot flash per day compared with placebo.[30]

Acupuncture is a complementary medicine modality that originated in traditional Chinese

medicine practices.[31] Several early-phase, uncontrolled studies suggest that acupuncture may reduce hot flashes in postmenopausal women or in breast cancer patients receiving tamoxifen treatment.[32,33] However, controlled studies of acupuncture have shown mixed results, as reviewed by Carpenter and Neal.[34] Because treatment options for hot flashes are limited, especially for breast cancer patients on hormonal therapy, there has been a strong interest in further evaluation of acupuncture for this indication.[35,36] We conducted a randomized, controlled trial to determine whether true acupuncture is superior to sham acupuncture for the treatment of hot flashes in breast cancer patients.

PATIENTS AND METHODS

Study Design

This was a randomized, controlled, subject-blinded trial. The duration of the intervention was 4 weeks. The primary end point was hot flash frequency at week 6. At week 7, patients randomly assigned to the sham acupuncture (control) group were crossed over to receive true acupuncture and were evaluated 6 weeks later.

Study Participants

Informed consent was obtained before participant enrollment according to a clinical trial protocol approved by the institutional review board at Memorial Sloan-Kettering Cancer Center. Recruitment took place between November 2002 and December 2005. Inclusion criteria were as follows: undergoing treatment for breast cancer at Memorial Sloan-Kettering Cancer Center; Karnofsky performance score more than 60; and an average of 3 or more hot flashes per day during a 1-week period with a baseline diary. Exclusion criteria were as follows: planned surgery, chemotherapy, radiotherapy, immunotherapy, or initiation or cessation of hormonal therapy during the trial or within 3 weeks before the trial; pharmacologic treatment of hot flashes or any use of SSRIs, unless SSRI dose remained stable for 4 weeks prior to study; skin infection; acupuncture treatment in the 6 weeks prior to study; or acupuncture given specifically for the treatment of hot flashes in the previous 6 months.

Random Assignment

Random assignment of participants was accomplished using a secure, password-protected, institutional computer system that stratified by using permuted blocks of random length. The system is designed to ensure that allocation cannot be guessed before a patient is registered and cannot be changed afterwards, thus ensuring full allocation concealment. The randomization strata were (1) concurrent treatment (yes/no) with any of the following: selective estrogen receptor modulator, gonadotropin-releasing hormone analog, or aromatase inhibitor; (2) concurrent use of either a hot flash medication or an SSRI; (3) baseline hot flash frequency of more than 7 flashes per day; and (4) menopausal status at diagnosis. After participant registration and random assignment, a research assistant who was otherwise unconnected with the trial accessed allocation and telephoned the acupuncturist with the details of allocation. Patients, researchers, and others involved in patient care were blind to the study group; only the acupuncturists and the designated research assistant were aware of which patients received true and which received placebo treatment.

Intervention

Study participants received twice-weekly treatments for 4 weeks (a total of eight treatment sessions in weeks 1 through 4). The first treatment was given on the day of randomization (day 1). The point prescription was changed during the trial. (See Statistical Methods.) Table 1 shows the final set of 19 acupuncture points used in the true acupuncture group. This prescription was derived from previous reports and from expert opinion, as found in standard acupuncture textbooks. The sham and true acupuncture treatments were delivered by several licensed acupuncturists (not always by the same acupuncturist), according to the staff schedule. All acupuncturists had at least 3 years of formal postgraduate training, had practiced continuously from 3 to 25 years, and were not blinded to treatment-group assignment.

In the true acupuncture group, the needles used were stainless-steel filiform, needles sized 0.20 × 30 mm and manufactured by Seirin Corp (Shizuoka, Japan). After sterile swabbing of the skin, needles were inserted 0.25 to 0.5 inches into the skin at the designated acupuncture points and were manipulated manually to obtain De Qi.[31] No electrical stimulation or other interventions were applied.

In the sham acupuncture group, Streitberger sham needles sized 0.30 × 30 mm and manufactuered by Asiamed (Pullach, Germany)[37] were applied a few centimeters away from the points listed in Table 1. Rather than penetrating the skin, the needle retracted inside its handle after insertion through an adhesive tape placed on a plastic supporting ring. This type of sham needle has been shown to have high participant credibility and has been successfully implemented in randomized, controlled trials.[38] The frequency and duration of the sham acupuncture intervention were identical to those of true acupuncture. To ensure consistency in technique, the therapists were coached by a

Table 1. Acupuncture Point Prescription

Prescription		
Point	Meridian	Location
DU 14	du mai	On the midline at the base of the neck, in the depression below the spinous process of the 7th cervical vertebra (C7)
GB 20	gallbladder	Below the occiput, in the hollow between the origins of the sternomastoid and trapezius muscles
BL 13	bladder	1.5 cun* lateral to the lower border of the spinous process of the 3rd thoracic vertebra (T3)
PC 7	pericardium	At the wrist joint, between the tendons of palmaris longus and flexor carpi radialis
H 6	heart	On the radial side of the tendon of flexor carpi ulnaris, 0.5 cun proximal to wrist crease
K 7	kidney	On the medial aspect of the lower leg, in the depression 2 cun superior the depression between the medial malleolus and the Achilles tendon, on the anterior border of Achilles tendon
ST 36	stomach	Below the knee, 3 cun inferior to the lateral and inferior aspect of the patella, one finger breadth lateral to the anterior crest of the tibia
SP 6	spleen	On the medial side of the lower leg, 3 cun superior to the prominence of the medial malleolus, in a depression close to the medial crest of the tibia
Ear shen men	—	Slightly above the anthelical bifurcation into crura, at the margin of the lower side of the superior anthelical crus facing the fossa, in the concavity of the triangular fossa
Ear sympathetic point	—	On the inferior anthelical crus at the intersection with the protruding helical brim of the ascending helix, usually slightly covered by the helical brim

*A cun is an acupuncture measurement unit that is equivalent to the width of the participant's thumb at the distal phalanx.

single acupuncturist who also observed treatments periodically for integrity. Participants randomly assigned to the control group were offered eight sessions of true acupuncture starting at week 7. To aid the blinding process, all patients were asked to relax on the treatment table, gentle music was played, and an eye pillow was offered. In both groups, needles were retained for 20 minutes and then were removed. Participants with lymphedema were not administered needles in the affected arm.

Evaluation

The primary outcome measurement was hot flash frequency. Participants were asked to record the number of hot flash episodes each day. At baseline, participants completed a diary for 1 week within 3 weeks of randomization. Details of SSRIs and medications taken for hot flashes were recorded and were categorized as either no treatment at enrollment or during study or as treatment that was started, stopped, reduced, increased, or maintained during study.

Participants then completed a hot flash diary for 1 day at days 7, 14, 21, 28, and 35 after randomization and again for 1 week starting 6 weeks after randomization. Those randomly assigned to true acupuncture completed a second diary for 1 week at 26 weeks. Those randomly assigned to the sham acupuncture control group were offered the true acupuncture treatment at week 7. If they agreed to cross over to the true acupuncture group, they were asked to complete diaries at 12 and 32 weeks, which were the equivalent of 6 and 26 weeks after their first true acupuncture session. Control participants who declined further acupuncture were asked to complete further diaries only at week 26.

Immediately after the needles were applied during the first treatment session, participants were administered a credibility-of-treatment rating scale.[39] They were asked to answer four questions about their treatment on a five-point, Likert scale that ranged from strongly disagree to strongly agree. This scale was used to determine whether participants were able to distinguish between true and placebo treatments.

Participants were asked at 6 weeks and at 6 months after treatment initiation for details of any non–study-administered treatment for hot flashes. At 6 weeks, participants were asked in which group they thought they were allocated (true *v* sham) and why they thought so.

Statistical Methods

Sample-size calculations were based on an initial (unpublished) pilot of 14 participants. The mean baseline hot flash frequency was 7.4, the correlation between baseline and follow-up was 0.64, and the standard deviation (SD) was 2.3. As a conservative measure, we used the upper 75th percentile of the distribution for the SD (2.8) and the lower 75th percentile of the correlation (0.54). By assuming a 25% reduction in hot flash frequency in the placebo group, we specified that a minimum clinically significant difference would be equivalent to a 50% reduction in the true acupuncture group, which would be the equivalent of 1.9 fewer hot flashes per day. This required a total sample size of 66 assessable participants for a power of 90% and an alpha of 5%.

Our prespecified, primary analysis was to compare hot flash frequency at 6 weeks between groups by analysis of covariance, using baseline hot flash frequency and randomization strata as covariates. Differences in the credibility scores were assessed by *t* test. Analysis of medication-use data combined started treatment with increased treatment and combined stopped treatment with reduced treatment. Fisher's exact test was used to test for differences between the groups. All analyses were on the intent-to-treat principle and were conducted using Stata 9.2 (STATA Corp, College Station, TX).

When the study was initially started, 27 participants were accrued and were treated with a set of points different than those shown in Figure 1. At this point, there was a change in staffing. The new group of acupuncturists believed that a different set of points (Table 1) would be more appropriate. We prespecified that we would accrue sufficient patients on the new point prescription to meet the original sample size requirements and that our primary analysis would include only patients on the new point prescription. Seventy-two participants were accrued to this new regimen. Data presented here derived solely from those 72 participants.

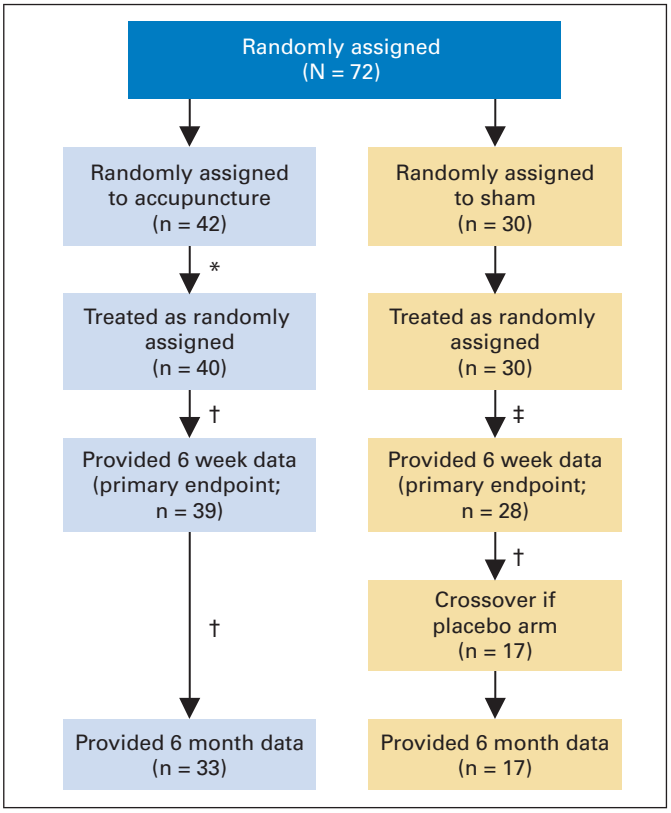

Fig 1. Participant flow (description and number of participants). Reasons for withdrawals/drop-outs: (*) one had scheduling conflict, one had disease progression; (†) lost to follow-up; (‡) partial/incomplete diary.

RESULTS

The flow of participants through the trial is shown in Figure 1. Compliance with follow-up was good, with 67 of 72 randomly assigned participants providing data for the primary end point. Baseline data are shown in Table 2. Although there is a chance imbalance in the number of patients per group, the groups are otherwise well matched.

Hot flash frequency over time is shown in Table 3 (absolute number) and in Figure 2 (percentage of baseline). Hot flash frequency was reduced in a similar fashion during the first 2 weeks of the treatment phase in both groups by approximately 20%. Afterwards, the reduction in the sham acupuncture group appears to remain the same, whereas hot flash frequency decreased by approximately another 10% in the true acupuncture group. In the principal analysis (hot flash frequency at week 6), acupuncture was associated with 0.8 fewer hot flashes per day than placebo, but the difference was not statistically significant (95% CI, −0.7 to 2.4; $P = .3$).

When participants in the sham acupuncture group were crossed over to the true acupuncture group at week 7, hot flash frequency was reduced by approximately another 20% at week 12. Hot flash frequency was reduced from 7.3 (SD, 5.5) to 5.4 (SD, 3.8), a difference of 1.9 hot flashes per day (95% CI, −0.4 to 4.1). Treatment improvements were maintained at 6 months. There are no obvious differences between groups ($P = .3$) in changes in medication use.

Credibility scores are very similar in each group ($P = .99$), which suggests that blinding was maintained. Participant guesses as to treatment allocation at the poststudy debriefing are given in Table 4.

Table 2. Baseline Characteristics of Sample

Variable	True Acupuncture	Sham Acupuncture
No. of participants	42	30
Age		
Median	55	56
Interquartile range	48-59	49-59
Other treatment		
Tamoxifen		
No. of participants	20	10
%	48	33
Aromatase inhibitors		
No. of participants	8	9
%	19	30
SSRIs		
No. of participants	16	9
%	38	30
Postmenopausal		
No. of participants	38	29
%	90	97
Lymphedema*		
No. of participants	24	18
%	60	60
Credibility scores†		
No. of participants	35	29
Mean	3.8	3.8
Standard deviation	0.4	0.5

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.
*Participants with lymphedema received needle application in one arm only.
†Maximum credibility score, 5; lowest credibility score, 1.

Table 3. Frequency of Hot Flashes per Day

Timepoint	Acupuncture	Placebo	Between-Group Comparison 95% CI	*P*
Baseline				
No. of participants	42	29		
Mean No. of hot flashes	8.7	10.0		
SD	3.9	6.1		
During treatment				
Day 7			−1.2 to 1.8	.7
No. of participants	39	28		
Mean No. of hot flashes	7.3	7.9		
SD	4.4	5.0		
Day 14			−1.4 to 1.4	.99
No. of participants	37	28		
Mean No. of hot flashes	6.8	7.5		
SD	4.4	6.1		
Day 21			−2.3 to 1.5	.7
No. of participants	37	29		
Mean No. of hot flashes	6.9	8.1		
SD	4.8	6.0		
Day 28			−2.7 to 0.9	.3
No. of participants	38	27		
Mean No. of hot flashes	5.8	7.8		
SD	4.8	5.9		
Post-treatment				
Day 35			−2.5 to 1.0	.4
No. of participants	37	25		
Mean No. of hot flashes	5.9	7.5		
SD	4.7	5.2		
Week 6*			−2.4 to 0.7	.3
No. of participants	39	28		
Mean No. of hot flashes	6.2	7.6		
SD	4.2	5.7		
Week 12				
No. of participants	—	17		
Mean No. of hot flashes	—	5.8		
SD	—	3.9		
Month 6				
No. of participants	33	17		
Mean No. of hot flashes	6.1	6.8		
SD	4.9	5.7		

Abbreviation: SD, standard deviation.
*Principal end point.

Although differences between groups approach statistical significance ($P = .069$ by Fisher's exact test), almost all participants who made a guess (55 of 59; 93%) explained the reason for their guess in terms of a change in symptoms; regardless of true allocation, participants who experienced a decrease in symptoms guessed that they were in the acupuncture group, and participants who experienced little change guessed that they had been assigned to the control group.

Only very minor adverse effects, such as slight bleeding or bruising at the needle site, were reported, and none required further medical intervention. A total of 14 grade 1 adverse events (of about 560 acupuncture sessions) were recorded by 12 participants as definitely, probably, or likely due to a study intervention. One participant, who was in the sham group, used off-study medication; no subject used acupuncture treatment off-study.

DISCUSSION

In this randomized, controlled trial, both true and sham acupuncture were associated with an initial reduction in hot flash frequency. The reduction by sham acupuncture appeared to reach a plateau after 2 weeks, whereas the reduction by true acupuncture appeared to continue until week 4, when the treatment period ended. Although there was a greater reduction in hot flashes in the true acupuncture group at week 6 (the primary end point), differences between groups were small and did not reach statistical significance. When the participants in the sham group were crossed over to the true acupuncture group, a further reduction of hot flash frequency was observed. The reduction was maintained at a 6-month follow-up. These results did not meet our predefined criteria for clinical significance.

Previous, uncontrolled studies[32,33] typically have reported reductions in hot flashes following acupuncture. In a study without a nontreatment or a sham control, both acupuncture and applied relaxation reduced hot flashes in breast cancer patients.[40] When acupuncture and sham acupuncture are evaluated in the same study, the results have been mixed. In a moderately sized, randomized trial comparing true and sham acupuncture for the treatment of menopausal hot flashes (N = 29), Huang et al[41] reported a statistically significant difference between true and sham acupuncture for nocturnal hot flashes. In a report of two randomized, controlled studies (one including transdermal placebo and transdermal estrogen treatment, the other including oral estrogen, acupuncture, and applied relaxation), Zaborowska et al[42] showed that oral estrogens, acupuncture, and

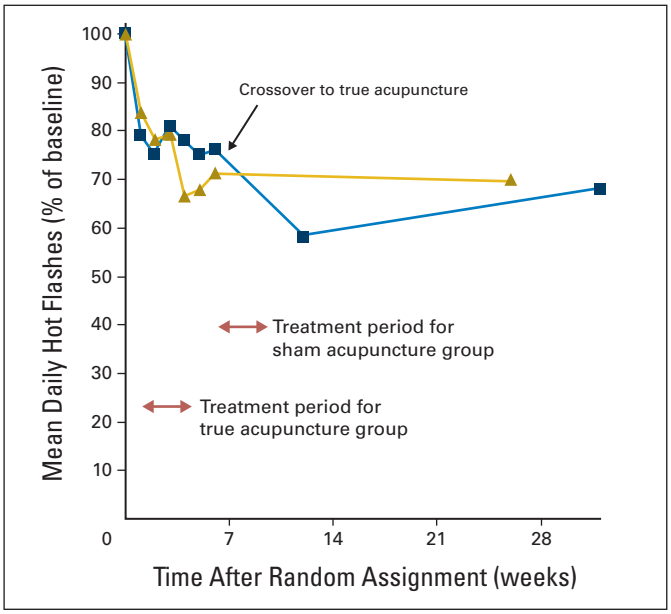

Fig 2. Hot flashes frequency by time on study. Baseline = 100%. Treatment period: week 1 to week 4. (—▲—) true acupuncture group; (—■—) sham acupuncture group.

applied relaxation were all superior to a transdermal, placebo patch treatment. However, the comparison between acupuncture and transdermal placebo was nonrandomized.

In contrast, Vincent et al[43] randomly assigned 103 postmenopausal women to true acupuncture or to needle application at nonacupuncture points as a control. Hot flash scores, which incorporated both frequency and severity, were reduced in both groups, but there was no significant difference between the two groups. Similarly, Wyon et al[44] found that both electroacupuncture and superficial needle application (sham) reduced hot flashes, with no significant difference between the two interventions.

There are several possible explanations of our findings in light of the above previous studies. First, it may be that the interventions used as sham controls were not entirely inactive. For example, it might be that needle application at nonacupuncture points[43,44] provides a physiologic stimulus that is at least partly active against hot flashes. This possibility is supported by the reports that acupuncture appeared better than a transdermal placebo patch[42] but not better than superficial needle application.[44]

Second, symptom improvement may result from the natural course of symptoms or from the psychological impact of treatment. In drug trials with a placebo control, the placebo effect on hot flashes frequency can vary from 13%[45,46] to 22%.[26] Improvement in our sham acupuncture group (24%) is close to that range. All trials of symptoms in which a certain baseline symptom severity is an eligibility criterion will be subject to regression to the mean. It is also widely believed that psychological impact of receiving treatment—the time and attention from a practitioner, and the patient's belief that they will be helped—is of therapeutic value. Both true and sham acupuncture also may create a relaxation effect, which can reduce hot flashes.[42,47] Kaptchuk et al[48] have shown in a randomized trial that a sham acupuncture technique, similar to that used in the current study, was superior to an inert pill for the treatment of pain, except during the 2-week placebo run-in.

The third possible explanation for our findings is that the acupuncture intervention may not have been optimal. This may be because the point prescription was inadequate. Most investigators select acupuncture points based on classical theory, previous research reports, and/or expert opinion. This is an inherent limitation of all acupuncture research, because there is no reliable and consistent way to determine what would constitute the ideal prescription.

The fourth possibility is that our method of symptom assessment evaluated hot flash frequency but not severity. However, pooled data from 968 participants in seven clinical trials showed a close correlation between hot flash frequency and hot flash scores.[49] Given the small effect size, it is unlikely that measuring hot flash severity would have changed the clinical implications of findings in this study.

Another limitation of our study is the reliance on self-reporting of hot flashes. We did not include physiological measurements,[50,51] such as skin conductance, because techniques available at the time were not easy to implement and because we felt that clinical significance ultimately depended on how patients perceived their symptoms.

Finally, our intervention period may not have been of sufficient duration. This possibility is supported by Figure 2, in which the reduction of hot flash frequency in the true acupuncture group started to deviate from the sham group after week 2 and reached a lower point at week 4, when the intervention period completed. Further reductions might have been seen if true acupuncture had continued beyond week 4. Moreover, additional reductions in hot flash frequency were observed in the sham acupuncture participants after they were crossed-over to true acupuncture.

The mechanism by which acupuncture might improve hot flashes is unclear. It has be hypothesized that acupuncture regulates neurotransmitters involved in thermoregulation.[52,53] Few data currently support this contention.

In conclusion, hot flash frequency in breast cancer patients was reduced following acupuncture. However, when compared with sham acupuncture, the reduction associated with the acupuncture treatment provided in the current study did not reach statistical significance. We cannot exclude the possibility that a longer and more intense acupuncture intervention could produce a larger reduction in hot flashes.

Table 4. Subject Guesses As to Allocation Post-Treatment

	True Acupuncture Allocation		Sham Acupuncture Allocation	
Guess	No.	%	No.	%
Acupuncture	18	43	5	17
Placebo	18	43	18	60
Unsure	4	10	5	17
No data	2	5	2	7

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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ERRATUM

The December 10, 2007, article by Deng et al, entitled "Randomized, Controlled Trial of Acupuncture for the Treatment of Hot Flashes in Breast Cancer Patients" (J Clin Oncol 25:5584-5590, 2007) contained errors.

The following authors were inadvertently omitted from the author list due to a misunderstanding of the authorship criteria:

Gabriella M. D'Andrea, Han Xiao, Steven Sugarman, Tiffany Troso-Sandoval, Andrew D. Seidman, Clifford A. Hudis (Breast Cancer Medicine Service), Alexandra S. Heerdt (Breast Cancer Surgery Service, Memorial-Sloan Kettering Cancer Center, New York, NY)

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Administrative support: Clifford A. Hudis

Provision of study materials or patients: Gabriella M. D'Andrea, Han Xiao, Steven Sugarman, Tiffany Troso-Sandoval, Andrew D. Seidman, Clifford A. Hudis, Alexandra S. Heerdt

Collection and assembly of data: Han Xiao

Final approval of manuscript: Clifford A. Hudis, Alexandra S. Heerdt

The authors have indicated that no potential conflicts of interest exist. The corrected author list is reprinted below in its entirety.

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The online version has been corrected in departure from the print.

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