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ORIGINAL ARTICLE

Acupuncture for hot flashes in hormone receptor-positive breast cancer: A pooled analysis of individual patient data from parallel randomized trials

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Abstract

Background: Hot flashes are a common side effect of endocrine therapy (ET) that contribute to poor quality of life and decreased treatment adherence.

Methods: Patients with breast cancer wo were receiving ET and experiencing hot flashes were enrolled through three parallel, randomized trials conducted in the United States, China, and South Korea. Participants were randomized to either immediate acupuncture (IA) or delayed acupuncture control (DAC). IA participants received 20 acupuncture sessions over 10 weeks, whereas DAC participants received usual care, then crossed over to acupuncture with a reduced intensity. The primary end point was a change in score on the endocrine symptom subscale of the Functional Assessment of Cancer Therapy (FACT)-Endocrine Symptoms between baseline and week 10. Secondary end points included the hot flash score and the FACT-Breast score. A planned pooled analysis of individual patient data was performed using longitudinal mixed models.

Results: In total, 158 women with stage 0–III breast cancer were randomized (United States, $n = 78$; China, $n = 40$; South Korea, $n = 40$). At week 10, IA participants reported statistically significant improvements in the endocrine symptom subscale score (mean change ± standard error: 5.1 ± 0.9 vs. 0.2 ± 1.0; $p = .0003$), the hot flash score (−5.3 ± 0.9 vs. −1.4 ± 0.9; $p < .003$), and the FACT-Breast total score (8.0 ± 1.6 vs. −0.01 ± 1.6; $p = .0005$) compared with DAC participants. The effect of the acupuncture intervention differed by site ($p = .005$).

Conclusions: Acupuncture led to statistically and clinically meaningful improvements in hot flashes, endocrine symptoms, and breast cancer-specific quality of life in women undergoing ET for breast cancer in the United States, China, and South Korea.

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KEYWORDS
acupuncture therapy, breast neoplasms, cross-over studies, endocrine therapy, hot flashes, multicenter study, quality of life, randomized controlled trials, symptom assessment, treatment outcome

INTRODUCTION

Breast cancer is a common disease worldwide, with 2.3 million new cases and 685,000 deaths occurring each year.[1] Approximately 75% of all breast cancers express estrogen and/or progesterone receptors. Selective estrogen receptor modulators and aromatase inhibitors, agents that block estradiol from binding to its receptor or lower circulating levels of the hormone, respectively, are mainstays of treatment in hormone receptor (HR)-positive breast cancers, reducing the risk of cancer recurrence and mortality.[2,3] However, side effects of endocrine therapy (ET) adversely affect the mood and quality of life (QoL) of patients who receive ET and contribute to noncompliance and early drug discontinuation.[4,5]

Hot flashes—sudden, temporary sensations of body warmth, flushing, and sweating—are a common side effect of ET, affecting up to 80% of patients who have breast cancer.[6–9] Studies have demonstrated that hot flashes are associated with higher ET discontinuation.[10–12] Therefore, strategies have been explored to reduce hot flashes in patients with breast cancer. It has been demonstrated in randomized trials that venlafaxine and gabapentin can reduce hot flashes, but these therapies are often associated with side effects, such as dizziness, dry mouth, difficulty sleeping, somnolence, and nausea.[13]

In addition to pharmacologic approaches, several studies have evaluated the effect of acupuncture on hot flashes among women with early breast cancer who are undergoing ET but have shown mixed results.[14–18] A recent meta-analysis of six randomized controlled trials (RCTs) testing the effect of acupuncture on hot flashes reported that acupuncture induced a significant reduction in the overall hot flash score, but not hot flash frequency, compared with controls.[19] In another meta-analysis of 13 RCTs, acupuncture was found to have a durable effect on overall menopausal symptoms, but there was no reduction in hot flash frequency ($p = .29$) or severity ($p = .24$).[20] Of note, current acupuncture studies have focused on US and European populations but provided little data regarding the effect on patients with breast cancer in Asian countries.[18,21]

We conducted a coordinated, multinational project consisting of three parallel but independent RCTs that used the same eligibility criteria, acupuncture protocol, and study measures with the intent to pool individual patient-level data from the trials.[22] The objective of the project was to evaluate the effect of an acupuncture intervention on hot flashes in breast cancer survivors undergoing ET in the United States, China, and South Korea and was developed as a collaboration between the Leonard P. Zakim Center for Integrative Therapies and Healthy Living at the Dana-Farber Cancer Institute (DFCI; Boston, Massachusetts, USA) and the Comprehensive and Integrative Medicine Institute (Daegu, Republic of Korea). Here, we present the primary analysis of the effect of an acupuncture intervention on hot flashes using pooled data from the three studies.

MATERIALS AND METHODS

Study participants

Three parallel RCTs were conducted from January 2019 to February 2022 at DFCI, Daegu Catholic University Medical Center (DCUMC), and Jiangsu Provincial Hospital of Traditional Chinese Medicine (JPHTCM). Inclusion criteria for eligibility were identical across sites: (1) histologically or cytologically proven, AJCC stage 0–III, HR-positive breast cancer with any human epidermal growth factor receptor 2 (HER-2) status; (2) completion of surgery and any chemotherapy or radiation therapy; (3) current adjuvant ET treatment, with or without suppression of ovarian function, for at least 4 weeks at study entry; and (4) persistent hot flashes for at least 4 weeks and at least 14 hot flashes per week (average, two daily) in the week before screening. Exclusion criteria included: (1) a planned change in ET agents during the study period, (2) unstable cardiac disease or myocardial infarction within 6 months of study entry, (3) uncontrolled seizure disorder or history of seizures, and 4) the use of acupuncture for hot flashes within 6 months of enrollment. Institutional review boards at each institution approved each corresponding trial (United States, ClinicalTrials.gov identifier NCT03783546; China, trial ChiCTR2100045888; Korea, trial KCT0003618).

Study design

A detailed description of the study design was previously published.[22] A core study protocol was developed and used in each trial with the intent of pooling data from the three protocols. Each site used the same core acupuncture protocol, eligibility criteria, and study measures but worked independently with their local regulatory groups for approval and oversight. The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard provided a self-monitoring toolkit to support study conduct at each site.[23]

Randomization

The trials were run independently and in parallel at the three sites using separate randomization schemes that were generated by the statistician at DFCI. Study participants from each site were randomized 1:1 into the immediate acupuncture (IA) arm or the delayed

acupuncture control (DAC) arm. Within each site, randomization was based on permuted blocks and was stratified by hot flash frequency at baseline (from two to six daily vs. seven or more daily).

Study interventions

Participants in the IA arm received a 10-week, standardized acupuncture protocol of two sessions per week (20 sessions total) that included manual acupuncture and electroacupuncture, in addition to usual care. After completion of the initial 10-week period, participants in the IA arm were followed for an additional 10 weeks without acupuncture. Participants in the DAC arm received usual care without acupuncture for the first 10 weeks, followed by 10 weeks of acupuncture using the same acupuncture protocol but administered only once weekly (10 sessions total). In total, nine locally credentialed acupuncturists performed acupuncture treatment across the sites (six at the US site, two at the China site, and one at the South Korea site).

The acupuncture intervention consisted of five core acupuncture points (SP-6, LI-11, Yintang, GV-20, and Shenmen/ear) plus six optional points (LR3, ST36, K3, PC7, CV6, and Heart/ear; see Table S1). Sites were instructed to use the five core points and were given the option of including the additional points. Notably, the US and South Korea sites used all 11 points, whereas the China site omitted one core point (Shenmen/ear) and one optional point (Heart/ear) because these points are located in the ear and were more painful for patients who received acupuncture according to the techniques used in China (see Table S2).

Manual acupuncture was used at the first session followed by electroacupuncture stimulation at the Yintang and GV-20 points in the subsequent sessions. Each session lasted for 30 minutes. Acupuncturists took part in in-person and/or video-recorded training before delivering the acupuncture intervention. The study teams also submitted self-monitoring kits for regular review and quality control and participated in monthly video conference meetings during the study period to resolve trial-related issues. For details based on Standards for Reporting Interventions in Clinical Trials of Acupuncture items, see Table S3.

Outcome measures

Local language versions of the endocrine symptom subscale (ESS) of the Functional Assessment of Cancer Therapy (FACT)-Endocrine Symptoms (version 4.0) were used for the primary outcome measure. Linguistically validated Chinese and Korean versions of the ESS were provided by the FACIT Group (https://www.facit.org/, last viewed at December 20, 2023). The FACT-Endocrine Symptoms instrument has been validated in women with breast cancer receiving ET and has been recommended for use in multinational trials of ET.[24–26] The ESS contains 19 items that specifically assess endocrine symptoms, including hot flashes, night sweats, vaginal dryness, and joint pain, with scores ranging from 0 to 76. Lower scores indicate worse endocrine symptoms. Previous studies have demonstrated that a change in the ESS score greater than one half a standard deviation is clinically meaningful.[27] Secondary measures included a daily hot flash diary and the FACT-Breast (FACT-B). The daily hot flash diary is a validated and reliable method of measuring the frequency and severity of hot flashes.[28] The hot flash score (HFS) is calculated by multiplying the frequency and severity of hot flashes recorded in the daily diary. The FACT-B measures breast cancer-specific QoL and consists of the FACT-General and the FACT breast cancer subscale.[29] The FACT-General contains four subscales: physical well-being, functional well-being, emotional well-being, and social/family well-being.[30] The Trial Outcome Index score is a composite of the FACT-B physical well-being, functional well-being, and breast cancer subscales.

Statistical analysis

The primary end point was change in the total score on the ESS from baseline to week 10 compared between the two study arms. Secondary end points included changes in the weekly HFS, the response rate (defined as the proportion of patients with a reduction ≥50% in the HFS between baseline and week 10), and changes in the total and subscale scores on the FACT-B and Trial Outcome Index between baseline and week 10. Changes in primary and secondary outcomes between weeks 10 and 20 and between the two study arms were evaluated as tertiary end points. The power estimates for differences between the IA and DAC arms for primary and secondary end points were based on a longitudinal mixed model with fixed effects of intervention and stratification by country to allow for differences in patients and practice patterns. Assumptions included an unbalanced design (sample size ratios of 2:1:1 for the United States, China, and South Korea, respectively), a 5% loss of measurement at week 10, and a two-sided, type-I error of 0.1. Under the assumption of modest improvements in the DAC arm of approximately 1.0 unit in the ESS score and a standard deviation of the change no greater than 8.7, a sample size of 160 participants (80 from DFCI, 40 from DCUMC, and 40 from JPHTCM) would provide at least 84% power to detect an intervention effect difference of 3.75. Patient characteristics were summarized descriptively. Changes in outcome measures relative to baseline were summarized descriptively with analyses based on longitudinal mixed modelling. The models were adjusted for site (United States, China, Korea) and the randomization stratification according to the number of hot flashes daily (from two to six vs. seven or more) and included as main effects treatment arm and time. Standard errors allowed for clustering of patients within sites with a compound symmetry covariance structure. Standard model diagnostics were used to assess the appropriateness of model fit. Estimates of change between any two time points were based on contrasts, and multiple comparisons adjustments used the Tukey–Kramer method. For statistical analyses, SAS version 9.4 (SAS Institute Inc.) was used.

RESULTS

Recruitment and patient demographics

Patients were enrolled between January 2019 and June 2021 (Figure 1). In total, 164 patients were recruited to the three trials and provided informed consent. Among these, 158 were randomized to IA ($n = 81$) or to DAC ($n = 77$), with 78 (49.4%) enrolled at DFCI, 40 (25.3%) enrolled at DCUMC, and 40 (25.3%) enrolled at JPHTCM. At DFCI, six patients who enrolled in the trial dropped out of the study before randomization. Discontinuation after randomization was mainly because of time commitments or disruption because of coronavirus disease 2019, with 12 (15%) in the acupuncture arm and 10 (13%) in the DAC arm withdrawing before 10 weeks. Overall, 136 of 158 (86%) randomized patients completed week-10 study measures, and 121 of 158 (77%) completed week-20 measures.

Table 1 presents the demographic and clinical characteristics of participants at baseline. There were no differences in demographic or

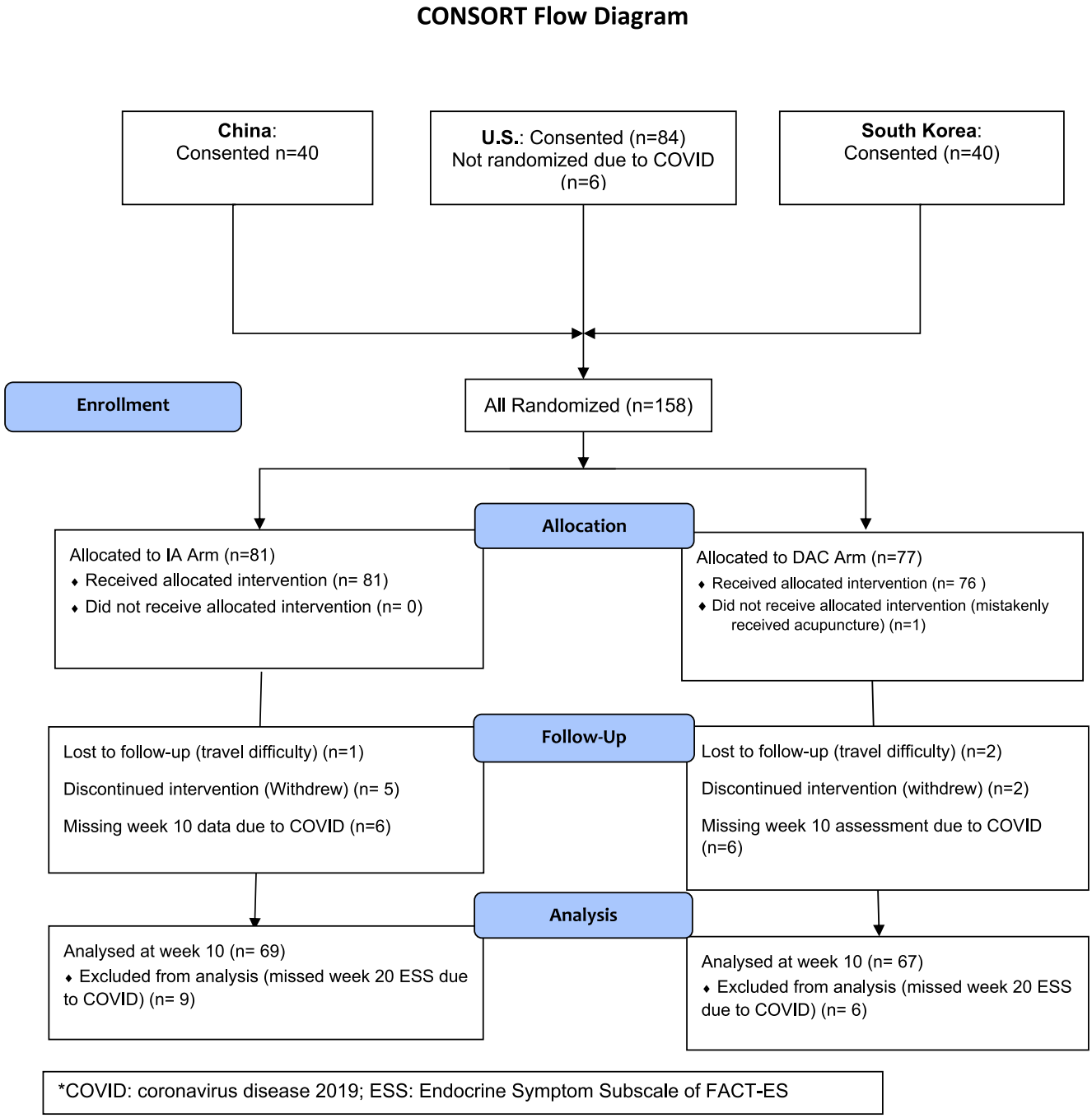

FIGURE 1 CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials; COVID, coronavirus disease; DAC, delayed acupuncture control; ESS, endocrine symptom subscale (ESS) of the Functional Assessment of Cancer Therapy-Endocrine Symptoms; IA, immediate acupuncture.

TABLE 1 Demographic and clinical characteristics of the three trials and the pooled populations.

	United States, No. (%)		South Korea, No. (%)		China, No. (%)		Pooled population, No. (%)	
	IA, *n* = 39	DAC, *n* = 39	IA, *n* = 20	DAC, *n* = 20	IA, *n* = 22	DAC, *n* = 18	IA, *n* = 81	DAC, *n* = 77
Age: Median [range], years	50 [31–72]	46 [33–66]	49.5 [39–64]	50 [38–73]	44.5 [34–65]	47 [25–59]	48 [31–72]	48 [25–73]
Sex								
Female	39 (100.0)	39 (100.0)	20 (100.0)	20 (100.0)	22 (100.0)	18 (100.0)	81 (100.0)	77 (100.0)
Race								
Asian	1 (2.6)	2 (5.1)	20 (100.0)	20 (100.0)	22 (100.0)	18 (100.0)	43 (53.1)	40 (51.9)
White	33 (84.6)	30 (76.9)	—	—	—	—	33 (40.7)	30 (39.0)
Black	3 (7.7)	3 (7.7)	—	—	—	—	3 (3.7)	3 (3.9)
Other	2 (5.1)	4 (10.3)	—	—	—	—	2 (2.5)	4 (5.2)
Tumor grade								
1	6 (15.4)	8 (20.5)	2 (10.0)	3 (15.0)	3 (13.6)	2 (11.1)	10 (13.0)	14 (17.3)
2	20 (51.3)	20 (51.3)	4 (20.0)	1 (5.0)	12 (54.5)	11 (61.1)	32 (41.6)	36 (44.4)
3	11 (28.2)	10 (25.6)	5 (25.0)	3 (15.0)	3 (13.6)	4 (22.2)	19 (24.7)	17 (21.0)
Missing	2 (5.1)	1 (2.6)	9 (45.0)	13 (65.0)	4 (18.2)	1 (5.6)	16 (20.8)	14 (17.3)
Hormone receptor status								
Positive	38 (97.4)	39 (100.0)	15 (75.0)	18 (90.0)	22 (100.0)	19 (100.0)	75 (92.6)	75 (97.4)
Missing	1 (2.6)	—	5 (25.0)	2 (10.0)	—	—	6 (7.4)	2 (2.6)
HER-2 status								
Negative	33 (84.6)	35 (89.7)	8 (40.0)	11 (55.0)	3 (13.6)	7 (38.9)	44 (54.3)	53 (68.8)
Positive	5 (12.8)	4 (10.3)	6 (30.0)	6 (30.0)	14 (63.6)	7 (38.9)	25 (30.9)	17 (22.1)
Missing/unknown	1 (2.6)	—	6 (30.0)	3 (15.0)	5 (22.7)	4 (22.2)	12 (14.8)	7 (9.1)
Use of endocrine medications								
Tamoxifen	45 (57.7)		35 (87.5)		17 (42.5)		44 (54.3)	53 (68.8)
Anastrozole	6 (7.7)		1 (2.5)		6 (15.5)		7 (8.6)	6 (7.8)
Letrozole	23 (29.5)		4 (10.0)		1 (2.5)		16 (19.8)	12 (15.6)
Exemestane	4 (5.1)		—		7 (17.5)		8 (9.9)	3 (3.9)
Goserelin	—		2 (5.0)		—		—	2 (2.6)
Lupron	19 (24.4)		2 (5.0)		—		9 (11.1)	12 (15.6)
Hot flash stratification								
Two to six daily	21 (53.8)	20 (51.3)	10 (50.0)	10 (50.0)	18 (81.8)	15 (83.3)	49 (60.5)	45 (58.4)
Seven or more daily	18 (46.2)	19 (48.7)	10 (50.0)	10 (50.0)	4 (18.2)	3 (16.7)	32 (39.5)	32 (41.6)
Hot flashes daily: Average ± SD	6.0 ± 3.6	6.9 ± 4.0	7.6 ± 6.0	7.4 ± 4.1	5.3 ± 3.4	4.5 ± 2.3	6.2 ± 4.3	6.5 ± 3.8
Hot flash score: Average ± SD	9.5 ± 6.8	11.0 ± 7.2	12.7 ± 9.0	13.7 ± 9.0	8.4 ± 7.9	6.4 ± 4.9	10.0 ± 7.8	10.6 ± 7.6
Time from diagnosis to study enrollment								
>2 years	13 (33.3)	17 (43.5)	8 (40.0)	9 (45.0)	4 (18.2)	2 (11.1)	25 (30.9)	28 (36.4)
<2 years	25 (64.0)	22 (56.4)	7 (35.0)	8 (40.0)	18 (81.8)	16 (89.0)	50 (61.7)	46 (59.8)

Abbreviations: DAC, delayed acupuncture control (with 50% reduced intensity between weeks 10 and 20); HER-2, human epidermal growth factor receptor 2; IA, immediate acupuncture; SD, standard deviation.

clinical characteristics between the two study arms. All participants were women. The median age was 48 years (range, 25–73 years). Most participants were Asian (n = 83; 53%) or White (n = 63; 40%). Ninety-five percent of recruited participants had confirmed HR-positive status, and 61.4% were negative for HER-2. Tamoxifen was the most used ET (n = 97; 61.4%), 52 participants (32.9%) were treated with an aromatase inhibitor, and 23 (15%) received ovarian suppression. The average number of hot flashes daily at baseline was 6.3. Almost two thirds of patients (n = 94; 60%) had from two to six episodes of hot flashes daily at baseline. Most patients were <2 years from diagnosis at the time of study enrollment (n = 96; 61%). Participants from China were significantly younger and were more likely to experience from two to six hot flashes daily (vs. six or more hot flashes daily) compared with participants from the other sites (82% vs. 48%–52%; p = .003 and p = .002, respectively).

Effect of acupuncture on endocrine symptoms and hot flashes

At baseline, the average± standard error (SE) ESS score was 50.3 ± 1.1 in the IA arm and 51.6 ± 1.1 in the DAC arm. The average ± HFS was 10.8 ± 0.6 in the IA arm and 11.0 ± 0.6) in the DAC arm. At week 10, participants in the IA arm reported a statistically significant improvement in ESS scores compared with the DAC arm (5.1 ± 0.9 vs. 0.2 ±1.0; p = .0003; see Table 2 and Figure 2A). The standard deviation of the difference in ESS from our data was 7.9. Using the definition based on 0.5 standard deviations would classify any change in the ESS score ≥3.95 as a clinically significant improvement.[27] Fifty-five of 136 patients achieved this benchmark (IA arm, 38 of 70 patients [54%]; DAC arm, 17 of 66 patients [26%]; Fisher exact p = .0009). In addition, the effect of the acupuncture intervention differed by site (p = .005), with the most significant benefit of acupuncture on the ESS observed in South Korea (change score = 8.5), followed by the United States (change score = 5.3), and China (change score = 1.7; Table 3).

The HFS was reduced at week 10 by an average ± SE of −5.3 ± 0.9 points from baseline in the IA arm and −1.4 ± 0.9 points in the DAC arm (p = .003). Notably, the significant difference in HFS between the IA and DAC arms had already appeared by week 5 (difference in change scores, −3.3 ± 1.3; p = .01; Table 2 and Figure 2B). Furthermore, 44 of 69 participants (64%) in the IA arm and 13 of 71 (18%) in the DAC arm reported a reduction ≥50% in the HFS (p < .0001).

Effect of acupuncture on QoL

At baseline, the total ± SE FACT-B score was 94.6 ± 2.1 in the IA arm and 97.0 ± 2.1 in the DAC arm. By week 10, the total score increased by 8.0 ± 1.6) in the IA arm and by 0.01 ± 1.6) in the DAC arm (p = .0005). Furthermore, the Trial Outcome Index score improved significantly in the IA arm compared with the DAC arm (mean ± SE difference in change score, 5.1 ± 1.6; p = .002; Table 2 and Figure 2C).

Changes during the follow-up phase

Between weeks 10 and 20, ESS scores did not change significantly in the IA arm (ESS, −0.4 ± 0.9 [p = .66]; HFS, 0.0 ± 1.0 [p = .99]). In the DAC arm that received weekly, reduced-schedule acupuncture during the same time, there were statistically significant improvements in the ESS score and the HFS relative to week 10 (ESS, 3.9 ± 1.0 [p = .0001]; HFS, −3.7 ± 1.0 [p = .0002]; Figure 2A,B).

Adverse events

There were no serious adverse events reported from the three trial sites in response to the acupuncture intervention in either the IA arm or the DAC arm.

DISCUSSION

In this multinational study, we found that a 10-week acupuncture intervention led to statistically and clinically meaningful improvements in endocrine symptoms, hot flashes, and breast cancer-specific QoL in women undergoing adjuvant ET in the United States, China, and South Korea. This was one of the first multinational studies in patients with breast cancer who were experiencing hot flashes using a common core study protocol and a pooled analysis of individual patient data from three parallel trials. Our results further suggest that the effects of acupuncture persisted for at least 10 weeks after the intervention in enrolled patients. Our exploratory analyses suggest that the reduced-intensity, once-a-week schedule produced significant reductions in hot flashes and endocrine symptoms.

Several other trials have evaluated the effect of acupuncture on hot flashes in women undergoing ET for breast cancer,[14–17] with various results. Mao et al. compared the effect of electroacupuncture versus gabapentin on hot flashes in 120 patients with breast cancer who received treatment with ET. The mean reduction in HFS was highest in the electroacupuncture group, followed by sham acupuncture, gabapentin, and placebo pills (−7.4 vs. −5.9 vs. −5.2 vs. −3.4, respectively; $p \leq .001$).[14] Lesi et al. reported a pragmatic RCT evaluating the effect of manual acupuncture on hot flashes in 190 in patients with breast cancer. In that study, the mean HFS was significantly reduced in the acupuncture arm compared with controls (mean difference, −11.4; 95% confidence interval, −16.4, −6.3; p < .001).[16] Consistent with these results, our study showed an average 49% reduction in the HFS and a 46% reduction in hot flash frequency. In addition, 64% of our participants who were randomized to IA reported a reduction 50% in the HFS compared with an 18% reduction in the DAC group. The reduction in both frequency and severity of hot flashes persisted in the IA arm up to 10 weeks after

TABLE 2 Changes in hot flashes and quality of life in patients with breast cancer between the immediate acupuncture and delayed acupuncture control groups at weeks 10 and 20 (longitudinal mixed model analysis).

Measures (score range)	Comparison	Treatment	Baseline estimate ± SE	Change ± SE	*p* within arm	IA vs. DAC, difference ± SE	*p* difference
Primary end point							
FACT-ESS (0–76)	Week 10 vs. baseline	IA	50.3 ± 1.1	5.1 ± 0.9	< .0001	4.9 ± 1.3	.0003
		DAC	51.6 ± 1.1	0.2 ± 1.0	.87		
Secondary and tertiary end points							
Daily hot flash score	Week 20 vs. week 10[b]	IA	55.4 ± 1.1	−0.4 ± 0.9	.66	−4.4 ± 1.4	.002
		DAC	51.7 ± 1.1	3.9 ± 1.0	.0001		
	Week 10 vs. baseline[a]	IA	10.8 ± 0.6	−5.3 ± 0.9	< .0001	−3.9 ± 1.3	.003
		DAC	11.0 ± 0.6	−1.4 ± 0.9	.13		
	Week 5 vs. baseline[b]	IA	6.7 ± 0.7	−4.1 ± 0.9	< .0001	−3.3 ± 1.3	.01
		DAC	10.2 ± 0.7	−0.8 ± 1.0	.41		
	Week 10 vs. week 5[b]	IA	5.5 ± 0.7	−1.3 ± 0.9	.18	−0.7 ± 1.4	.63
		DAC	9.6 ± 0.7	−0.6 ± 1.0	.53		
	Week 15 vs. week 10[b]	IA	5.5 ± 0.7	0.04 ± 1.0	.97	2.3 ± 1.4	.09
		DAC	7.3 ± 0.7	−2.3 ± 1.0	.02		
	Week 20 vs. week 15[b]	IA	5.5 ± 0.7	−0.04 ± 1.0	.97	1.4 ± 1.4	.33
		DAC	5.8 ± 0.7	−1.5 ± 1.0	.16		
	Week 20 vs. week 10[b]	IA	5.5 ± 0.7	0.0 ± 1.0	.99	3.7 ± 1.4	.008
		DAC	9.6 ± 0.7	−3.7 ± 1.0	.0002		
FACT-B total score (0–148)	Week 10 vs. baseline[a]	IA	94.6 ± 2.1	8.0 ± 1.6	< .0001	7.9 ± 2.3	.0005
		DAC	97.0 ± 2.1	0.01 ± 1.6	.99		
	Week 20 vs. week 10[b]	IA	102.6 ± 2.1	−2.9 ± 1.6	.08	−6.7 ± 2.3	.005
		DAC	97.0 ± 2.2	3.8 ± 1.7	.03		
FACT-B TOI (0–96)	Week 10 vs. baseline[a]	IA	58.2 ± 1.4	5.9 ± 1.1	< .0001	5.1 ± 1.6	.002
		DAC	60.1 ± 1.5	0.8 ± 1.2	.51		
	Week 20 vs. week 10[b]	IA	64.1 ± 1.5	−1.6 ± 1.1	.17	−4.8 ± 1.7	.005
		DAC	60.8 ± 1.5	3.2 ± 1.2	.009		

Note: Higher scores of on the FACT-ES and the FACT-B indicate greater improvement. Higher hot flash scores indicate worse hot flashes. The data were analyzed using longitudinal mixed models for data covering the 20-week intervention period (1) to compare changes between two time points within a treatment arm to assess whether there were statistically significant increases or decreases, and (2) to compare the changes between treatment arms. The models are adjusted for site (United States, China, Korea) and the randomization stratification of the number of hot flashes daily (two to six or seven and greater) and include as main effects treatment arm, time, and the interaction of treatment and time. Standard errors allow for clustering of patients within site with a compound symmetry covariance structure. Estimates of change between any two time points are based on contrasts with *p* values determined from *t*-tests. Multiple comparisons adjustments used the Tukey–Kramer method. The significant level is set at $p \leq .05$.

Abbreviations: DAC, delayed acupuncture control (with a 50% reduced acupuncture intensity from week 10 to week 20); FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-ESS, Functional Assessment of Cancer Therapy endocrine symptom subscale; IA, immediate acupuncture; SE, standard error; TOI, Trial Outcome Index.

[a]Indicates a predefined secondary end point.

[b]Indicates a predefined tertiary end point.

the end of acupuncture. In addition, persistent benefits were seen across endocrine symptoms and QoL, providing additional information about the durable benefit of acupuncture in reducing hot flashes and endocrine symptoms in this population.

We also observed that the effect of the acupuncture intervention on endocrine symptoms differed by site, with patients enrolled in South Korea deriving the most benefit from the intervention, whereas patients enrolled in China derived the least benefit. Given the design of this project, it is difficult to determine whether these differences reflect a differential response to acupuncture versus differences in populations, given that participants from China reported fewer hot flashes at baseline. In

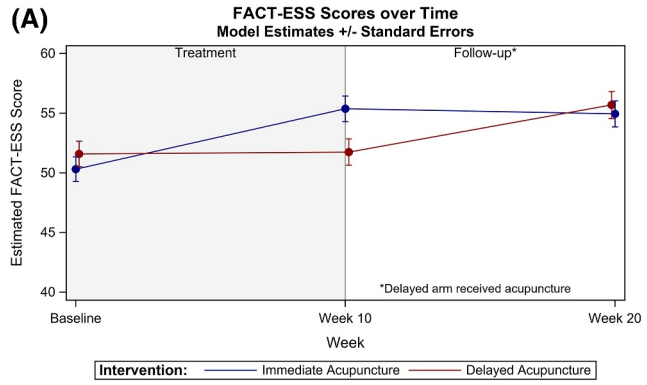

FIGURE 2 Estimated (A) Endocrine symptom subscale scores on the FACT-ES, (B) hot flash scores, and (C) FACT-B scores over time between the immediate acupuncture arm and the delayed acupuncture (control) arm from week 0 to week 10 and week 20 (the control arm received acupuncture between weeks 10 and 20 with 50% reduced intensity). FACT-B indicates Functional Assessment of Cancer Therapy-Breast, FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Symptoms.

addition, the site in China omitted two of the acupuncture points, including one core point, that were used in the United States and South Korea. Although these omissions may affect the intended therapeutic effect,[31] the extent of these omissions requires further study.

TABLE 3 Comparison of changes on the Functional Assessment of Cancer Therapy endocrine symptom subscale between baseline and week 10 between study sites.

Assessment	Estimate (adjusted 95% CI)	*p*
China vs. United States	−2.5 (−6.1 to 1.2)	.005
China vs. South Korea	−5.8 (−9.9 to −1.6)	
United States vs. South Korea	−3.3 (−6.9 to 0.4)	

Note: Changes between baseline and 10 weeks (post-pre) for outcomes were compared between treatments using linear models that were adjusted for site and number of hot flashes (stratification). In the models, the change score was a function of treatment, site, and stratification. Comparisons between treatments, or pairwise by site, were summarized with 95% confidence intervals. For pairwise site comparisons, the confidence intervals were adjusted using the Tukey–Kramer method to allow for multiple comparisons.

Abbreviation: CI, confidence interval.

Our studies have several limitations. First, we randomized patients to immediate versus delayed acupuncture rather than using an active control condition. This raises the possibility that the placebo effect could have contributed to the effect of the immediate acupuncture intervention on hot flashes. In particular, our studies did not apply sham acupuncture as a control condition. Recent systematic reviews suggest that sham acupuncture as a control method should be reconsidered[32] because current sham acupuncture devices used in acupuncture trials are not adequate inert controls.[33] Sham acupuncture techniques have also been shown to produce effects on biomarkers similar to those produced by real acupuncture techniques.[32] Furthermore, the acceptance of sham acupuncture within Asian cultures is not uniform; many acupuncture practitioners in Asian nations are opposed to the concept of using *fake needles* on their patients, which could potentially foster a sense of mistrust between health care providers and their patients.[34–37] Our population also lacked certain racial groups, notably, Black and Hispanic populations. Black patients with breast cancer report more hot flashes and other endocrine symptoms than their White counterparts.[38] Little is known about how these populations respond to acupuncture to treat hot flashes. Further studies are needed to expand acupuncture interventions in these populations. Finally, this project consisted of three independent trials rather than a single RCT. There were differences in the implementation of the protocol intervention across sites, such as points, needle sizes, and devices selections, which may partially explain our observed site differences.

In conclusion, in a pooled analysis of three clinical trials testing the effect of acupuncture on hot flashes in women with breast cancer, we found that a 10-week acupuncture intervention significantly reduced endocrine symptoms and hot flashes and improved breast cancer-specific QoL in patients undergoing ET in the United States, China, and South Korea. Additional trials are needed to evaluate the effect of acupuncture on hot flashes in more racially and ethnically diverse populations of patients with breast cancer and to determine whether improvements in hot flashes translate into better medication adherence, increasing the likelihood that

acupuncture not only could help patients feel better during ET but also may help to improve cancer-related outcomes in women with breast cancer.

AUTHOR CONTRIBUTIONS

Weidong Lu: Conceptualization, methodology, investigation, writing–original draft, writing–review and editing, and supervision. **Anita Giobbie-Hurder**: Methodology, formal analysis, writing–review and editing, software, and investigation. **Anna Tanasijevic**: Data curation, project administration, and writing–review and editing. **Sylvia Baedorf Kassis**: Methodology, project administration, writing–review and editing, and investigation. **Sung Hwan Park**: Investigation, resources, supervision, and funding acquisition. **Young Ju Jeong**: Funding acquisition, data curation, investigation, supervision, writing–review and editing, and resources. **Im Hee Shin**: Funding acquisition, data curation, resources, and writing–review and editing. **Chang Yao**: Funding acquisition, investigation, writing–review and editing, supervision, and resources. **Hyun Jung Jung**: Investigation and writing–review and editing. **Zhiyuan Zhu**: Data curation and investigation. **Chao Bao**: Investigation. **Ting Bao**: Writing–review and editing. **EunMee Yang**: Data curation and investigation. **Barbara E. Bierer**: Methodology, funding acquisition, supervision, investigation, writing–review and editing, and resources. **Jennifer A. Ligibel**: Conceptualization, funding acquisition, investigation, writing–review and editing, methodology, supervision, and resources.

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CONFLICT OF INTEREST STATEMENT

Ting Bao reports consulting fees from EISAI INC. and Nestle outside the submitted work. The remaining authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request to the primary author. In addition, summary results of this trial are available on ClinicalTrials.gov under the identifier NCT03783546. Inquiries regarding data availability can be directed to the corresponding author at weidong_lu@dfci.harvard.edu.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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