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ORIGINAL REPORT

Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT)

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ABSTRACT

Purpose
To determine the effectiveness of acupuncture for the management of hot flashes in women with breast cancer.

Patients and Methods
We conducted a pragmatic, randomized controlled trial comparing acupuncture plus enhanced self-care versus enhanced self-care alone. A total of 190 women with breast cancer were randomly assigned. Random assignment was performed with stratification for hormonal therapy; the allocation ratio was 1:1. Both groups received a booklet with information about climacteric syndrome and its management to be followed for at least 12 weeks. In addition, the acupuncture group received 10 traditional acupuncture treatment sessions involving needling of predefined acupoints. The primary outcome was hot flash score at the end of treatment (week 12), calculated as the frequency multiplied by the average severity of hot flashes. The secondary outcomes were climacteric symptoms and quality of life, measured by the Greene Climacteric and Menopause Quality of Life scales. Health outcomes were measured for up to 6 months after treatment. Expectation and satisfaction of treatment effect and safety were also evaluated. We used intention-to-treat analyses.

Results
Of the participants, 105 were randomly assigned to enhanced self-care and 85 to acupuncture plus enhanced self-care. Acupuncture plus enhanced self-care was associated with a significantly lower hot flash score than enhanced self-care at the end of treatment ($P < .001$) and at 3- and 6-month post-treatment follow-up visits ($P = .0028$ and .001, respectively). Acupuncture was also associated with fewer climacteric symptoms and higher quality of life in the vasomotor, physical, and psychosocial dimensions ($P < .05$).

Conclusion
Acupuncture in association with enhanced self-care is an effective integrative intervention for managing hot flashes and improving quality of life in women with breast cancer.

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INTRODUCTION

Patients with breast cancer have a higher incidence of bothersome hot flashes and climacteric syndrome than other women.[1] Hot flashes are more severe and longer lasting in women with breast cancer than in healthy postmenopausal women.[2] Adjuvant therapy often aggravates hot flashes and sweating, interfering with activities and sleep and ultimately leading to poor quality of life.[3] Because hormone replacement therapy is contraindicated for these women,[4] they have limited treatment options for menopausal symptoms[5]; these include antidepressant drugs[6] and self-care indications.[7] Self-care recommendations, such as increased fruit and vegetable intake, reduced caffeine and alcohol intake, and more regular exercise, are supported by only a few epidemiologic studies[8,9] and therefore not extensively used in clinical practice. Consequently, there is a need for safe, effective, and feasible interventions.

Patients with cancer often show interest in complementary and integrative modalities.[10,11] Acupuncture is one of the most frequently used

complementary therapies. Although several clinical trials have shown some effects of acupuncture on vasomotor symptoms in both healthy women[12] and women with breast cancer,[13-15] these results have been considered promising rather than conclusive in terms of efficacy.[16,17] In addition, there is a lack of systematic, well-conducted research investigating the effects of acupuncture treatment on hot flashes.[18] Our feasibility study[19] assessed the effects of acupuncture in a mixed sample of 35 patients with breast cancer experiencing vasomotor symptoms. In accordance with findings from other studies[20,21] at the end of the 10-week treatment period, 66% of patients had a reduction in hot flashes that varied from 50% to 75% compared with baseline.

The aim of this study was to investigate the effectiveness of an integrative approach using acupuncture plus enhanced self-care versus enhanced self-care alone for the management of hot flashes in women with breast cancer.

PATIENTS AND METHODS

Study Design and Participants

A two-group, pragmatic, multicenter, randomized controlled trial design was used. Participants received either acupuncture plus enhanced self-care (acupuncture arm) or enhanced self-care (control arm). The study focused on women with breast cancer experiencing at least moderate-level hot flashes. Recruitment took place at five specialist cancer hospitals and one primary health care center in northern Italy from March 2010 to October 2013. Patients were referred by clinicians or were self-referred after responding to advertisements displayed in the health centers. The institutional ethics committees of all participating centers approved the study protocol.

The inclusion criteria were as follows: diagnosis of breast carcinoma, age 18 to 65 years, intention to continue hormonal treatment throughout the study (for patients receiving this treatment), spontaneous or induced amenorrhea for at least 6 months, mean number of six or more hot flashes and/or daily mean score of 15 or greater on the Greene Climacteric Scale (GCS) during the week before enrollment, vasomotor syndromes for at least 6 weeks, an Eastern Cooperative Oncology Group performance status of 1 or greater, willingness to participate and follow physical activities or relaxation techniques or diet or attend self-help or mutual aid group sessions and be randomly assigned to one of the study groups, signed informed consent.

Exclusion criteria were as follows: ongoing chemotherapy or radiotherapy; concomitant treatment of climacteric syndromes such as systemic phytoestrogens, tibolone or analog, veralipride, or specific homoeopathic drugs; acupuncture treatment provided for climacteric syndromes in the previous year; use of hormone replacement therapy and/or antidepressant drugs in the previous month and no intention to discontinue; and no language or educational barriers to understanding the study purpose.

Random Assignment

Patient random allocation lists were generated centrally by a statistician before study initiation using a Microsoft Excel function and were stratified by hormonal therapy (gonadotropin-releasing hormone agonist, yes *v* no). Patients were allocated to the acupuncture or control arm at a 1:1 allocation ratio via a Web-based service that communicated allocation only after patient recruitment.

Interventions

Enhanced self-care. Because of the absence of guidelines on management of climacteric syndrome in women with a history of breast cancer, usual care varies among clinicians. To standardize usual care recommendations, we enhanced self-care by providing all patients with a detailed information booklet about climacteric syndrome management. The booklet (Appendix, online only) was developed by the research team after a consensus process and included details about hot flashes and cancer and recommendations on diet, physical exercise, and eventual psychological support. The content of the booklet was explained to all patients before random assignment, and booklets were then distributed. Patients were asked to follow self-care recommendations for at least 12 weeks from random assignment.

Acupuncture. Within 2 weeks of random assignment, in addition to self-care recommendations, the acupuncture group was offered 10 traditional Chinese medicine (TCM) acupuncture sessions once per week for 12 weeks. The treatment protocol identifies six TCM menopausal syndromes according to Maciocia's recommendations (Table 1).[22] At the beginning of each acupuncture session, a TCM evaluation of the tongue and radial pulses was performed to identify the prevailing syndrome and consequently choose appropriate acupoints in addition to three common acupoints (ie, SP 6, LI 11, CV 4). Patients received 20-minute acupuncture treatments based on the diagnosed TCM syndrome; moxibustion was provided as per TCM diagnosis. In some cases, supplementary points were punctured, but no more than 11 acupoints were used for each session. Sterile disposable 0.30 × 0.40 mm Huan Qiu needles (Suzhou Huanqiu Acupuncture Medical Appliance, Suzhou, People's Republic of China) were inserted bilaterally to a depth of 0.5 to 1 cm in most areas, except the hip, where the depth was 1 to 2 cm. They were manually manipulated to elicit the *de qi* sensation. No flicking or rotation of the needle took place once inserted. Participants with lymphoedema were not treated in the affected arm. No other complementary therapy was recommended during the course of acupuncture. Conversation between acupuncturists and patients was kept to a minimum to limit nonspecific treatment effects.

The treatment was provided at three of the five specialist cancer hospitals (two recruitment centers referred to the same location) and the primary health care center. Four acupuncturists, who were trained to a 4-year–degree level and had at least 20 years of clinical experience, were trained according to the treatment protocol.

Outcomes

The primary outcome measure was daily mean hot flash score (HFS) assessed at week 12.[23] HFS was calculated by multiplying the mean number of daily hot flashes that occurred during the week before assessment by the mean daily severity (1, mild; 2, moderate; 3, severe). Number and severity of hot flashes were recorded in patients' diaries 1 week before random

Table 1. TCM Syndromes Recorded Before First Acupuncture Session and Moxibustion Use

TCM syndrome	Acupuncture Points	Patients	
		No.	%
Kidney yin emptiness	LU7, KI6, KI3, KI10, HE6, KI7	14	16.40
Kidney yin and yang deficiency	KI3, LU7, KI6, HE6, BL52, KI7, ST36, CV6, GV20, BL23	15	17.65
Kidney and liver yin and yang deficiency and yang escape from liver	LR3, LI4, GB20, KI6, PC7, LU7, LR2, ST37	31	36.40
Kidney and heart disharmony	KI6, LU7, CV14, KI2, PC6, KI3, KI13, HT6, KI7, HT8, LU7, CV15, DU24, ST37	9	10.59
Phlegm or qi stasis	CV17, PC6, SP9, SP10, ST40, LU7, KI6,CV6, CV10, TE6, ST28	14	16.47
Blood stasis	SP4, PC6, KI14, SP10, BL17, CV4, CV6, LR3, LU7	0	—
Not indicated		2	2.30
Use of moxibustion		29	34.2

Abbreviation: TCM, traditional Chinese medicine.

assignment (baseline), 1 week before the scheduled visit at the end of treatment (week 12; primary time point), and 3 and 6 months later (3- and 6-month follow-up visits).

Secondary outcomes were climacteric symptoms and quality of life measured by the GCS and Menopause Quality of Life (MenQoL) scales at the end of treatment (week 12) and at the post-treatment follow-up visits at months 3 and 6. The GCS provides a brief measure of climacteric syndrome.[24] It is self-administered and can be used to assess changes in different menopausal symptoms. This scale indicates the extent to which the respondent is currently bothered by any of the symptoms, from 0 (not at all) to 3 (extremely bothered). Three main symptom areas are measured—psychological, physical, and vasomotor—using 21 items, with a final score ranging from 0 to 63.

The MenQoL questionnaire is a tool to assess health-related quality of life (HRQoL) in the immediate postmenopausal period.[25] It is self-administered and consists of 29 items in a Likert-scale format, ranging from 0 (not bothered) to 6 (extremely bothered). Each item assesses the impact of one of four menopausal symptom domains, as experienced over the last month: vasomotor, psychosocial, physical, and sexual. Means are computed for each subscale by dividing the sum of the items in the domain by the number of items within that domain; the final score ranges from 1 to 8. In addition, demographic information, clinical characteristics, and information about current self-care activities (eg, physical exercise and psychological support) were recorded at the screening visit. At the baseline interview conducted immediately before random assignment, participants were asked if they expected (by the end of treatment) their symptoms to be completely gone, much better, a little better, or about the same. At the end of treatment, patients were asked if they were satisfied with the treatment received (not at all, poorly, a lot, or completely) and which treatment they would select if they could.

Adherence to the enhanced self-care recommendations (ie, physical exercise, psychological support, and weight loss) was also assessed at scheduled visits. Adverse events likely to be related to acupuncture treatment were also recorded. All outcomes and clinical data were collected on the patient report form by research investigators who were not involved in the acupuncture treatment. The research coordinator was responsible for recording data in the centralized database.

Statistical Methods

To calculate the sample size, we used the baseline mean HFS (30.4) and standard deviation ($\pm$ 15) of patients included in a previous pilot study.[19] To yield 80% power to detect a 20% significant (at the two-sided 5% level) difference in mean HFS between two groups and allow a 10% attrition rate, we planned to enroll 210 patients in 24 months. Because of slow accrual, recruitment was prolonged for an additional 18 months and closed for administrative reasons with 190 patients and a study power greater than 80%. We described sociodemographic, clinical, and outcome variables using means and standard deviations or medians and ranges for continuous variables and percentages for categorical variables by group. Differences in participant characteristics at baseline were tested using χ^2 tests for categorical variables and *t* tests as appropriate. The analysis was based on the intention-to-treat principle, and all randomly assigned patients were analyzed. The baseline observation carried forward was used

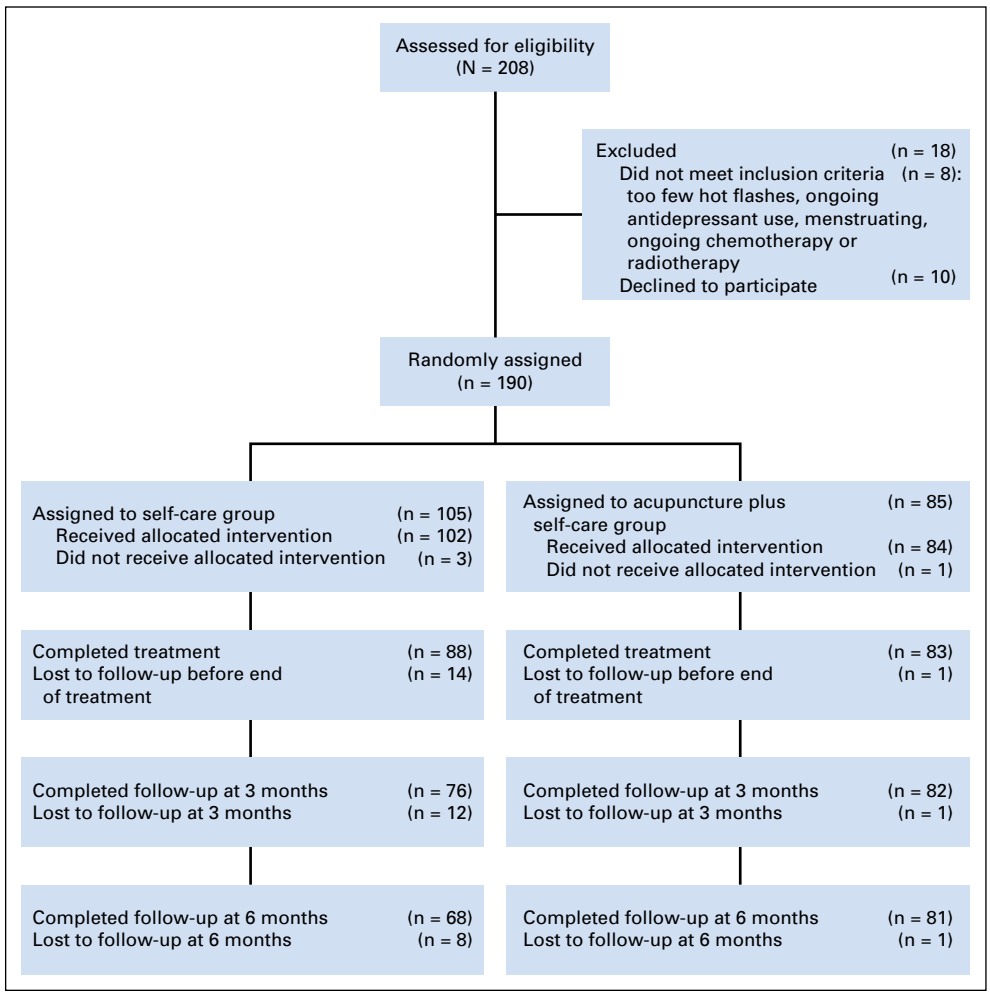

Fig 1. CONSORT diagram.

to impute missing values. If patients had at least one assessment beyond baseline, the last observation was carried forward. No imputation was performed for missing values of the physical examination. A per-protocol analysis was repeated considering only the participants who, at the end of treatment (week 12), had fulfilled the study protocol for the primary and secondary outcomes.

For primary and secondary outcomes, we analyzed mean differences between groups at each time point using *t* tests. All statistical analyses were performed using STATA software (version 12.0; STATA, College Station, TX), and *P* values less than .05 were considered significant.

RESULTS

Figure 1 shows the number of patients assessed for eligibility, randomly assigned, and evaluated. Of the 200 eligible patients, 10 refused to participate because they were unwilling to be assigned to the self-care alone arm (none declined because of acupuncture). Of the 190 patients enrolled and randomly assigned, 105 were allocated to the enhanced self-care group and 85 to the acupuncture plus enhanced self-care group. Stratified randomization and slow accrual might explain this difference. In the control group, three women did not start the treatment, and 14 women were lost to follow-up for the following reasons: they did not complete the assigned treatment, they did not comply with the follow-up schedule, or they could not be contacted. In the acupuncture group, one woman did not start the treatment, and one did not comply with the acupuncture sessions. At the end of treatment, 88 and 83 patients had reported the primary outcome measure in the control and acupuncture arms, respectively.

Participants' median age was 49 years. The majority had a secondary school degree and were employed. Almost all were receiving hormonal therapy for breast cancer, and nearly half were receiving gonadotropin-releasing hormone analogs in combination. Women were evenly distributed between the two arms in terms of demographic and clinical characteristics (Table 2).

The intention-to-treat analyses at the end of treatment (week 12) revealed a mean HFS of 22.7 and 11.3 in the control and acupuncture groups, respectively, with an estimated difference of −11.4 (95% CI, −16.4 to −6.3; $P < .001$; Table 3; Fig 2). The per-protocol analyses at week 12 yielded similar results; the acupuncture group reported lower HFS than the control one. The difference in mean HFS was 9.3 (95% CI, −14.2 to −4.4; $P < .001$).

To address the baseline (although nonsignificant) difference in HFS, we conducted a post hoc analysis with mean change in HFS as the primary outcome. The acupuncture group showed a greater reduction in HFS compared with the control group (−20.8 *v* −4.6; $P < .001$). There was also a statistically significant difference in HFS between the two groups at 3- and 6-month follow-up visits: −7.9 (95% CI, −13.0 to −2.7; $P = .0028$) and −8.8 (95% CI, −14.0 to −3.6; $P = .001$), respectively.

Similar results were observed for the GCS score and the MenQol domains (Table 3). The between-group differences in GCS were −6.8 (95% CI, −9.4 to −4.2), −3.7 (95% CI, −6.3 to −1.1), and −4.7 (95% CI, −7.4 to −2.0) at week 12 and at 3- and 6-month follow-up visits, respectively, with a significantly lower score for the acupuncture group ($P < .001$, $P = .0063$, and $P < .001$, respectively).

Similarly, the acupuncture group reported lower scores in MenQol vasomotor, psychosocial, and physical domains at all time points. There were no significant differences between groups in sexual domain scores. There were no differences between groups in enhanced self-care activities at any time point except for physical exercise, which was significantly more frequent in the control group than in the acupuncture group at the end of treatment ($P = .04$; Table 4).

Table 2. Baseline Sociodemographic and Clinical Characteristics of Participants by Group

Characteristic	Enhanced Self-Care Group (n = 105) No.	%	Acupuncture Plus Enhanced Self-Care Group (n = 85) No.	%
Age, years				
Median	49		50	
Range	31-65		27-63	
No. of children				
Median	1		1	
Range	0-3		0-3	
Weight, kg				
Mean	64.93		65.10	
SD	13.83		10.99	
Educational qualification				
Primary school	4	3.81	2	2.35
Secondary school	86	81.90	70	82.35
University degree	15	14.29	13	15.29
Occupational status				
Unemployed	4	3.85	3	3.53
Stay at home	16	15.38	8	9.41
Employed	84	80.77	74	87.06
At least one relevant comorbidiy	39	37.14	23	27.06
Ongoing treatment of breast cancer				
HT	38	36.19	36	42.35
HT plus GnRH	56	53.33	40	47.06
Other treatment	4	8.16	3	6.67
None	11	10.48	9	10.59
Hot flash score				
Mean	27.31		32.27	
SD	17.06		25.31	
Greene Climateric Scale score				
Mean	20.65		19.56	
SD	10.05		8.71	
Menopause Quality of Life score				
Vasomotor				
Mean	6.32		6.52	
SD	1.34		1.44	
Psychosocial				
Mean	4.3		4.15	
SD	1.77		1.75	
Physical				
Mean	3.98		3.96	
SD	1.46		1.34	
Sexual				
Mean	4.13		4.06	
SD	2.26		2.24	
Expectation of symptom control				
None	1	1.00	0	0.00
Mild improvement	33	33.00	17	20.24
Significant improvement	59	59.00	63	75.00
Complete control of symptoms	7	7.00	4	4.76
Current self-care activity				
Physical activity	71	68.27	61	72.62
Psychological support	21	20.39	19	22.35

Abbreviations: GnRH, gonadotropin-releasing hormone; HT, hormone therapy; SD, standard deviation.

Table 3. Hot Flash Score, Climacteric Syndrome, and Quality of Life Outcomes at End of Treatment (week 12) and at 3- and 6-Month Follow-Up Visits by Group

Outcome	Enhanced Self-Care Group (n = 105)		Acupuncture Plus Enhanced Self-Care Group (n = 85)		Difference Between Groups (Δ)	95% CI	*P*
	Mean	SD	Mean	SD			
Hot flash score							
Week 12	22.70	19.40	11.34	14.75	−11.36	−16.39 to −6.33	.000
3-month follow-up	21.88	18.95	14.02	16.31	−7.86	−12.99 to −2.73	.0028
6-month follow-up	21.03	20.06	12.20	15.40	−8.82	−14.04 to −3.61	.001
Greene Climacteric Scale							
Week 12	18.30	9.99	11.52	7.37	−6.78	−9.35 to −4.21	.000
3-month follow-up	17.17	9.35	13.47	8.96	−3.70	−6.34 to −1.06	.0063
6-month follow-up	17.26	8.16	12.57	8.16	−4.70	−7.35 to −2.04	< .001
Menopause Quality of Life							
Vasomotor domain							
Week 12	5.94	1.56	4.36	1.68	−1.58	−2.05 to −1.12	.000
3-month follow-up	5.61	1.65	4.33	1.65	−1.28	−1.76 to −0.81	.000
6-month follow-up	5.60	1.75	4.23	1.76	−1.38	−1.88 to −0.87	.000
Psychosocial domain							
Week 12	3.76	1.65	2.96	1.52	−0.79	−1.25 to −0.34	< .001
3-month follow-up	3.60	1.66	2.90	1.60	−0.70	−1.17 to −0.23	.0039
6-month follow-up	3.67	1.83	2.96	1.69	−0.71	−1.22 to −020	.0064
Physical domain							
Week 12	3.56	1.47	2.89	1.08	−0.67	−1.05 to −0.29	< .001
3-month follow-up	3.50	1.51	3.01	1.38	−0.49	−0.91 to −0.07	.02
6-month follow-up	3.51	1.54	3.02	1.40	−0.50	−0.92 to −0.07	.02
Sexual domain							
Week 12	3.52	2.10	3.18	2.06	−0.34	−0.94 to 0.26	.25
3-month follow-up	3.47	2.14	3.37	2.13	−0.10	−0.71 to 0.52	.75
6-month follow-up	3.70	2.22	3.15	2.06	−0.55	−1.17 to 0.07	.08

Abbreviation: SD, standard deviation.

At the end of treatment, 16% of patients in the acupuncture group were not compliant with self-care indications, whereas only 5.8% were noncompliant in the control arm. All patients in the acupuncture group were satisfied with the treatment received and trial arm assigned; in the control group, 72% and 35% were satisfied, respectively ($P < .001$). Twelve patients in the acupuncture arm experienced mild adverse events (muscle pain, headache, and one menstrual bleed). No serious adverse effects were reported.

DISCUSSION

Our study shows that women with breast cancer treated with acupuncture plus enhanced self-care for 12 weeks experienced fewer vasomotor symptoms than women who received self-care alone. Acupuncture was associated with improvements in all HRQoL outcomes except the sexual dimension, suggesting a

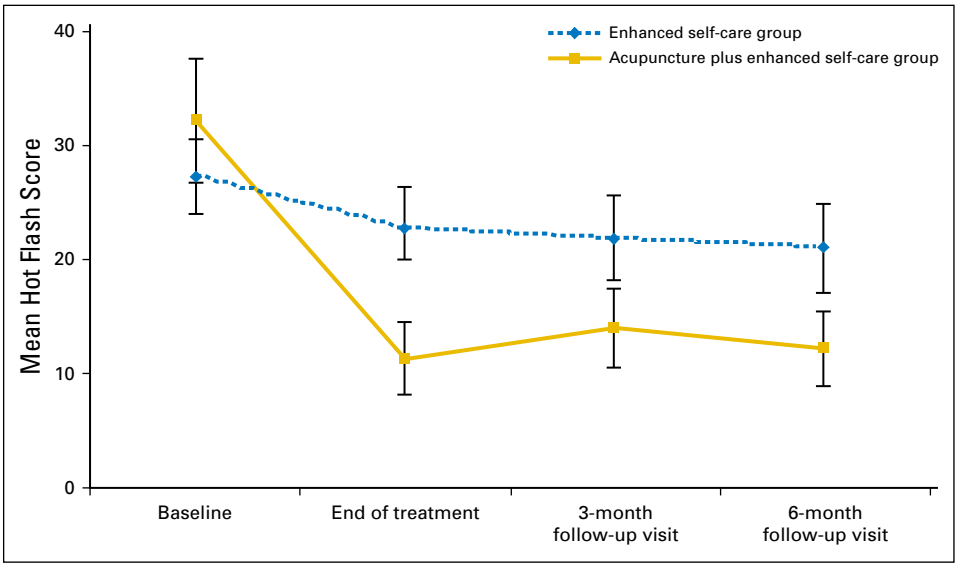

Fig 2. Change in hot flash score in the enhanced self-care group (n = 105) and the acupuncture plus enhanced self-care group (n = 85) at end of treatment (week 12) and at 3- and 6-month follow-up visits.

Table 4. Enhanced Self-Care Compliance at End of Treatment (week 12) and at 3- and 6-Month Follow-Up Visits by Group

Outcome	Enhanced Self-Care Group (n = 105)		Acupuncture plus Enhanced Self-Care Group (n = 85)		Difference Between Groups (Δ)	95% CI	*P*
	No.	%	No.	%			
Weight loss							
Week 12					0.71	−0.30 to 1.73	.17
Mean	−0.13		0.58				
SD	3.66		2.81				
3-month follow-up					−0.55	−1.87 to 0.76	.41
Mean	0.73		0.18				
SD	4.29		4.05				
6-month follow-up					0.60	−1.08 to 2.28	.48
Mean	−0.02		0.58				
SD	5.26		5.03				
Psychological support							
Week 12	23	29.49	26	33.77			.57
3-month follow-up	14	21.54	16	22.86			.85
6-month follow-up	12	22.22	17	24.29			.79
Physical activity							
Week 12	74	94.87	66	84.62			.03
3-month follow-up	65	97.01	68	94.44			.46
6-month follow-up	55	100	69	97.18			.21

Abbreviation: SD, standard deviation.

specific effect of acupuncture.[26] These effects persisted for at least 6 months after the end of treatment and were not associated with significant adverse effects during the study period.

Menopausal symptoms significantly impair women's HRQoL, particularly women with breast cancer.[27] Effective pharmacologic therapies, such as clonidine,[6] venlafaxine,[14] and gabapentin,[28] are associated with adverse effects; however, many women with breast cancer are reluctant to take drugs for hot flashes.[29-31]

Several clinical trials have suggested a role for acupuncture[12,13,15,17,32] in managing moderate to severe hot flashes in women with breast cancer. However, the superiority of acupuncture has not been demonstrated when using sham acupuncture as a control or nonoptimal acupuncture intervention in women with mixed menopausal symptoms.[18,33,34] By using enhanced self-care[7] as a control, we focused on effectiveness (rather than efficacy), which best reflects the likely clinical response in practice. We acknowledge that this design does not allow estimation of the size of the effect resulting from needling itself or from other placebo-related factors, such as patient−provider interaction.[35-37] Attempts were made to balance and control the potential impact of the latter by providing both groups with a booklet about climacteric syndrome management options and ensuring that therapists in the acupuncture group limited the communication and time spent with patients to the minimum needed for quality treatment. Notably, study participants did not differ in acupuncture response expectancy.[38]

We must also recognize the improvement in outcome variables at the end of treatment with lifestyle modification.[39] During the study, the control group was significantly more compliant in following self-care recommendations than the acupuncture group; this difference may suggest that acupuncture alone was highly effective in reducing hot flashes, as confirmed by patient satisfaction at the end of treatment. A greater compliance with self-care recommendations in this group might have further reduced vasomotor symptoms.

The study limitations should be highlighted. A departure from the predefined allocation ratio was observed at the end of the study; however, baseline patient characteristics between groups were still balanced. In addition, the dropout rate was different between groups both during and after treatment, with a higher rate in the control arm. Disappointment among control group members, as previously reported in other randomized controlled trials,[40] was the primary reason for higher dropout rates in our trial. Although most participants understood the need for a control group, other participants reported disappointment about not receiving acupuncture. We tried to minimize this by offering, at the end of the study, those participants who were part of the control group acupuncture outside of the study. Unfortunately, this was not feasible for all participating centers. Nevertheless, a secondary analysis indicated that baseline characteristics did not differ significantly between the participants who dropped out and those who did not (data not reported).

Our results should be extended with caution to clinical settings in which medications to treat hot flashes are commonly prescribed, because in our study they were not permitted. A duration of acupuncture effects was reported at 3- and 6-month follow-up visits in our trial, which supports findings from other prospective studies[41-43]; however, our results are corroborative rather than definitive because of substantial missing data in the control group.

In conclusion, AcCliMaT—a multicenter pragmatic trial with a standardized TCM acupuncture protocol—confirmed that acupuncture is an effective and safe intervention for severe

menopausal symptoms in women with breast cancer. Further research could help to identify which variables predict treatment response and the optimal duration of acupuncture. Because these findings seem both statistically and clinically meaningful, we hope the practice of treating vasomotor symptoms in women with breast cancer will change.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

REFERENCES

1. Harris PF, Remington PL, Trentham-Dietz A, et al: Prevalence and treatment of menopausal symptoms among breast cancer survivors. J Pain Symptom Manage 23:501-509, 2002
2. Mar Fan HG, Houédé-Tchen N, Chemerynsky I, et al: Menopausal symptoms in women undergoing chemotherapy-induced and natural menopause: A prospective controlled study. Ann Oncol 21:983-987, 2010
3. Savard MH, Savard J, Quesnel C, et al: The influence of breast cancer treatment on the occurrence of hot flashes. J Pain Symptom Manage 37: 687-697, 2009
4. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 288:321-333, 2002
5. Morrow PK, Mattair DN, Hortobagyi GN: Hot flashes: A review of pathophysiology and treatment modalities. Oncologist 16:1658-1664, 2011
6. Boekhout AH, Vincent AD, Dalesio OB, et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: A randomized, double-blind, placebo-controlled trial. J Clin Oncol 29:3862-3868, 2011
7. North American Menopause Society: Treatment of menopause-associated vasomotor symptoms: Position statement of the North American Menopause Society. Menopause 11:11-33, 2004
8. Daley A, Stokes-Lampard H, Thomas A, et al: Exercise for vasomotor menopausal symptoms. Cochrane Database Syst Rev 11:CD006108, 2014
9. Anderson D, Seib C, McGuire A, et al: Decreasing menopausal symptoms in women undertaking a web-based multi-modal lifestyle intervention: The Women's Wellness Program. Maturitas 81:69-75, 2015
10. Philp HA: Hot flashes: A review of the literature on alternative and complementary treatment approaches. Altern Med Rev 8:284-302, 2003
11. Vickers AJ, Cassileth BR: Unconventional therapies for cancer and cancer-related symptoms. Lancet Oncol 2:226-232, 2001
12. Borud EK, Alraek T, White A, et al: The acupuncture on hot flushes among menopausal women (ACUFLASH) study, a randomized controlled trial. Menopause 16:484-493, 2009
13. Hervik J, Mjåland O: Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. Breast Cancer Res Treat 116:311-316, 2009
14. Walker EM, Rodriguez AI, Kohn B, et al: Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: A randomized controlled trial. J Clin Oncol 28: 634-640, 2010
15. Bokmand S, Flyger H: Acupuncture relieves menopausal discomfort in breast cancer patients: A prospective, double blinded, randomized study. Breast 22:320-323, 2013
16. Lee MS, Kim KH, Choi SM, et al: Acupuncture for treating hot flashes in breast cancer patients: A systematic review. Breast Cancer Res Treat 115: 497-503, 2009
17. Dodin S, Blanchet C, Marc I, et al: Acupuncture for menopausal hot flushes. Cochrane Database Syst Rev 7:CD007410, 2013
18. Garcia MK, McQuade J, Haddad R, et al: Systematic review of acupuncture in cancer care: A synthesis of the evidence. J Clin Oncol 31:952-960, 2013
19. Lesi G, Gramenzi A, Garavini CM, et al: Acupuncture in the management of menopausal symptoms in women diagnosed with breast cancer: An uncontrolled experimental pilot study. Eur J Integr Med 4:15, 2012 (abstr OP 014)
20. Porzio G, Trapasso T, Martelli S, et al: Acupuncture in the treatment of menopause-related symptoms in women taking tamoxifen. Tumori 88: 128-130, 2002
21. Baccetti S, Da Frè M, Becorpi A, et al: Acupuncture and traditional Chinese medicine for hot flushes in menopause: A randomized trial. J Altern Complement Med 20:550-557, 2014
22. Maciocia G. Diagnoses in Chinese Medicine: A Comprehensive Guide. New York, NY, Churchill Livingstone, 2004
23. Sloan JA, Loprinzi CL, Novotny PJ, et al: Methodologic lessons learned from hot flash studies. J Clin Oncol 19:4280-4290, 2001
24. Greene JG: Constructing a standard climacteric scale. Maturitas 29:25-31, 1998
25. Hilditch JR, Lewis J, Peter A, et al: A menopause-specific quality of life questionnaire: Development and psychometric properties. Maturitas 24:161-175, 1996
26. Linde K, Niemann K, Schneider A, et al: How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. BMC Med 8:75, 2010
27. Ganz PA, Rowland JH, Desmond K, et al: Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 16:501-514, 1998
28. Loprinzi CL, Sloan J, Stearns V, et al: Newer antidepressants and gabapentin for hot flashes: An individual patient pooled analysis. J Clin Oncol 27: 2831-2837, 2009
29. Nelson HD, Vesco KK, Haney E, et al: Nonhormonal therapies for menopausal hot flashes: Systematic review and meta-analysis. JAMA 295: 2057-2071, 2006
30. Stearns V: Clinical update: New treatments for hot flushes. Lancet 369:2062-2064, 2007
31. Mao JJ, Leed R, Bowman MA, et al: Acupuncture for hot flashes: decision making by breast cancer survivors. J Am Board Fam Med 25:323-332, 2012
32. Mao JJ, Bowman MA, Xie SX, et al: Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: A randomized placebo-controlled trial. J Clin Oncol 33:3615-3620, 2015
33. Deng G, Vickers A, Yeung S, et al: Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. J Clin Oncol 25:5584-5590, 2007
34. Davies FM: The effect of acupuncture treatment on the incidence and severity of hot flushes experienced by women following treatment for breast cancer: A comparison of traditional and minimal acupuncture. Eur J Cancer 37:S438, 2001 (suppl 6)
35. White AR, Filshie J, Cummings TM: Clinical trials of acupuncture: Consensus recommendations for optimal treatment, sham controls and blinding. Complement Ther Med 9:237-245, 2001
36. Park JJ, Bang H: Methodological advances needed in analysis and interpretation of sham acupuncture validation studies. Acupunct Med 29: 168-169, 2011
37. Pirotta M, Ee C, Teede H, et al: Acupuncture for menopausal vasomotor symptoms: Study protocol for a randomised controlled trial. Trials 15:224, 2014 Erratum: Trials 16:89, 2015
38. Linde K, Witt CM, Streng A, et al: The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain 128:264-271, 2007
39. Duijts SF, van Beurden M, Oldenburg HS, et al: Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized, controlled, multicenter trial. J Clin Oncol 30:4124-4133, 2012
40. Peter M, Joy B, Jacqueline F, et al: Receiving or not receiving acupuncture in a trial: The experience of participants recovering from breast cancer treatment. Complement Ther Clin Pract 20:291-296, 2014

41. Frisk JW, Hammar ML, Ingvar M, et al: How long do the effects of acupuncture on hot flashes persist in cancer patients? Support Care Cancer 22: 1409-1415, 2014

42. Kim KH, Kang KW, Kim DI, et al: Effects of acupuncture on hot flashes in perimenopausal and postmenopausal women: A multicenter randomized clinical trial. Menopause 17:269-280, 2010

43. Borud EK, Alraek T, White A, et al: The Acupuncture on Hot Flashes Among Menopausal Women study: Observational follow-up results at 6 and 12 months. Menopause 17:262-268, 2010

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicentre Randomized Controlled Trial (AcCliMaT)

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Appendix

Enhanced Self-Care Brochure

The following advice has already proven useful and effective for women with climacteric syndrome and breast cancer diagnosis.

Diet. A diet based on vegetables and fresh fruit reduces many symptoms of estrogen deficiency. Therefore, we recommend eating plenty of vegetables such as carrots, dandelion, ginger and leeks, onions, turnips, celery, watercress, lettuce, pumpkin, tomato, broccoli, and so on. In particular, the consumption of vegetables belonging to the cabbage family, such as cabbage, turnip, radish, broccoli, cauliflower, and arugula, is a valuable aid in preventing cancer.

Attention: We have not included vegetables high in starch, like potatoes.

We recommend using seasonal vegetables; raw vegetables are most recommended in warm weather or as a side dish to animal proteins. Vegetables can also be cooked (eg, using boiling steam or pressure), except in cases of individual intolerance.

Please reduce your intake of red meat, especially sheep and cattle (no more than 300 g per week); white meat and fish are recommended.

It is useful to eat fish at least twice a week, and clinical evidence suggests a fish intake of about 35 g per day. It is better to choose small fish and fish caught offshore.

Consider increasing the consumption of fiber and antioxidant elements, because they can decrease the absorption of lipids and exogenous cholesterol.

Staple food should be cereals, especially whole grains or seed grains (eg, brown rice, millet, oats, spelled, buckwheat, wheat, and barley), because the refining process eliminates most fiber, B vitamins, and approximately 25% of the protein.

Foods such as cereals and legumes increase the sense of satiety, helping those who want to lose weight, and slow down the absorption of sugar because of their high fiber content. Those who are not used to these foods must introduce them gradually to allow time for the intestine to adapt, remembering to chew well and eat slowly.

Some legumes are available as fresh peas, green beans, broad beans, and other types of beans; others are available dried, such as lentils, adzuki beans, chickpeas, soybeans, and peanuts.

Limit your intake of salt to no more than 5 g per day, and limit intake of foods preserved in salt. Choose instead to use sea salt, and enrich food with herbs such as rosemary, sage, oregano, basil, rue, or other herbs.

Consider minimizing your sugar intake, increasing fiber and complex carbohydrates and dividing calorie intake throughout the day.

It is strongly advised to avoid fizzy drinks and sweets as well as the consumption of white sugar, fructose, and chocolate.

Moderate alcohol consumption may be associated with the appearance of insomnia and hot flashes, especially when consumed before bedtime, so it is advisable to reduce or avoid consumption of alcohol.

The use of caffeine-containing beverages can facilitate the onset of hot flashes and insomnia, especially when taken before bed; therefore, it is advisable to reduce your intake of coffee.

If you need to reduce your weight, please reduce your caloric intake to prevent significant weight gain.

Exercise. Physical activity has therapeutic value only if done methodically and with constant frequency (at least twice per week).

Please choose from among the following activities:

- Running or walking for at least half an hour a day
- Swimming
- Aerobics
- Cycling
- Gymnastics
- Tennis
- Dance
- Yoga

Psychological support. Stress has a negative impact on quality of life, especially in postmenopausal women, and can cause a variety of symptoms that worsen in some pathologic conditions.

For this reason, you must also consider the following opportunities:

- Psychological support from psychologists or psycho-oncologists, self-help groups, or leisure activities

General advice for coping with hot flashes:

- Wear cotton and other natural fibers and avoid synthetic fibers
- Dress in layers

Always remember that for the entire period of the study you are asked not to use antidepressant medications, hormone replacement therapy, homeopathic therapies for climateric syndrome, phytoestrogens, veralipride, tibolone, or similar treatments.

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