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TITLE: Acupuncture for Hot Flashes in Hormone Receptor-Positive Breast Cancer, a Randomized Controlled Trial

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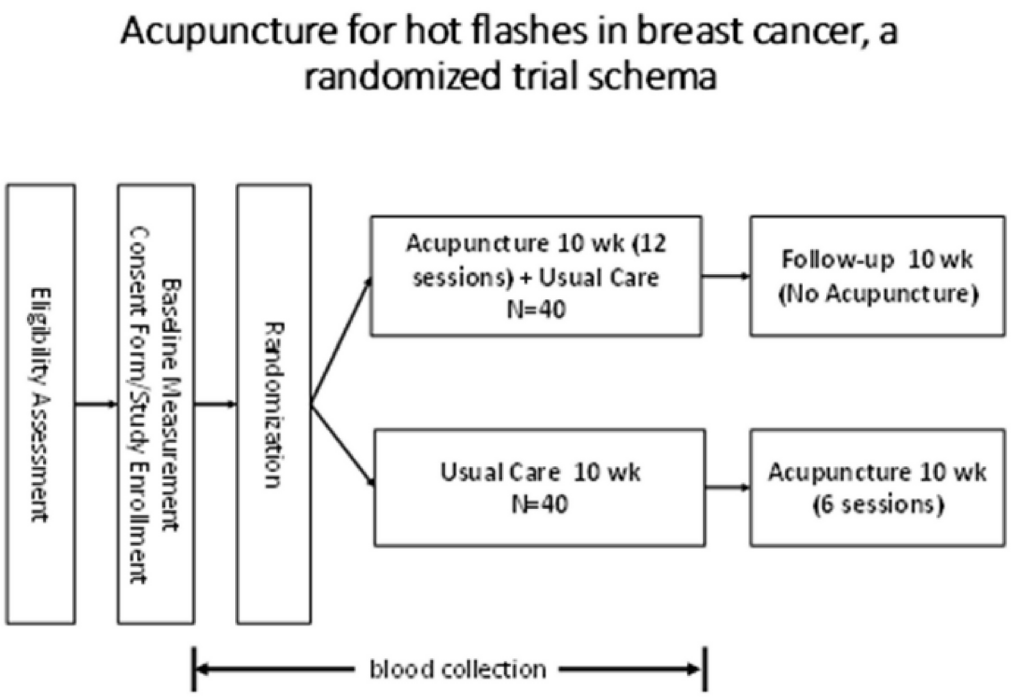
SCHEMA


Acupuncture for hot flashes in breast cancer, a randomized trial schema
Eligibility Assessment
Baseline Measurement Consent Form/Study Enrollment
Randomization
Acupuncture 10 wk (12 sessions) + Usual Care N=40
Follow-up 10 wk (No Acupuncture)
Usual Care 10 wk N=40
Acupuncture 10 wk (6 sessions)
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1. ABSTRACT

Hot flashes are common side effects in breast cancer patients that affect mood, sleep and quality of life. Hot flashes vary by race and ethnicity, endocrine therapies, proinflammatory cytokines, and polymorphisms in genes. Previous studies found significant racial and ethnic differences among Caucasian, Asian and African American women in physiology and clinical menopausal symptoms. Preliminary evidence suggests that acupuncture may reduce hot flashes in breast cancer patients undergoing adjuvant endocrine therapy, although results have varied and sample sizes of these trials have generally been small. In addition, the biological mechanisms underlying the impact of acupuncture on hot flashes is largely unknown.

This project is a randomized controlled study of acupuncture for hormone receptor-positive breast cancer patients with persistent hot flashes. This study will assess the effect of acupuncture therapy versus usual care on hot flashes, health-related quality of life (QOL), sleep quality, and symptom burden in breast cancer patients. The effect of a high dose acupuncture versus a low dose acupuncture will also be assessed. Additional outcomes will include profiling inflammatory biomarkers and evaluating changes from the acupuncture intervention.

This study plans to enroll 85study subjects with stage I-III, hormone receptor-positive breast cancer who are undergoing adjuvant endocrine therapy and experiencing persistent hot flashes. Participants will be randomized to an immediate acupuncture group or to a delayed acupuncture control group. Participants in the immediate acupuncture arm will receive a standardized acupuncture protocol, 20 sessions over a 10 weeks period, while the participants in the control arm will receive usual care for 10 weeks. After the 10 week intervention or control period, participants in the immediate acupuncture arm will cross over to receive usual care as a follow-up for additional 10 weeks, while the participants in the control arm will receive 10 sessions of acupuncture over the next 10 weeks.

Patient-reported outcomes will include the Daily Hot Flash Diary (DHFD), Functional Assessment of Cancer Therapy- Breast Cancer (FACT-B), the Endocrine Subscale (FACT-ES), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and a sleep diary. In addition, objective movements from Actigraphy and peripheral venous blood samples will be collected. Safety data will be measured using NCI-CTCAE v.4.023. Measurements and questionnaires will be collected at three time points during the study period: baseline, week 10, and week 20. Two additional collections of the Hot Flash Diary will be made in weeks 5 and 15 for a total of 5-time points for that assessment. Blood samples will be collected at baseline and week 10.

Data collected from this study will provide important information to evaluate the effectiveness of acupuncture in reducing hot flashes and related symptoms in breast cancer patients, and shed light on the potential biomedical mechanisms of acupuncture.

2. BACKGROUND AND RATIONALE

Acupuncture has been practiced in Asia and other parts of world for thousands of years. Experimental and clinical evidence over the past forty years suggest that acupuncture has beneficial effects in a number of conditions relevant to cancer populations, including chronic pain, anxiety and nausea.[1, 2] In the past 15 years, emerging clinical evidence, largely from randomized clinical trials, suggests that acupuncture be recommended for symptom relief during cancer treatment.[2-5] Given these data, The National Comprehensive Cancer Network (NCCN), an alliance of the nation's leading cancer centers, has recommended acupuncture in its guidelines for the following conditions: adult cancer pain, chemotherapy-induced nausea and vomiting (CINV), cancer-related fatigue, and palliative care.[6]

2.1 Hot flashes in breast cancer patients

Breast cancer is the most common cancer diagnosed among women in the United States. In 2012, there were 1.7 million women diagnosed with the disease worldwide. According to the American Cancer Society, approximately 252,710 new cases of invasive breast cancer are expected among women in the United States in 2017.[7] In addition, there are more than 2.8 million breast cancer survivors in the United States. Estrogen receptor-positive (ER-positive) breast cancer is the most common subtype of breast cancer, accounting for 70% of breast cancers diagnosed each year. Hormonal therapies, agents that reduce systemic estrogen levels (aromatase inhibitors) or block circulating estrogen from binding to receptive proteins in breast cancer cells (tamoxifen), are the mainstay of treatment for this type of breast cancer. Although these treatments have been demonstrated to reduce the risk of breast cancer recurrence and mortality by 30-50%, they also induce symptoms to endocrine deprivation, including hot flashes, vaginal dryness, and joint pains.

Hot flashes are a sensation of sudden, temporary onset of body warmth, flushing, and sweating. Hot flashes are common side effects of breast cancer treatments and can affect mood and quality of life.[8] Hot flashes also often lead to poor sleep quality in breast cancer patients. Poor sleep is correlated with worse quality of life, and some preliminary studies have suggested a link between sleep quality and disease outcomes.[9, 10] It is estimated that the prevalence of hot flashes ranges from 51% to 81% among breast cancer patients.[11] Tamoxifen therapy is associated with hot flashes in over 50% of women and the incidence of hot flashes after treatment with aromatase inhibitors has been reported to be 34 to 58%.[12-14] The prevalence of hot flashes may be even greater in women who undergo menopause as a result of chemotherapy or ovarian suppression, which is increasingly used in combination with tamoxifen and aromatase inhibitors in young women with breast cancer. Hot flashes vary by race and ethnicity, endocrine therapies, proinflammatory cytokines, and polymorphisms in genes. Previous studies found significant racial and ethnic differences among Caucasian, Asian and African American women in physiology and clinical symptoms.[15]

Some evidence suggests that hot flashes may be more persistent and less amenable to treatment in patients receiving hormonal therapy for breast cancer. Hot flashes and other menopausal

symptoms can contribute to discontinuation and non-adherence to hormonal therapy, which may impact long-term prognosis in women with early breast cancer. A number of strategies have been examined to reduce hot flashes in breast cancer patients undergoing hormonal therapy, such as antidepressants (e.g. venlafaxine) and anticonvulsants (e.g. gabapentin). These drugs can reduce hot flash frequency and severity by up to 50%; however, these therapies are often associated with side effects such as dizziness, dry mouth, trouble sleeping, somnolence and nausea. Furthermore, for many patients, there is a stigma attached with antidepressant use.[16]

2.1.1. Symptom Burden in Breast Cancer

In addition to hot flashes and sleep quality, many breast cancer patients also reported other concurrent clusters of symptoms that may or may not be directly caused by hormonal therapies. Symptom burden is the sum of the severity and impact of symptoms reported by patients with a given disease or treatment[17]. Symptoms can be caused by the disease itself as well cancer treatment. Multiple symptoms are additive and can significantly affect functions and quality of life for cancer patients. It is well recognized that breast cancer patients experience a significant number of symptoms during and after chemotherapy, including pain, fatigue, depression and anxiety. [18, 19] [20, 21]

2.2 Acupuncture clinical trials for hot flashes

A number of trials have evaluated the impact of acupuncture on hot flashes in women undergoing treatment for breast cancer.[3, 22-24] There are no other studies which have offered acupuncture for the treatment of hot flashes for women who have had breast cancer although there have been other active studies about hot flashes.

Two well-designed trials suggest that acupuncture maybe as effective as non-hormonal pharmacologic therapies for hot flashes.[3, 25] One trial compared electroacupuncture (EA) versus gabapentin (GP) in reduction of hot flashes scores in breast cancer patients (n=120).[3] Participants were randomly assigned to receive 8 weeks of EA or GP once per day with validated placebo controls (sham acupuncture (SA) or placebo pills (PP)). The primary endpoint was change in the hot flash composite score (HFCS) between SA and PP at week 8. At week 8, among all treatment groups, the mean reduction in HFCS was greatest in the EA group, followed by sham acupuncture, gabapentin, and placebo pill (-7.4 v -5.9 v -5.2 v -3.4; P = < 0.001). The authors concluded that EA may be more effective than GP, with fewer adverse effects.[3] In another RCT study, investigators randomly assigned 50 breast cancer survivors with hot flashes to receive 12 weeks of acupuncture (n = 25) or venlafaxine (n = 25) treatment.[25] The study found that both groups exhibited significant decreases in hot flashes, depressive symptoms, and other quality-of-life symptoms. These changes were similar in both groups, suggesting that acupuncture was as effective as venlafaxine.

However, systematic reviews and meta-analysis that have evaluated the existing literature of acupuncture for hot flashes have concluded that the existing studies have yet to provide convincing evidence to suggest that acupuncture was an effective treatment of hot flashes in patients with breast cancer, although acupuncture did appear to have a beneficial effect more

broadly on menopause-related quality of life in breast cancer patients.[26-29] A systematic review and meta-analysis published in 2017 identified 13 unique RCTs (n=844), in which 7 studies compared acupuncture with sham acupuncture and 4 studies compared acupuncture with therapy by hormone or other medications.[28] The sample size ranged from 31 to 120, and the average age of enrolled subjects ranged from 50 to 61 years-old. Significant between-study heterogeneity was found in the effects of acupuncture on the frequency of hot flashes (times/day) (I^2 = 67%), the severity of hot flashes (visual analog scale) (I^2 = 93%) and menopausal symptoms (menopause symptom scales) (I^2 = 76%). The authors reported that no significant reduction in the frequency of hot flashes was observed in subjects treated with acupuncture as compared with control subjects (n=124 in 4 trials) (-1.01, 95% CI:-3.1, 1.08, P = 0.34). Furthermore, acupuncture did not significantly reduce the severity of hot flashes (n=140 in 3 trials, (mean difference= -4.35, 95% CI:-13.10, 4.39, P = 0.33). However, in 6 trials (n=207), the authors found that acupuncture significantly reduced general symptoms of menopause as measured by menopause symptom scales (Mean difference = -3.28, 95% CI:-5.75, -0.80, P = 0.009).[28] Another systematic review published in 2015 found eight acupuncture studies involved women with breast cancer. All studies showed significant within-group improvement from the baseline for true acupuncture. Between-group (true acupuncture vs sham acupuncture) effect size (ES) estimates for daytime and nighttime hot flashes ranged from 0.04 to 0.9. The authors concluded that the current level of evidence is insufficient to either support or refute the benefits of acupuncture for the management of hot flashes in cancer patients.[26] More studies are thus needed to evaluate the impact of acupuncture on hot flashes in women with breast cancer being treated with hormonal therapy.

2.3 Mechanisms of acupuncture for hot flashes

The mechanisms through which acupuncture could alleviate hot flashes and other menopausal symptoms remain largely unknown. No significant increase of estrogen, follicle-stimulating hormone (FSH) and estradiol levels was found in two separated clinical trials, in which ER-positive breast cancer patients were treated with acupuncture for hot flashes.[30, 31] It has been suggested that acupuncture may regulate cytokines and the autonomic nervous system. It has been acknowledged that an insufficient number of acupuncture studies have examined biomarkers or cytokines. Many experts in this field have called for more work that focuses on the underlying molecular mechanisms of acupuncture in future trials. [28]

Proinflammatory cytokines have been linked with not only the development of breast cancer but also quality of life of women with breast cancer. Evidence suggests that the secretion of proinflammatory cytokines could modulate immune activity and accelerates the development of distressing symptoms in women with breast cancer. Increased levels of Interleukin-1 (IL-1) and Interleukin-6 (IL-6) are associated with pain and sleep disturbances in breast cancer survivors;[32] The interleukin-1 receptor antagonist (IL-1RA) is also linked to post-treatment fatigue in breast cancer survivors.[33, 34] Other increased inflammatory biomarkers have been found in women who are taking aromatase inhibitors and are experiencing arthralgia, fatigue, and insomnia. These inflammatory biomarkers include monocyte chemoattractant protein-1 (MCP-1), Eotaxin, C-reactive protein (CRP) and vitamin D-binding protein (VDBP). These findings suggest a possible shared inflammatory mechanism underlying these common symptoms.[35]

It has been suggested that hot flashes among breast cancer patients might be potentially influenced by serum interleukin-8 (IL-8), macrophage inflammatory protein-1-β (MIP-1β), and IL-6.[36, 37] Two studies reported that plasma IL-8, tumor necrosis factor alpha (TNF-α) are significantly higher in women with hot flashes compared to women who do not experience hot flashes. One study reported that hot flash intensity was significantly and positively associated with elevated plasma levels of IL-8 and TNF-α in the homogeneous healthy postmenopausal population that had undetectably low estradiol levels (n=202).[37] Another study found positive associations of serum concentrations of IL-8, MIP-1β, and IL-6 with degree of hot flashes not only in premenopausal, perimenopausal, and postmenopausal women but also in women who underwent bilateral oophorectomy (n=129).[36] These studies suggest that hot flashes have a linkage to increased IL-8 levels potentially in part by mediating activation of TNF-α-induced pathways. Given that these pro-inflammatory cytokines are important mediators of two critical cellular signaling pathways, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway[38, 39], investigating and profiling of STAT family and NF-κB in our current study will help our understanding of the potential linkage between systematic inflammation and hot flashes, as well as other cytokine-driven symptoms experienced in breast cancer patients, including joint pain, fatigue and insomnia.

Many acupuncture studies suggest that acupuncture may modulate the autonomic nervous system and up-regulate the parasympathetic system.[40] It is widely acknowledged that acupuncture can

stimulate the secretion of endorphins, alter autonomic nerve function, and affect many neurotransmitters and circulating cytokines.[40] A statistically significant reduction of Interleukin-17 (IL-17) from baseline has been reported in an acupuncture trial for musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors. [41] IL-17 is a proinflammatory cytokine mainly produced by T cells. It has been shown that the anti-inflammatory effects of acupuncture are mediated by downregulation of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-10.[42-44] In addition, an animal study also suggest that acupuncture inhibits JAK/STAT pathway.[45] Thus, we hypothesize that acupuncture may be a potentially effective therapy for hot flashes in breast cancer patients via downregulating proinflammatory cytokines and related transcription factors, such as IL-8, TNF-α, IL-6, STAT1, STAT3 and NF-κB.

Significance:

Seeking a therapy that provides clinical benefit to reduce hot flashes with minimum side effects for breast cancer patients undergoing adjuvant hormonal therapy is urgently needed. Ideally, this therapy would not only address hot flashes alone but also would simultaneously reduce the totality of symptom burden such as insomnia, fatigue, pain, depression and anxiety.

In our proposed trial, we are primarily interested in the generalizability of acupuncture effectiveness as a nonpharmaceutical therapy for reducing hot flashes in breast cancer patients in a setting of real clinical practice. Our main hypothesis of the study is that acupuncture would provide additional clinical benefits in the reduction of hot flashes in breast cancer patients who are receiving usual care while undergoing adjuvant endocrine therapy than patients who are receiving usual care without acupuncture. Our current study would potentially provide needed evidence to support the use of acupuncture for reducing hot flashes, improving quality of life and minimizing symptom burden for breast cancer patients.

3. OBJECTIVES

Primary Objective:

To test the impact of acupuncture (versus wait list control) on the frequency and severity of hot flashes, as measured through hot flash diaries, in hormone receptor-positive breast cancer patients undergoing adjuvant hormonal therapy.

Secondary objectives:

1. To test the impact of acupuncture (versus wait list control) on quality of life (FACT-G), breast cancer symptoms (FACT-B), and menopausal symptoms (FACT-ES) in hormone receptor positive breast cancer patients undergoing adjuvant endocrine therapy.

2. To test the impact of acupuncture (versus wait list control) on sleep quality and duration (as measured by Pittsburgh Sleep Quality Index (PSQI) and Actigraphy) and patients' perception

of their sleep quality (as measured by the sleep diary and Insomnia Severity Index) in hormone receptor-positive breast cancer patients undergoing adjuvant hormonal therapy and symptom burden.

3. To explore the effects of a high dose (20 sessions) versus a low dose (10 sessions) of the same acupuncture protocol on the frequency and severity of hot flashes in hormone receptor-positive breast cancer patients undergoing adjuvant hormonal therapy.

4. To evaluate the impact of acupuncture on expression of inflammatory biomarkers, such as NF-κB, STAT-1 and STAT-3, and associated cytokines IL-8, TNF-alpha and IL-6, and T-cells.

4. ELIGIBILITY

4.1 Inclusion Criteria:

1. History of histologically or cytologically proven Stage I-III breast cancer with estrogen receptor positive with HER-2 positive or negative tumor; Stage 0 or DCIS is allowable;
2. Premenopausal or postmenopausal status;
3. Completed all primary chemotherapy and surgery;
4. Currently undergoing adjuvant hormonal therapy (e.g. Tamoxifen and/or Aromatase inhibitors) with or without ovarian function suppression for at least 4 weeks at study entry; the use of Trastuzumab after adjuvant chemotherapy is allowed;
5. Reported persistent hot flashes for at least 4 weeks AND more than 14 episodes of hot flashes per week (2 hot flashes per day) during the week prior to the study entry;
6. Age ≥ 18 years;
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
8. Signed informed consent.

4.2 Exclusion Criteria:

1. Undergoing chemotherapy or planned surgery, chemotherapy, change doses and regimen of hormonal therapy during the study period;
2. Unstable cardiac disease or myocardial infarction within 6 months prior to study entry;
3. Uncontrolled seizure disorder or history of seizure;
4. Active clinically significant uncontrolled infection;
5. Use of acupuncture for hot flashes within 6 months prior to the study entry;
6. Uncontrolled major psychiatric disorders, such as major depression or psychosis;
7. Newly starting pharmacologic treatment of hot flashes such as selective serotonin reuptake inhibitors (SSRIs) and/or anti-convulsant for less than 4 weeks prior to study entry. Participants may continue with medications or therapies for the treatment of hot-flashes while participating in the study if the medication has been taking for more than 4 weeks prior to study entry AND the dose of the medication is going to be kept consistently during the study.

4.3 Inclusion of Women, Minorities and Other Underrepresented Populations

This protocol will be open to women and minorities. Women comprise approximately 98% of the breast cancer patients at Dana-Farber Cancer Institute.

Minorities represent 10-20% of the breast cancer patients at Dana-Farber. Previous trials have demonstrated that 7-25% of patients enrolled on clinical trials are minorities.

5. STUDY DESIGN AND PROTOCOL OVERVIEW

This is a randomized controlled trial that evaluates the impact of acupuncture versus usual care on hot flashes among breast cancer survivors who are undergoing adjuvant endocrine therapy and experiencing hot flashes. The usual care in the current study is defined as the current standard of care with non-hormonal pharmacotherapy of western medicine.[46]

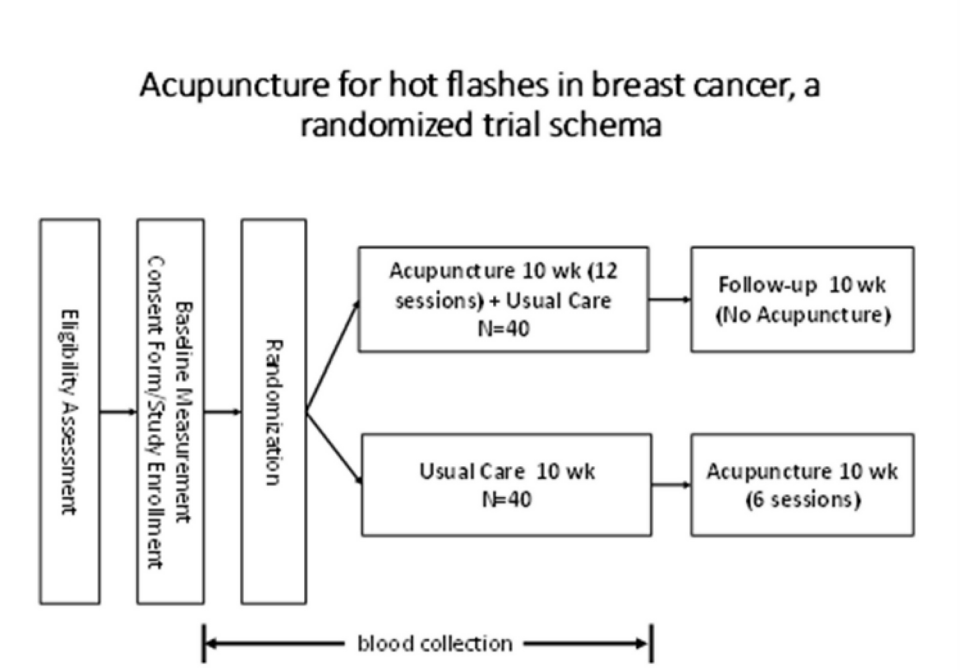
Female breast cancer patients (n=85 enrolled; 80 will be randomized) who have completed standard surgery, chemotherapy and currently undergoing adjuvant endocrine therapy, with or without ovarian function suppression, and/or anti-HER2 therapy, with a frequency of hot flashes greater than 14 episodes per week will be recruited into the study.

Study participants will be randomized into the intervention arm (the immediate acupuncture arm, n=40) or into the control arm (the delayed acupuncture arm, n=40). The study participants in the intervention arm will receive a standardized acupuncture protocol for a 10-week period (20 sessions: twice a week for 10 weeks); the study participants in the control arm will receive standard usual care without acupuncture for 10 weeks. After the completion of the 10 weeks main study period, participants in the immediate acupuncture arm will cross over to the usual care as a follow-up without acupuncture for additional 10 weeks, and participants in the control arm will cross over to receive the same acupuncture protocol for 10 weeks (10 sessions: once a week for 10 weeks) before exiting the study (Figure 1).

Measurements with questionnaires will be collected at baseline (before the treatment), and at weeks 10 and 20 after enrollment. The sleep diary will be collected at three time points: baseline, week 10, and week 20. The Hot Flash Diary will also be collected at week 5 and week 15 for a total of five time points for this measurement, so assess rate of change in hot flashes. Blood samples will also be collected at baseline week 10.

The primary endpoint will be the change in mean weekly hot flash score from baseline to week 10 between the two arms. The secondary endpoints will include changes from baseline in mean weekly hot flash score at week 20; and the mean total scores and subscores of Functional Assessment of Cancer Therapy- Breast Cancer (FACT-B), the Endocrine Subscale (FACT-ES); and the Pittsburgh Sleep Quality Index (PSQI) at week 10, and week 20 between two arms; changes in mean weekly hot flash score in the high dose (immediate) acupuncture arm and the low dose (control) acupuncture will also be compared. Other secondary endpoints include changes in Insomnia Severity Index (ISI) score as well as changes in sleep efficiency, onset latency, number and duration of awakenings, and number of nighttime hot flashes interfering with sleep, as assessed by the sleep diary, from baseline to week 10 and week 20. Tertiary endpoints will include assessment changes in NF-κB, STAT-1 and STAT-3, and associated cytokines including IL-8, TNF-α, IL-6, and T-cells in the two study arms. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for safety reporting.

Figure 1. Study schema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Acupuncture 10 wk (12 sessions) + Usual Care N=40
Follow-up 10 wk (No Acupuncture)
Usual Care 10 wk N=40
Acupuncture 10 wk (6 sessions)
blood collection

6. SUBJECT RECRUITMENT AND ENROLLMENT

Study participants will be recruited from the patient populations of the Breast Oncology Center at the Dana-Farber Cancer Institute.

We will utilize multiple active recruitment techniques to maximize participation and generalizability. We will use the following strategies to identify potential participants:

- Review of clinic schedules and patient lists for medical oncologists at Dana-Farber Cancer Institute to identify patients with Stage I-III breast cancer who are undergoing adjuvant endocrine therapy. HIPAA waivers will be obtained from the DF/HCC IRB to review these patient lists.
- Advertisements in patient areas (see appendix IX. for the brochure of study)
- Advertisement of the study to DFCI patients that are on relevant listservs (e.g., DFCI's Young and Strong newsletter) (see Appendix X).
- Advertisement of study via the "Rally with Partners" newsletter. Rally with Partners is an online platform that shares research opportunities with members of its listserv (see Appendix XI).

For potential participants identified through patient lists, we will contact providers (medical oncologists) and request permission to contact their patients. Providers will be asked to indicate any patients who should not be approached regarding participation in this study. Once potential participants are identified, they will be contacted during a clinic visit or through mailings. For patients with upcoming clinic visits, the research coordinator will approach potential patients in clinic. For patients without an upcoming clinic visit, invitations letters will be mailed with a reply card to indicate interest and an opt-out card (see Appendix VIII for recruitment letters that will be send to potential participants). For patients who are self-identified through advertisements in clinic or respond to advertisements in newsletters/listservs, we will obtain permission from a treating physician before speaking to patients about participation in the study.

Interested subjects identified through these recruitment strategies will be screened by study staff either in person or by phone initially. A screen form based on the Daily Hot Flash Diary will be used to document the frequency and severity of hot flashes, and if potentially eligible, study staff will contact the patient to schedule a visit to review the protocol and sign informed consent. All participants must have the approval of a treating provider in order to participate in the study.

6.1 Registration Procedures

6.2 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS), in which OnCore will be used for subject registration. Registration must occur prior to the initiation of any protocol intervention. Any participant not registered to the protocol before protocol intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin the protocol intervention. Issues that would cause delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive the protocol intervention following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

6.3 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

7. SPECIMEN/DATA COLLECTION PROCEDURES

Data Collection:
We plan to use REDCap (Research Electronic Data Capture) for collecting patient-reported outcome data in an encrypted tablet in this study. REDCap is a free, secure, HIPAA compliant web-based application hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS). Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, developed this software application for electronic collection and management of research and clinical study data. Data collection is customized for each study or clinical trial by the research team with guidance from ERIS REDCap administrators. REDCap's stream-lined process for rapidly developing databases requires little database design experience. REDCap provides a user-friendly interface to program web-based case report forms with real-time data entry validation. REDCap is built around HIPAA guidelines and is 21 CFR Part 11 capable. Data collected from REDCap can be easily exported to common data analysis packages: Microsoft Excel, SAS, Stata, R, or SPSS for analysis.[47] The REDCap study database will be password protected and will be stored on a secure network drive.

In REDCap, data validation checks will be performed at the time of the data submission, and onscreen error and caution messages will inform the study staff of any inconsistencies so that the data can be corrected immediately. Programmatic data validation checks will be conducted by the biostatistician, and the biostatistician will collaborate with the study staff to resolve any data inconsistencies.

Baseline data collection will take place after informed consent, but prior to revealing the intervention assignment. The baseline assessments will be repeated at the end of the 10th week, and end of the 20th week (post crossover). In addition, the Hot Flash Diary will be repeated at two more time points, 5th week and 15th week. Study measures will be collected according to the following schedule (Table 1.):

Participants who complete all the study surveys/logs will receive a $10 incentive gift card at week 10 and again at week 20.

Table 1. Schedule of Study Measures:

Measures						
Study Phase	**Screening**	**Baseline**	**Treatment**		**Crossover/follow-up**	
Week	-1	0	5	10	15	20
Consent form		X				
Demographics	X	X				
DHFD (7days)	X	X	X	X	X	X
FACT-B		X		X		X
FACT-ES		X		X		X
PSQI		X		X		X
Actigraphy		X		X		X
Blood Sample Collection		X		X		
Medication/Supplements Log		X		X		X
Sleep Diary		X		X		X
Insomnia Severity Index		X		X		X
AES		X				
NCI-CTCAE			At each acupuncture session (20 or 10) per study arm			
ATF			At each acupuncture session (20 or 10) per study arm			

Note: DHFD: Daily Hot Flash Diary; FACT-B: Functional Assessment of Cancer Therapy- Breast Cancer; FACT-ES: Functional Assessment of Cancer Therapy-Endocrine Subscale; PSQI: Pittsburgh Sleep Quality Index; NCI-CTCAE: the National Cancer Institute-Common Terminology Criteria for Adverse Events; AES: Acupuncture Expectancy Scale; ATF: Acupuncture Treatment Form

Study measures will be collected by the study CRCs. Assessments will be coordinated with acupuncture visits whenever possible, so that patient convenience is maximized. The following measures will be collected:

7.1 Daily Hot Flash Diary (DHFD)

The Daily Hot Flash Diary (DHFD) was originally developed by North Central Cancer Treatment Group (NCCTG).[48] It is a validated, reliable method for collecting subjective data of both frequency and severity of hot flashes. Participants are also asked to record the frequency of hot flashes and the severity of hot flashes on a scale ranging from 1 to 4 (1, mild; 2, moderate; 3, severe; 4, very severe) each day. The mean hot flash score (HFS) is calculated by multiplying the frequency by the severity of hot flashes recorded in the daily diary. DHFD and its generated HFS have been extensively used in many interventional trials in breast cancer populations, including pharmaceutical and non-pharmaceutical such as acupuncture trials. It has been noted that in using the DHFD, patients on the placebo arm have reported a reduction of hot flashes by mean of 1.5 hot flashes per day (24% reduction) and 2.8 score units (26% reduction) from baseline to the end of first 4 weeks. In the current study, the diary will be administered verbally by study staff prior to enrollment, and recorded daily for 7 days before starting 1st acupuncture as baseline, then daily for 7 days during week 5, week 10, week 15 and week 20. The weekly average hot flash scores (HFS) will be used as the primary endpoint of the study.

7.2 Functional Assessment of Cancer Therapy-Breast (FACT-B)

The FACT-B is a breast cancer-specific Quality of Life instrument of the FACIT system, which consists of FACT-General (FACT-G) and breast cancer subscale (BCS).[49] It has the following subscales: physical well-being (7 items), functional well-being (7 items), emotional well-being (6 items), social/family well-being (7 items), and breast cancer subscale (10 items). A total FACT-B score is calculated by summing the subscales. The instrument has a total of 37 items asking respondents to rate how true each statement is for the past 7 days. Response scales range from 0 (not at all) to 4 (very much). The breast cancer subscale is a 10-item self-report subscale intended to assess quality of life for breast cancer specific concerns. This subscale assesses common issues for women who have undergone treatment for breast cancer such as hair loss, feelings of attractiveness, and ability to feel like a woman. The FACT-B demonstrates good internal consistency (Cronbach's α=0.88) and discriminative validity, and is sensitive to change. A minimal clinically important difference (MCID) has been defined as 7-8 points on total FACT-B score, 2-3 points on the BCS, and 5-6 points on the Trial Outcome Index (TOI).[50] The Trial Outcome Index is a simple sum of the Physical Well-Being and Functional Well-Being, and BCS, is intended as a summary index of functional status to be used as a clinical trails endpoint.

7.3 Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES)

FACT-ES was developed to be typically used in combination with the FACT-B. The FACT-ES is intended to assess quality of life in breast cancer patients on endocrine therapies.[51] In addition to 5 subscales in FACT-B, the FACT-ES contains an additional 19-item endocrine symptom subscale that specifically assesses menopausal symptoms, including hot flashes, vaginal dryness,

and loss of libido. FACT-ES was validated in women with breast cancer receiving endocrine therapy and has been used in clinical trials.[52, 53] The FACT-ES demonstrates good internal consistency, test-retest reliability, and sensitivity to change. Same as FACT-B, the higher scores indicated an improvement in quality of life or well-being.

7.4 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 19-item self-reported questionnaire that assesses sleep quality for the preceding month. This measure has been validated. The majority of studies report Cronbach α values of 0.70 to 0.83. For the purposes of this study, the questionnaire was modified to ask about sleep quality for the preceding 48 hours. Other studies have also previously altered the PSQI to measure shorter time periods, and researchers have justified this by noting that more recent events might be easier to remember and less impacted by recall bias. PSQI questions are grouped into 7 equally weighted component scores, on a 0 to 3 scale, that are summed to yield a global PSQI score. The global score ranges from 0 to 21, and the higher the score, the worse the sleep quality. A global score of >5 indicates subjective insomnia, which has been used as a cutoff point to investigate clinically significant sleep problems.[53-55]

7.5 Actigraphy Movement Device:

The Actigraphy is a wristwatch-like electronic accelerometer-based physical activity device that is used to determining wake versus sleep state based upon movements. It is worn continuously (24 hours/day, 7 days/ week) on either arm for the period of measurement.[56-58] The output is in the form of number of movements per unit of time. The pattern of movement has been used as an objective measure for sleep, and correlates for fatigue. The following data will be measured: a. counts per hour of time in bed; b. efficiency, defined as the number of hours slept over the number of hours spent in bed multiplied by 100 (%); c. average awake time (minutes) per hour of sleep; and d. number of awakenings per hour of sleep. Counts are based on the frequency and intensity of the acceleration at each 60-second epoch and are calculated by the software. Participants will wear the Actigraphy wrist watch for one week at baseline and one week at week 10 and week 20 to record measures of sleep-wake schedules and sleep quality. A number of studies have demonstrated the reliability, validity, utility, accuracy, and responsiveness of this approach in differentiating between physical and sedentary activities and determining the level of daily activity ($p < 0.0001$). Test-retest reliability was very high for 12 different activities ($r=.98$). This device has been shown to be a useful tool in correlative and intervention studies of sleep and fatigue in breast cancer populations.[56] One study team member will be responsible for cleaning and scoring all sleep data for the selected participants.

7.6 Medication/Supplement Log

A patient medication log will be kept and administered to track the usage and dose of support medications as well as dietary supplements including herbal medicine. Support medications include, but are not limited to: (1) Anti-depressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine

(Brisdelle, Paxil), Sertraline (Zoloft), Venlafaxine (Effexor), and Desvenlafaxine (Pristiq); (2) Antiseizure medications: Gabapentin; (3) Dietary supplements include, but are not limited to: Vitamin E, Black cohosh, Dong quai root, Evening primrose oil, Flaxseed, Ginseng root, Omega-3 fatty acid, Red clover extract, and Soy supplements; (4) Sleep medications; (5)Mixtures of multi-herbal formulas (Traditional Chinese Medicine, TCM), either in a patient pill form or in a personalized tea/liquid form. Data for the medication log will be collected at each scheduled visit.

7.7 Acupuncture Expectancy Scale (AES)

The AES consists of four items measuring the expectation of improvement of illness (symptom), enhanced coping, increased vitality, and symptom alleviation due to acupuncture therapy. Participants are asked to endorse their expectancy of acupuncture for specific symptoms (e.g., joint pain for breast cancer survivors, and fatigue for patients undergoing radiation therapy). Subjects are asked to rate from 1 to 5 on a five-point Likert scale, with 1 indicating "Not at all agree" and 5 indicating "Completely agree" with the expected improvement as result of acupuncture. Possible scores range from 4 to 20, with higher scores indicating greater expectancy. Preliminary validation showed that the AES has a single factor structure with an acceptable reliability coefficient. Additionally, the score on the AES was positively correlated with both the perceived effectiveness of acupuncture treatment and the confidence in acupuncture care. The AES will be administered once before the randomization process. [59, 60]

7.8 Acupuncture Treatment Form (ATF)

An acupuncture treatment form will be generated by the treating acupuncturist at each acupuncture treatment. The form will document the following items: acupuncture points used, patient-reported acupuncture intensity, patient immediate responses, and any acupuncture-related adverse events.

7.9 NF-Kb, STAT-1 and STAT-3, and associated cytokines IL-8, TNF-alpha and IL-6, and T-cells Measurement

Venous blood will be collected at baseline and at week 10. Assays will be performed at the Harvard Catalyst Central Laboratory (HCCL) and Dr. David Frank's Lab at Dana-Farber Cancer Institute. Briefly, for each sample, 10 mL of venous blood will be collected into EDTA and Serum tubes.. Samples will be centrifuged for 15 minutes at 1000 x g within 30 minutes of collection and then aliquot and stored at -80 °C for future measurements.

The plasma levels of interferon gamma (IFNγ), tumor necrosis factor-α (TNF-α), interleukin-1β(IL-1β), IL-6, IL-8, and IL-17A will be determined using a Millipore cytokine seven-plex panel assay (MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel) (Milliplex MAP kits, EMD Millipore, Billerica, MA, USA). The plasma levels of interferon-inducible protein-10 (IP10), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1β (MIP-1β) will be measured using a Millipore cytokine three-plex panel assay (MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel) (Milliplex MAP kits, EMD Millipore, Billerica, MA, USA). These assays will be processed according to the

manufacturer's instructions. STAT-1, STAT-3 and NF-κB expression levels will be measured at Dr. David Frank's Lab. Samples will be measured in duplicate, and the average of the 2 values will be used in the statistical analysis.

7.10 Sleep Diary

Weekly sleep diary will be collected at three time points: baseline, week 10, and week 20. Participants will be instructed to complete the diary upon awakening to minimize recall bias. The format of the sleep diary and wording of the questions have been modeled after the Consensus Sleep Diary, a standardized and validated tool for collecting subjective sleep patterns.[63,64] Using the diary, participants will keep track of their time to bed with intention of sleeping, amount of time it took to fall asleep, number and total duration of awakenings, final awakening time, number and duration of napping, and number of hot flashes interfering with sleep. This information will then be used to assess various sleep-related parameters, such as sleep onset latency, wake after sleep onset, number of nightly awakenings, total sleep time, and sleep efficiency.

7.11 Insomnia Severity Index

Insomnia Severity Index (ISI) is a widely used, validated patient-reported questionnaire for assessing insomnia severity.[65] It is composed of 7 questions, each scored on a 5-point scale (range 0-4) and the total scores ranging from 0 to 28. Higher scores correspond to a more severe insomnia and an 8-point reduction are considered clinically meaningful. The ISI will be collected at three time points: baseline, at week 10, and week 20.

8. STUDY INTERVENTIONS

8.1 Overview

It is expected that each patient who is assigned to the immediate acupuncture arm will receive acupuncture twice per week for 10 weeks for a total of 20 sessions. The participants on the usual care/wait list control arm will continue their standard usual care with their physicians and care team. The crossover will take place after the 10th week. After crossover, the participants initially on the usual care/waiting list arm will receive the identical acupuncture protocol but a less frequent schedule from week 11 to week 20: once per week for a total of 10 sessions. The participants who were initially treated with acupuncture will enter a follow-up phase of usual care for 10 weeks from week 11 to week 20.

8.2 Usual Care

Usual care in the current study is defined as the current standard of care with non-hormonal pharmacotherapy of western medicine.[46] Participants should not receive acupuncture or acupuncture-like therapy during the usual care portion of study follow-up.

8.3 Acupuncture

The acupuncture protocol outlined below is based on the best evidence available in this specialty. The following data is collected: 1) an English- and Chinese-language literature review of previous clinical studies of acupuncture used for hot flashes;[3, 61] 2) English- and Chinese-language acupuncture text books that describe treatment strategies for hot flashes; [62] and 3) our own clinical experience with breast cancer patients treated at the Leonard P. Zakim Center for Integrative Therapies and Healthy Living at DFCI.

Treatments will be administered by experienced, licensed and credentialed DFCI oncology acupuncturists who have been specifically trained to administer this study's acupuncture protocol. To facilitate study recruitment and to reduce traveling time, participants will be offered the option to receive treatments at the Zakim Center clinic or at the private clinics of the study acupuncturists in the Greater Boston Area. Participants will be provided with a list of the private clinic locations (see Appendix XII) and will communicate their preferences for treatment location to study staff at the time of consent.

Private Clinic Details

The locations and operating hours of the private clinics are:

1) **Name:** Weidong Lu
   Location: 55 Chapel Street, Suite 004, Newton, MA 02458
   Phone number: (617) 244-2833
   Available Time: Thursday 9am-5:00pm, Saturday 9 am to 5 pm
2) **Name:** Dongyan Yu
   Location: 271 Great Road, Suite 2, Action, MA 01720
   Phone number: (978) 257-7891
   Available Time: Tuesday 8 am -5pm, Thursday 8 am- 5pm, Saturday by appointment

3) **Name:** Zhiping Li
   Location: 48 Cummings HWY, Roslindale, MA 02131
   Phone: (617) 323-7809
   Available Time: Monday-Saturday 10 am to 5 pm, except on Tuesdays
4) **Name:** Joy Yue Zhang
   Location: 175 Littleton Rd. Unit 6, Westford, MA 01886
   Phone: (978) 692-8889
   Available Time: Monday, Tuesday, Friday 8 am to 6 pm; Thursday 12 noon-6pm

At these private clinics, the acupuncture treatment will be provided by the study-trained DFCI staff acupuncturists listed above. These acupuncturists are also responsible for administering the study protocol in the Zakim Center. Participants that opt for off-site treatment will be asked to remain at the same site with the same acupuncturist throughout their study treatment course. All study acupuncturists are licensed acupuncturists and have obtained certificates from CITI program for research ethics and human subject protection as required by DFCI, and in-person training with the study protocol.

As the lead acupuncturist and the study PI, Dr. Weidong Lu is responsible for conducting protocol training sessions for staff acupuncturists. Each acupuncturist will take a pre-trial training course for this clinical research protocol. The study PI will train all study acupuncturists and periodically observe the treatment technique being performed to ensure the quality of the treatment. The study team will also provide continued oversight of treatments that are delivered at the acupuncturists' private clinics. Oversight will include close monitoring and communications, including site visits by the study PI; monthly conference calls and in-person meetings.

For these off-site appointments, the Zakim research staff will facilitate the first appointment at the private clinic by working with the acupuncturist and the study participant. For the remainder of the appointments, the study acupuncturist will work with the study participant to coordinate the remaining acupuncture visits. Quickbase, A HIPAA-compliant online communication tool, will be used to transmit information related to study appointment scheduling. The private clinics will only provide acupuncture treatment; all other scheduled assessments will take place at DFCI main campus. Hardcopies of study related documents will be returned to the study team and will be stored in the study folders of each study participant. No study-related documents will remain at the private clinics.

Acupuncture Protocol

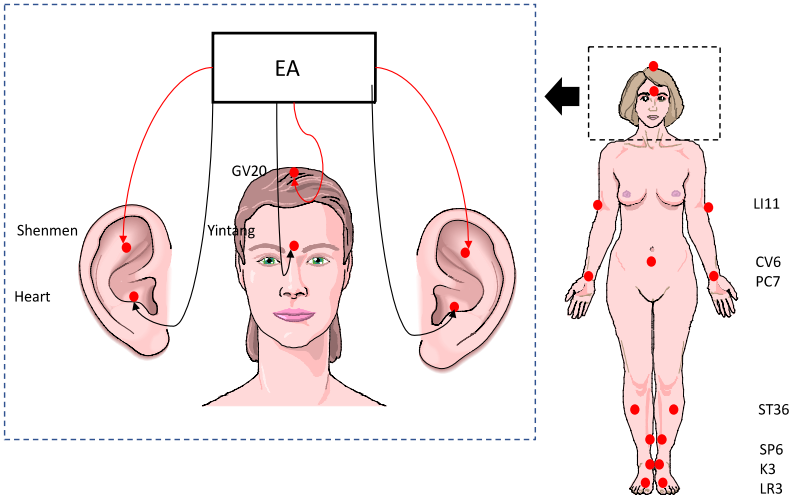
It is expected that each patient who is assigned to the immediate acupuncture arm will receive acupuncture twice per week for a total of 20 sessions. The participants on the usual care/wait list control arm will continue their standard usual care with their physicians and care team. The usual care in the current study is defined as the current standard of care with non-hormonal pharmacotherapy of western medicine. The crossover will take place after the 10th week. After crossover, the participants initially on the usual care/waiting list arm will receive the identical acupuncture protocol but a less frequent schedule from week 11 to week 20: once per week for a total of 10 sessions. The participants who were initially treated with acupuncture will enter a

follow-up phase without acupuncture for 10 weeks from week 11 to week 20, while the standard usual care will be provided.

If a study patient misses an acupuncture treatment, the patient will be asked to make up the missed treatment session so that a total of 20 sessions (or 10 sessions after crossover) of acupuncture will be provided. We will determine that a participant is compliant with the acupuncture protocol if the study participants complete overall at least 15 out of 20 planned sessions (75%) during the main treatment period. The total number of acupuncture sessions received will be recorded for each participant. Any side effects related to the acupuncture will be collected by treating acupuncturists.

Figure 2 and Table 2 present the names and locations of acupuncture points. (Figure 2, Table 2.).

Figure 2. Acupuncture protocol for hot flashes in breast cancer



During the main study period, acupuncture will be administered twice per week for ten weeks, for a total of 20 sessions. In the post-crossover period for the usual care (control) group, acupuncture will be administered once per week for ten weeks, for a total of 10 sessions.

The acupuncture protocol will use a two-phase, step-up protocol to gradually increase the treatment area and treatment intensity. Based on our experience at the Zakim Center, this protocol will reduce the initial anxiety of participants to the treatment and maximize the treatment intensity. The phase 1 treatment will take place at the first visit, in which only manual acupuncture will be employed. The phase 2 treatment will take place from the second to twentieth visit, in which an electroacupuncture stimulation will be added. Use of electroacupuncture is a typical practice at Zakim Center. In post-crossover acupuncture, phase 1 will be the first visit and the phase 2 will start at the 2nd visit and extend to the 10th visit.

At each visit, participants will be asked to lie down in a supine position on a massage table with

the arms, legs and abdomen exposed to the treatment. The skin on the acupuncture points will be prepared with 70% ethyl alcohol. Then, acupuncture needles (0.20x25 mm, and 0.25x 40 mm) will be inserted into acupuncture points bilaterally. The depth of insertions at each point will be between 5-15 mm, except on points on the head and ears, which will be between 2-5 mm. Depth of needling to access acupuncture channels will vary due to differences in patient size and body characteristics. After insertion, acupuncture needles will be manually manipulated in order to obtain the De Qi sensation. The De Qi sensation is defined as the acupuncturist feeling a tugging or grasping sensation from the needle manipulation and the patient feeling soreness, fullness, heaviness or local distension at local needling sites. The De Qi sensation will be required on at least 2 points bilaterally on the lower extremity and at least 1 point bilaterally on the upper extremity. During phase 2 of the treatment protocol, and after De Qi is obtained, electroacupuncture will be administered to a subset of acupuncture points. Six pairs of microalligator clips from the AWQ-104L electroacupuncture machine (Lhasa OMS, Inc.) will be connected with the needles at GV20 and Yintang on the head; Shenmen and Heart, on the ears bilaterally, with the negative poles on the Yintang/Heart and the positive poles on GV20/Shenmen. The stimulation parameters will be set at a 2/10 Hz alternating wave pattern, with a 40 or 350 μs pulse-widths. The targeted stimulation intensity reported by the patient will be at 3 or 4 on the scale from 0 to 10 (0 being feeling nothing at all and 10 being the strongest one can imagine). The patient will be asked to report sensations and should feel comfortable with the intensity of the electrostimulation. The usage of an infrared heat lamp during the session, a common practice in an acupuncture session, maybe used on the feet of the patient. The needles will remain in place for 30 minutes. The patient will be left alone in the treatment room with dimmed lights. A call bell will be available to the study patient during the treatment period. After 30 minutes of treatment, needles will be manually manipulated again before removal. De Qi sensation is not required at this time. The patient will leave the treatment room after the treatment. A complete list of acupuncture points that will be used is listed in Table 2. A total of 19 needles will be used during each acupuncture session at each phase respectively. Additionally, the following rules are applied: a) the selections of LI11 and PC7 points will be determined based upon locations of symptoms reported by participants: if the participants had axillary lymph node dissection (ALND) or has lymphedema, the affected limb won't be needled; b) the electrostimulation may be omitted at Shenmen/ear and Heart/ear pending the tolerability of each participant; c) if the participant refuses electrostimulation, manual acupuncture may be performed without electrostimulation. The number of needles will be counted at the end of each session.

8.4 Adverse Events

Individuals receiving acupuncture will be asked about acupuncture-related adverse events at each acupuncture treatment. Any acupuncture-related injuries will be reported to study investigators. Any reported events will be evaluated for the likelihood that they occurred as a result of acupuncture (clearly related, likely related, maybe related, doubtfully related, or clearly NOT related). Participants will also be provided a phone number to contact study staff at DFCI to report potential acupuncture-related adverse events.

Table 2. Acupuncture Points and Locations

Name	Pinyin Name	Location	Innervations
LR3	Taichong	On the dorsum of the foot, in the depression distal to the junction of the first and second metatarsal bones.	The branch of the deep peroneal nerve.
ST36	Zusanli	3 cun below Dubi, one finger-breadth from the anterior crest of the tibia, in m. tibialis anterior.	Superficially, the lateral aural cutaneous nerve and the cutaneous branch of the saphenous nerve; deeper, the deep peroneal nerve.
SP6	Sanyinjiao	3 cun directly above the tip of the medial malleolus, on the posterior border of the medial aspect of the tibia.	Superficially, the medial crural cutaneous nerve; deeper, in the posterior aspect, the tibial nerve.
K3	Taixi	In the depression between the medial malleolus and tendo calcaneus, at the level with the tip of the medial malleolus.	The medial crural cutaneous nerve, on the course of the tibial nerve.
LI11	Quchi	When the elbow is flexed, the point is in the depression at the lateral end of the transverse cubital crease, midway between Chize and the lateral epicondyle of the humerus.	The posterior antebrachial cutaneous nerve; deeper, on the medial side, the radial nerve.
PC7	Daling	In the meddle of the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis.	Deeper, the median nerve.
CV6	Qihai	On theanterior midline, 1.5 cun below the umbilicus.	The anterior cutaneous branch of the eleventh intercostal nerve.
Extra2	Yintang	Midway between the medial ends of the two eyebrows.	N/A
GV20	Baihui	On the midline of the head; 7 cun directly above posterior hairline; approximately on midpoint of line connecting apexes of two auricles.	The branch of the great occipital nerve.
Ear point 1	Shenmen	Superior and central to the tip of the triangular fossa, between the junction of the superior crus and inferior crus of antihelix. It is not at the tip of the triangular fossa, but slightly inward and slightly upward from where the triangular fossa descends from the superior crus toward deeper regions of the triangular fossa.	auricular branches of the vagus nerve (ABVN)
Ear point 2	Heart	deepest, most central area of the Inferior concha	auricular branches of the vagus nerve (ABVN)
Cun: The CUN-system is a proportional measurement system used in Chinese acupuncture.			

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

9.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or

Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen

emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission respite care

9.1.3 **Expectedness**

Adverse events can be 'Expected' or 'Unexpected.'

9.1.3.1 **Expected adverse event**

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

9.1.3.2 **Unexpected adverse event**

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

9.1.3.3 **Attribution**

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.

- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.

- Unrelated - The AE is clearly NOT related to the study treatment.

9.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

9.3 Reporting Requirements

In this study, each investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

It is the responsibility of the study investigators to report serious adverse events to the study sponsor and/or others as described below.

9.4 Reporting

9.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last session of treatment must be reported to the Principal Investigator/co-PIs on the SAE form. This includes events meeting the criteria outlined in Section 9.1.2, as well as the following:

Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Participating investigators must report each serious adverse event to the Principal Investigator/Co-PIs within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Weidong Lu, MB, MPH, PHD

617-967-4900 (phone)

Weidong_lu@dfci.harvard.edu

And

Jennifer Ligibel, MD

617-632-3800 (phone)

Jligibel@partners.org

617-632-1930 (fax)

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

9.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Principal Investigator/co-PIs on the toxicity Case Report Forms.

9.5 Reporting to the Institutional Review Board (IRB)

All serious adverse events will be directly reported to the DFCI Office for Human Research Studies (OHRS).

The DF/HCC Principal Investigators will submit SAE reports to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

9.6 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Principal Investigators and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

10. STATISTICAL CONSIDERATIONS

10.1 Randomization and Accrual

In this study, the target sample size is 85 participants (80 will be randomized; 40 in the immediate arm, 40 in the delayed arm) We will replace participants who were enrolled/registered but not randomized for any reason.

Patients with hot flashes will be randomly assigned to the immediate acupuncture arm or to the wait list control arm in a 1:1 allocation. The randomization will be based on the permuted block method, and will be stratified by hot flash or night sweat frequency at baseline (2-6 per day versus 7 or more per day).

10.2 Endpoints

The primary clinical endpoint is change from baseline in mean weekly HFS score between acupuncture and usual care arms at the end of week 10. HFS is a composite entity of both frequency and severity of hot flashes (number times mean severity). Secondary endpoints will include response rate, changes in the total and subscores in Functional Assessment of Cancer Therapy- Breast Cancer (FACT-B), the Endocrine Subscale (FACT-ES), Pittsburgh Sleep Quality Index (PSQI), changes in sleep quality and duration, as assessed by Actigraphy, changes in patients' perception of sleep quality, as assessed by the sleep diary and Insomnia Severity Index (ISI), and changes in plasma proinflammatory cytokines. The response rate is defined as the proportion of patients in whom there is 50% or greater reduction in HFS score between baseline and 10th week. As tertiary endpoints, we will assess changes in the primary and secondary outcomes between weeks 10 and 20. We will explore the effects of twice per week versus once per week acupuncture sessions by comparing changes in HFS scores and secondary outcomes for patients enrolled to the immediate acupuncture group (baseline compared with week 10) and usual care (week 11 compared with week 20, during which time these patients receive acupuncture once per week).

10.3 Sample Size and Statistical Power

10.3.1 Sample Size

Sample size estimates are based on the mean weekly HFS, which is the primary clinical outcome. The target sample size is 85 participants (80 will be randomized; 40 immediate acupuncture and 40 usual care).

Table 3. Key Outcomes from Previously Published Acupuncture Hot Flash Trials

Authors	N	Control Type	Primary Measure	Baseline acu	Baseline control	Post treatment acu	Post treatment control	% Change from Baseline acu arm	% Change from Baseline control arm	Δ absolute difference between two proportions
Lesi	190	self care	Daily HFS	32.27± 25.31	27.31± 17.06	11.34 ±14.75	22.70± 19.40	-65%	-17%	-48%
Mao	120	sham acu	Daily HFS	15.5± 9.4	13.1± 9.6	8.1± 8.1	7.2± 5.9	-48%	-45%	-3%
Walker	50	venlafaxine	Hot Flash Frequency	9.44 ±5.18	6.39± 2.93	~50% reduction	~50% reduction	-50%	-50%	0%
Deng	72	sham acu	Hot Flash Frequency	8.7± 3.9	10.0± 6.1	5.8 ±4.8	7.8 ±5.9	-33%	-22%	-11%

acu: acupuncture; HFS: Hot Flash Score

Based upon data from four acupuncture trials published on *Journal of Clinical Oncology* (Table 3.)[3, 23-25], which all investigated the effect of acupuncture on hot flashes in breast cancer populations, the percentage reduction of acupuncture arms in these trials is around 50%, while the percentage reduction in the control arms ranged from 17% to 50% due to various types of control designs. Since our current study uses usual care as the control arm, which is similar to Lesi's study design, it is reasonable to anticipate a 17%-20%

reduction in our usual care arm. For purposes of design, we assume a 20% relative percent change in HFS between pre- and post-treatment (10 weeks) in our usual care arm. If the correlation between pre- and post- measurements for each participant is at least 0.5, then based on the control arm in the Lesi data, the estimated standard deviation of the relative percent change will be no larger than approximately 60%. For a sample of 40 participants per intervention arm, and allowing for a 5% loss from measurement between pre-treatment and 10 weeks, there will be approximately 85% power to detect a difference in average percent change of -39% (-20% vs. -59%, effect size = 0.66) using a Wilcoxon rank-sum test and assuming a standard deviation of 60% and a 0.1 two-sided significance level.

10.4 Data Analysis

Data will be analyzed according to the intention-to-treat principle. Baseline demographic, disease characteristics, prior treatment, and comorbidities will be compared at baseline using the relevant descriptive methods for continuous and categorical variables.

For the primary outcome of change in HFS between pre-treatment and 10 weeks, the relative percent change (100*(post – pre)/pre) will be estimated and compared between intervention arms using a Wilcoxon rank-sum test.

The proportions of participants with at least a 50% reduction in HFS between the two time points will be compared using Fisher's exact test. If we assume that approximately 15% of participants in the usual care arm will have a 50% reduction in HFS during the first 10 weeks, a Fisher's exact test with a 0.1 two-sided significance level will have 85% power to detect an absolute difference of 30% (i.e., 15% vs. 45%) when the sample size in each group is 40.

11. DATA AND SAFETY MONITORING PLAN

11.1 Data Reporting

We will use REDCap to collect, manage, and monitor data for this study. In addition, REDCap will be also used to collect data from patient reported questionnaires.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by DF/HCC IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the reporting policy.

12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. SHARING OF RESULTS WITH SUBJECTS

Individual results will not be shared with study participants or participants' care teams. However, the aggregate study results will be shared with study participants in a plain language summary (PLS) (Appendix XVI) once primary study analyses are complete. We will also disseminate an experience survey (XVII) to participants who receive the PLS. This survey will ask participants to share their impressions of the results return process.

Participants will be sent a notification letter via email (if email was previously provided to the study team) or by mail. Participants will be asked to reach out to study staff if they are interested in receiving the plain language summary and the experience survey. Study staff will reach out by phone if participants do not respond to the letter within 30 days. Two phone call attempts will be made.

Once notified of the consent form changes, interested participants will receive the study results via email and will complete the survey via RedCap link. Participants will also be given the option to receive both the PLS and survey via hardcopy in the mail, if preferred.

The coded, deidentified results of the experience survey will be shared with study collaborators at the Multi-Regional Clinical Trials Center at Brigham and Women's/Harvard.

14. REFERENCES

1. Choi TY, Lee MS, Kim TH, Zaslawski C, Ernst E. Acupuncture for the treatment of cancer pain: a systematic review of randomised clinical trials. Support Care Cancer. 2012;20: 1147-1158.
2. Shen J, Wenger N, Glaspy J, et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: A randomized controlled trial. JAMA. 2000;284: 2755-2761.
3. Mao JJ, Bowman MA, Xie SX, Bruner D, DeMichele A, Farrar JT. Electroacupuncture Versus Gabapentin for Hot Flashes Among Breast Cancer Survivors: A Randomized Placebo-Controlled Trial. J Clin Oncol. 2015;33: 3615-3620.
4. Crew K, Capodice J, Greenlee H, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. J Clin Oncol. 2010;28: 1154-1160.
5. Molassiotis A, Bardy J, Finnegan-John J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. J Clin Oncol. 2012;30: 4470-4476.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Available from URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive [accessed Oct. 25, 2016, 2916].
7. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. CA Cancer J Clin. 2017;67: 439-448.
8. Hutton B, Yazdi F, Bordeleau L, et al. Comparison of physical interventions, behavioral interventions, natural health products, and pharmacologics to manage hot flashes in patients with breast or prostate cancer: protocol for a systematic review incorporating network meta-analyses. Syst Rev. 2015;4: 114.
9. Soucise A, Vaughn C, Thompson CL, et al. Sleep quality, duration, and breast cancer aggressiveness. Breast Cancer Res Treat. 2017;164: 169-178.
10. Trudel-Fitzgerald C, Zhou ES, Poole EM, et al. Sleep and survival among women with breast cancer: 30 years of follow-up within the Nurses' Health Study. Br J Cancer. 2017;116: 1239-1246.
11. Dorjgochoo T, Gu K, Kallianpur A, et al. Menopausal symptoms among breast cancer patients 6 months after diagnosis: a report from the Shanghai Breast Cancer Survival Study. Menopause. 2009;16: 1205-1212.
12. Jones SE, Cantrell J, Vukelja S, et al. Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. J Clin Oncol. 2007;25: 4765-4771.
13. Hong D, Bi L, Zhou J, et al. Incidence of menopausal symptoms in postmenopausal breast cancer patients treated with aromatase inhibitors. Oncotarget. 2017;8: 40558-40567.
14. Morales L, Neven P, Timmerman D, et al. Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients. Anticancer Drugs. 2004;15: 753-760.
15. Im EO, Ko Y, Chee W. Ethnic differences in the clusters of menopausal symptoms. Health Care Women Int. 2014;35: 549-565.

16. Leon-Ferre RA, Majithia N, Loprinzi CL. Management of hot flashes in women with breast cancer receiving ovarian function suppression. Cancer Treat Rev. 2017;52: 82-90.
17. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr. 2007: 16-21.
18. Schneider A, Kotronoulas G, Papadopoulou C, et al. Trajectories and predictors of state and trait anxiety in patients receiving chemotherapy for breast and colorectal cancer: Results from a longitudinal study. Eur J Oncol Nurs. 2016;24: 1-7.
19. Lim CC, Devi MK, Ang E. Anxiety in women with breast cancer undergoing treatment: a systematic review. Int J Evid Based Healthc. 2011;9: 215-235.
20. Boltong A, Aranda S, Keast R, et al. A prospective cohort study of the effects of adjuvant breast cancer chemotherapy on taste function, food liking, appetite and associated nutritional outcomes. PLoS One. 2014;9: e103512.
21. Boltong A, Keast R. The influence of chemotherapy on taste perception and food hedonics: a systematic review. Cancer Treat Rev. 2012;38: 152-163.
22. 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. 2009.
23. Lesi G, Razzini G, Musti MA, et al. Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT). J Clin Oncol. 2016;34: 1795-1802.
24. 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. 2007;25: 5584-5590.
25. 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. 2010;28: 634-640.
26. Garcia MK, Graham-Getty L, Haddad R, et al. Systematic review of acupuncture to control hot flashes in cancer patients. Cancer. 2015;121: 3948-3958.
27. Lee MS, Kim KH, Choi SM, Ernst E. Acupuncture for treating hot flashes in breast cancer patients: a systematic review. Breast Cancer Res Treat. 2009;115: 497-503.
28. Chien TJ, Hsu CH, Liu CY, Fang CJ. Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis. PLoS One. 2017;12: e0180918.
29. Chen YP, Liu T, Peng YY, et al. Acupuncture for hot flashes in women with breast cancer: A systematic review. J Cancer Res Ther. 2016;12: 535-542.
30. Dong H, Ludicke F, Comte I, Campana A, Graff P, Bischof P. An exploratory pilot study of acupuncture on the quality of life and reproductive hormone secretion in menopausal women. J Altern Complement Med. 2001;7: 651-658.
31. Liljegren A, Gunnarsson P, Landgren BM, Robeus N, Johansson H, Rotstein S. Reducing vasomotor symptoms with acupuncture in breast cancer patients treated with adjuvant tamoxifen: a randomized controlled trial. Breast Cancer Res Treat. 2012;135: 791-798.
32. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res. 2006;12: 2759-2766.
33. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in

breast cancer survivors. Psychosom Med. 2002;64: 604-611.
34. Perrier S, Caldefie-Chezet F, Vasson MP. IL-1 family in breast cancer: potential interplay with leptin and other adipocytokines. FEBS Lett. 2009;583: 259-265.
35. Bauml J, Chen L, Chen J, et al. Arthralgia among women taking aromatase inhibitors: is there a shared inflammatory mechanism with co-morbid fatigue and insomnia? Breast Cancer Res. 2015;17: 89.
36. Yasui T, Uemura H, Tomita J, et al. Association of interleukin-8 with hot flashes in premenopausal, perimenopausal, and postmenopausal women and bilateral oophorectomized women. J Clin Endocrinol Metab. 2006;91: 4805-4808.
37. Huang WY, Hsin IL, Chen DR, et al. Circulating interleukin-8 and tumor necrosis factor-alpha are associated with hot flashes in healthy postmenopausal women. PLoS One. 2017;12: e0184011.
38. Banerjee K, Resat H. Constitutive activation of STAT3 in breast cancer cells: A review. Int J Cancer. 2016;138: 2570-2578.
39. Shostak K, Chariot A. NF-kappaB, stem cells and breast cancer: the links get stronger. Breast Cancer Res. 2011;13: 214.
40. Li QQ, Shi GX, Xu Q, Wang J, Liu CZ, Wang LP. Acupuncture effect and central autonomic regulation. Evid Based Complement Alternat Med. 2013;2013: 267959.
41. Bao T, Cai L, Giles JT, et al. A dual-center randomized controlled double blind trial assessing the effect of acupuncture in reducing musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors. Breast Cancer Res Treat. 2013;138: 167-174.
42. Hadianfard M, Bazrafshan E, Momeninejad H, Jahani N. Efficacies of Acupuncture and Anti-inflammatory Treatment for Carpal Tunnel Syndrome. J Acupunct Meridian Stud. 2015;8: 229-235.
43. Lim HD, Kim MH, Lee CY, Namgung U. Anti-Inflammatory Effects of Acupuncture Stimulation via the Vagus Nerve. PLoS One. 2016;11: e0151882.
44. McDonald JL, Cripps AW, Smith PK, Smith CA, Xue CC, Golianu B. The anti-inflammatory effects of acupuncture and their relevance to allergic rhinitis: a narrative review and proposed model. Evid Based Complement Alternat Med. 2013;2013: 591796.
45. Liu R, Xu N, Yi W, Huang K, Su M. Electroacupuncture effect on neurological behavior and tyrosine kinase-JAK 2 in rats with focal cerebral ischemia. J Tradit Chin Med. 2012;32: 465-470.
46. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2016;34: 611-635.
47. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42: 377-381.
48. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. J Clin Oncol. 2001;19: 4280-4290.
49. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol. 1997;15: 974-986.
50. Eton DT, Cella D, Yost KJ, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004;57: 898-910.

51. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas. 1996;24: 161-175.
52. Lewis JE, Hilditch JR, Wong CJ. Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, MENQOL-Intervention questionnaire. Maturitas. 2005;50: 209-221.
53. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28: 193-213.
54. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998;45: 5-13.
55. Gentili A, Weiner DK, Kuchibhatla M, Edinger JD. Test-retest reliability of the Pittsburgh sleep quality index in nursing home residents. J Am Geriatr Soc. 1995;43: 1317-1318.
56. Moore CM, Schmiege SJ, Matthews EE. Actigraphy and Sleep Diary Measurements in Breast Cancer Survivors: Discrepancy in Selected Sleep Parameters. Behav Sleep Med. 2015;13: 472-490.
57. Grutsch JF, Wood PA, Du-Quiton J, et al. Validation of actigraphy to assess circadian organization and sleep quality in patients with advanced lung cancer. J Circadian Rhythms. 2011;9: 4.
58. Madsen MT, Huang C, Gogenur I. Actigraphy for measurements of sleep in relation to oncological treatment of patients with cancer: a systematic review. Sleep Med Rev. 2015;20: 73-83.
59. Mao JJ, Armstrong K, Farrar JT, Bowman MA. Acupuncture expectancy scale: development and preliminary validation in China. Explore (NY). 2007;3: 372-377.
60. Mao JJ, Xie SX, Bowman MA. Uncovering the expectancy effect: the validation of the acupuncture expectancy scale. Altern Ther Health Med. 2011;16: 22-27.
61. Yang C, Liu L, Zhu Z, Gou H. Acupuncture methods and points selection pattern for treating female menopausal syndrome. Journal of Clinical Acupuncture and Moxibustion. 2014;30.
62. Cheng XN. Chinese Acupuncture and Moxibustion. Beijing: Foreign Languages Press, 1999:590.
63. Carney C, Buysse DJ, Ancoli-Israel S, et al. The Consensus Sleep Diary: Standardizing Prospective Sleep Self-Monitoring. Sleep. 2012;35(2): 287-302.
64. Maich KHG, Lachowski AM, Carney CE. Psychometric Properties of the Consensus Sleep Diary in Those with Insomnia Disorder. Behav Sleep Med. 2018;16(2):117-134.
65. Bastien CH, Vallieres A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med. 2001;2(2):297-307.

15. APPENDICES

Appendix I. Daily Hot Flash DiarY (DHFD)

Protocol #: **Participant ID #:**

Weekly Hot Flash Diary

For EACH DAY please record: (A) the number hot flashes in each hot flash severity category and (B) the total number of hot flashes per day (adding hot flashes for all severity levels). *Hot Flash scores (grey areas) are for research staff only.

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
Hot Flash Severity	__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY		__ __/__ __/__ __ MM DD YY	
	Total	*Hot Flash Score	Total	*Hot Flash Score	Total	*Hot Flash Score	Total	*Hot Flash Score	Total	*Hot Flash Score	Total	*Hot Flash Score	Total	*Hot Flash Score
How many **mild** hot flashes did you experience today? (Duration: Lasting less than 5 minutes. Physical Symptoms: Warmth, felt uncomfortable, red face)														
How many **moderate** hot flashes did you experience today? (Duration: Lasting up to 15 minutes. Physical Symptoms: Head, neck, ears or whole body felt warm; tense, tight muscles; clammy skin, change in heart rate or rhythm; some sweating; dry mouth)														
How many **severe** hot flashes did you experience today? (Duration: Lasting up to 20 minutes. Physical Symptoms: Warmth, sometimes described as a raging furnace or burning up; a change in heart rate or rhythm; feel faint; headache; severe sweating; weakness, a pricking or stinging sensation over skin)														
How many **very severe** hot flashes did you experience today? (Duration: Lasting up to 45 minutes. Physical Symptoms: Boiling heat, rolling sweat, difficulty breathing, feel faint, felt dizzy, feel and/or legs cramping, a change in heart rate and felt slightly sick to the stomach)														
Total Hot Flashes per day														

Adapted from North Central Cancer Treatment Group
Sloan et. al., *J. Clin Onc* 2001

Protocol #: **Participant ID #:** _____

Hot Flash Definitions

One or more of these descriptions may help you categorize your hot flash as mild, moderate, severe, or very severe. Your hot flash may include any, but not necessarily all of the following characteristics:

	Mild	Moderate	Severe	Very severe
Physical symptoms	o Warmth o Felt uncomfortable o Red face	o Head, necks, ears, or body felt warm o Tense/tight muscles o Clammy (wet skin) o Heart speeds up/changes beat o Some sweating o Dry mouth	o Warmth (raging furnace or burning up) o Heart speeds up/changes beat o Felt faint o Headache o Weakness (pricking, stinging feeling over skin) o Chest heaviness	o Boiling heat o Rolling sweat o Difficulty breathing o Felt faint, dizzy o Heart speeds up/changes beat o Legs cramping o Felt slightly sick to stomach
Emotional symptoms	Not expected	o Irritation o Agitation (restless) o Tired o Embarrassment	o Embarrassment o Anxiety (feeling of a panic attack)	o Distress o Had urge to escape o Difficulty functioning
Action needed	Usually no action taken	o Used a fan o Took off clothing/wore lighter clothing o Drank water o Opened windows	o Stopped what you were doing o Removed clothes o Opened windows o Kept house cooler o Frequently used fans	o Took a cold shower o Held ice to skin
If occurred at night (night sweat)	N/A	o Awakened sometimes o Needed to uncover	o Awakened often o Removed covers and/or clothes	o Awakened frequently o Changed sheets or pajamas

Adapted from North Central Cancer Treatment Group
Sloan et. al., *J. Clin Onc* 2001

Appendix II. Functional Assessment of Cancer Therapy- Breast Cancer (FACT-B)

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix III. Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES)

FACT-ES (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
ES1	I have hot flashes/hot flushes	0	1	2	3	4
ES2	I have cold sweats	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
ES4	I have vaginal discharge	0	1	2	3	4
ES5	I have vaginal itching/irritation	0	1	2	3	4
ES6	I have vaginal bleeding or spotting	0	1	2	3	4
ES7	I have vaginal dryness	0	1	2	3	4
ES8	I have pain or discomfort with intercourse	0	1	2	3	4
ES9	I have lost interest in sex	0	1	2	3	4
ES10	I have gained weight	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
ES11	I have breast sensitivity/tenderness	0	1	2	3	4
ES12	I have mood swings	0	1	2	3	4
ES13	I am irritable	0	1	2	3	4
BRM1	I have pain in my joints	0	1	2	3	4

Appendix IV. Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index

Name_____ Date_____

Instructions:
The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all the questions.

1. During the past month, when have you usually gone to bed at night?
   usual bed time_____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   number of minutes_____

3. During the past month, when have you usually got up in the morning?
   usual getting up time_____

4. During the past month, how many hours of *actual* sleep did you get at night? (This may be different than the number of hours you spend in bed).
   hours of sleep per night_____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you……

(a) Cannot get to sleep within 30 minutes

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(b) Wake up in the middle of the night or early morning

Not during the past month____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

(c) Have to get up to use the bathroom

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(d) Cannot breathe comfortably

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(e) Cough or snore loudly

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(f) Feel too cold

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(g) Feel too hot

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(h) Had bad dreams

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(i) Have pain

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

(j) Other reason(s), please describe_____
_____
___

How often during the past month have you had trouble sleeping because of this?

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

   Very good_____
   Fairly good_____
   Fairly bad_____
   Very bad_____

7. During the past month, how often have you taken medicine (prescribed or " over the counter") to help you sleep?

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month____	Less than once a week_____	Once or twice a week_____	three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

   No problem at all_____
   Only a very slight problem__
   Somewhat of a problem_____
   A very big problem_____

10. Do you have a bed partner or roommate?

    No bed partner or roommate _____
    Partner/roommate in other room _____
    Partner in same room, but not same bed____
    Partner in same bed _____

11. How often do you feel tired during the following times during the day?

Morning:

0	1	2	3
most days	often	occasionally	never

Afternoon:

0	1	2	3
most days	often	occasionally	never

Evening:

0	1	2	3
most days	often	occasionally	never

Appendix V. Acupuncture Expectation Scale

Name of participant: _____

Date: _____

ACUPUNCTURE EXPECTATION SCALE

Every individual may have different expectation for the effects of acupuncture. If we use the following sentences to describe your expectation of acupuncture's effect on your hot flash symptoms after the entire course of acupuncture therapy, how much do you agree? For each statement, please choose the closest answer.

	Not at all agree	A little agree	Moderately agree	Mostly agree	Completely agree
My hot flash symptoms will improve a lot	1	2	3	4	5
I will be able to cope with my hot flash symptoms better	1	2	3	4	5
The symptoms of my hot flashes will disappear	1	2	3	4	5
My energy level will increase	1	2	3	4	5

Appendix VI. Acupuncture Treatment Form

Name of patient:_____ Hospital ID# :_____Date of Visit :_____Number of Sessions:_____out of 12/6

1. Please make "X" below to indicate the points used, *De Qi* sensation, and electro-stimulation used at today's session:

Points	LR3	K3	SP6	ST36	CV6	HT7	LI11	GV20	Y.T.	S.M.	Heart	Note
L												
R												
DeQi												
e-stim												

2. Please record on the line below regarding the electroacupuncture parameters used at today's session:
   Frequency: _____Hz; Pulse width: _____(40/350)μS; Pulse mode:_____(DD/Conti.)
3. Please ask the study patient when you have <u>just completed the adjustment</u> of during the treatment session today and make a "X" below: "Please tell me, on a scale from 0 to 10, the intensity of the needling sensation you are experiencing right now; 0 is that you do not feel anything at all and 10 is the strongest sensation you could imagine."

Intensity Score	0	1	2	3	4	5	6	7	8	9	10
X											

4. At the end of the session, please make "X" below on the patient's immediate responses for today's treatment:

	Question Items	**Yes**	**No**	**Unknown**
a	Did the patient appear to be relaxed?			
b	Was the patient dozed off during the treatment?			
c	Did the patient still feel the "tapping" sensation at the end of the session?			
d	Was the pulse/heart rate of the patient slower than the beginning of the session?			
e	Has the patient's skin temperature of hands noticeably changed (either warmed up or cooled down)?			
	Other observations?			

5. Did the patient report any adverse event per CTCAE v4.0 at this visit? Please make a circle below:
NO YES, If " YES" is answered, please describe the details here:

Adverse Event	**Start Date**	**Stop Date**	**Grade (1-5)** Mild, Moderate, Severe, Life Threatening, Fatal	**Attribution** unrelated, unlikely, possible, probable, definite	**Comments**
Skin bruise					
Hematoma					
Skin infection					
Presyncope					
Syncope					
Nausea					

6. Was today's session completely followed the study protocol requirement?

Question Item	YES	NO	If "no", please explain here
Was today's session completely followed the study protocol requirement?			

Signature of acupuncturist Name of acupuncturist

Appendix VII. Medication Log

Date: _____

The following are possible medications or supplements you might be using at home after chemotherapy. You might be taking medications that are not in the list as well. Please indicate ALL prescription medications AND over-the-counter medications you have taken at home **in the past 5 days**.

Medication Treatment Log

Name of Medication	Did you take any of these?		Dose of each pill (5 mg? or 10 mg?)	How MANY pills did you take EACH TIME?	How OFTEN did you take it EACH DAY?	Date Started (MM/DD/YY)	Date Stopped (MM/DD/YY)	For staff use only Total dose in the past 5 days
Tamoxifen	Y	N						
Fulvestrant (Faslodex)	Y	N						
Anastrozole (Arimidex)	Y	N						
Letrozole (Femara)	Y	N						
Exemestane (Aromasin)	Y	N						
Gosrelin (Zoladex)	Y	N						
Leuprolide (Lupron)	Y	N						
Clonidine (Catapres)	Y	N						
Methyldopa	Y	N						
Venlafaxine (Effexor)	Y	N						
Escitalopram (Lexapro)	Y	N						
Paroxetine (Paxil)	Y	N						
Fluoxetine (Prozac)	Y	N						
Gabapentin (Neurontin)	Y	N						
Duloxetine (Cymbalta)	Y	N						
Pregabalin (Lyrica)	Y	N						
Dietary Supplements:	Y	N						
	Y	N						
	Y	N						
	Y	N						
Herbs:	Y	N						
	Y	N						

Appendix VIII. Patient Recruitment Letter

Date

Dear,

We are conducting a research study to explore whether acupuncture can help reduce the symptoms associated with hot flashes. Hot flashes and night sweats are common side effects of hormonal medications like tamoxifen and aromatase inhibitors that are used to treat breast cancer. These symptoms can affect mood, sleep, and quality of life. Though prescription medications can reduce hot flashes and night sweats for some patients, they are not helpful for all patients and can sometimes cause other side effects. New treatments are needed to help reduce hot flashes and night sweats in women with breast cancer.

This study is being done to see if acupuncture can help reduce the number and intensity of hot flashes and night sweats that women experience during breast cancer treatment. The acupuncture program will take place in the Leonard P. Zakim Center for Integrative Therapies and Healthy Living at the Dana-Farber Cancer Institute. If you decide to participate, you will be involved with the study for about 20 weeks. Participants will be randomly assigned to one of two groups – an immediate acupuncture group or a delayed acupuncture group. The immediate acupuncture group will receive 20 acupuncture sessions over the first 10 weeks after joining the study. The delayed acupuncture group will receive 10 acupuncture treatments after a 10-week waiting period. All participants will be asked to complete a set of questionnaires and to keep a hot flash diary.

This study has been approved by the Institutional Review Board of the Dana-Farber Cancer Institute.

Please complete the response card and return it in the envelope provided. If we do not hear back from you within a month, we will follow-up with a call to see if you are interested in the study. If you have any questions or would like to discuss study participation, please contact [Study Coordinator] at 617-632-XXXX. Participation is voluntary and your decision will not affect your care at the Dana-Farber Cancer Institute in any way.

Thank you for considering this study.

Sincerely,

Dr. Weidong Lu and Dr. Jennifer Ligibel

Principal Investigators

Appendix IX. Study Flyer

Hot flashes are common in women being treated for breast cancer.

This study is being done to see if acupuncture treatments can help reduce hot flashes.

Talk to your doctor about whether this study is a good fit for you.

The Acupuncture for Hot Flashes Study

DANA-FARBER CANCER INSTITUTE

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

www.dana-farber.org

For more information, please contact:

[Study Coordinator]

[CRC Phone Number]

[CRC Email Address]

Principal Investigator:

Weidong Lu, MB, MPH, PhD

1/19/2024 10:28 AM

(Dana-Farber)

Do you have Hot Flashes?

Are you receiving hormone therapy for breast cancer?

Ask your doctor about

The Acupuncture for Hot Flashes Study

A Dana-Farber study for Hot Flashes associated with hormone therapy

You may be able to join this study if:

- ✓ You have already completed any planned chemotherapy and/or surgery
- ✓ You are currently receiving hormone therapy for stage I-III breast cancer, for example:
  - Tamoxifen (Nolvadex, Soltamox)
  - Anastrozole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)
  - Other hormone therapies
- ✓ You are experiencing persistent Hot Flashes

Study participants will be **randomly** assigned to one of the following groups:

Immediate Acupuncture Group

- 10-week acupuncture treatment schedule (20 total sessions)
  - Twice a week for 10 weeks
- 10-week follow-up period

Delayed Acupuncture Group

- Initial 10-week delay
- 10-week acupuncture treatment schedule (10 total sessions)
  - Once a week for 10 weeks

Frequently Asked Questions

What is acupuncture?

- Acupuncture is a complementary therapy in which thin, sterile, disposable needles are inserted into various spots on the body with the goal of reducing hot flashes.

Can I choose my treatment schedule?

- No – you will be randomly assigned to one of the two groups. You should only agree to participate if you are willing to follow *either* schedule.

How long is the study?

- If you are eligible to join the study you will be involved in the study for about 20 weeks.

If I join, what do I have to do?

- ✓ Keep a Hot Flash diary
- ✓ Complete a series of questionnaires
- ✓ Undergo a blood draw before you start and at week 10
- ✓ Follow the assigned acupuncture schedule

Appendix X. Recruitment Language for DFCI Listservs

Do you experience frequent hot flashes while receiving hormonal therapy for breast cancer? If yes, you may be eligible for a study investigating whether acupuncture treatments can help reduce the frequency and severity of hot flashes in women receiving hormonal therapy for breast cancer. You may be able to join this study if:

- You have completed any planned chemotherapy and/or surgery for your breast cancer
- You are currently receiving hormonal therapy for stage I-III breast cancer, for example:
    - Tamoxifen (Nolvadex, Soltamox)
    - Anastrozole (Arimidex)
    - Letrozole (Femara)
    - Exemestane (Aromasin)
    - Other hormonal therapies
- You are experiencing persistent hot flashes

If you are interested in participating or would like to learn more about this study, please contact the research manager at atanasijevic@partners.org or 617-632-5584.

Appendix XI. Information on Rally at Partners Healthcare

Headline: Do you experience frequent hot flashes while receiving hormonal therapy for breast cancer?

Summary
We are studying whether acupuncture treatments can help reduce the frequency and severity of hot flashes in women receiving hormonal therapy for breast cancer.

Custom URL: https://rally.partners.org/study/acupuncture_hot_flash

Category
• Breast Cancer
• Acupuncture
• Hormones

Project Image

Funding Source: Other
At which institutions is the project being conducted? Dana Farber Cancer Institute
IRB Organization Dana Farber Cancer Institute
IRB Protocol Number 18-371
Recruitment Start Date 02/01/2019
Recruitment End Date 02/29/2020
Team
Principal Investigator Weidong Lu, MB, PhD, MPH
Email Address (for internal use only) weidong_lu@dfci.harvard.edu
Phone Number (for internal use only) 6176324350
PI Organization Dana Farber Cancer Institute
Project Contact Anna Tanasijevic, MPH, anna_tanasijevic@dfci.harvard.edu, 6176325584

Research
What are you studying?
This study is being done to see if acupuncture can help reduce the number and intensity of hot flashes and night sweats that women experience during breast cancer treatment. Hot flashes and night sweats are common side effects of hormonal medications like tamoxifen and aromatase inhibitors that are used to treat breast cancer. These symptoms can affect mood, sleep, and quality of life. Though prescription medications can reduce hot flashes and night sweats for some

patients, they are not helpful for all patients and can sometimes cause other side effects. New treatments are needed to help reduce hot flashes and night sweats in women with breast cancer.

Why is it important?
Acupuncture is a complementary therapy in which hair-thin, sterile disposable needles are inserted into various spots on your skin, with the goal of affecting body's natural healing system. Acupuncture has been tested in clinical trials in cancer patients and has been shown to be helpful in treating a number of side effects of cancer treatment, such as nausea and vomiting from chemotherapy. A few early studies have suggested that acupuncture may help to lessen hot flashes, but more information is needed about the benefits of acupuncture in breast cancer patients.

Clinical Trial Phase: This project does not study a drug or biologic product. Not applicable.

Eligibility
Who can participate?

- Women with a history of Stage I-III hormone-receptor positive breast cancer;
- Must have completed all primary chemotherapy and surgery; Must be receiving hormonal therapy (e.g. Tamoxifen and/or Aromatase inhibitors) with or without ovarian function suppression for at least 4 weeks at study entry;
- Must have persistent hot flashes for at least 4 weeks AND have more than 14 episodes of hot flashes per week (2 hot flashes per day) during the week prior to the study entry.

Who cannot participate?

- Cannot be undergoing chemotherapy or planned surgery during the study period;
- Cannot change hormonal therapy regimen during the study period;
- Cannot have used acupuncture for hot flashes within 6 months prior to the study entry;
- Cannot be starting a new medication-based treatment for hot flashes, such as selective serotonin reuptake inhibitors (SSRIs) and/or anti-convulsant for less than 4 weeks prior to study entry. Participants may continue with medications or therapies for the treatment of hot-flashes while participating in the study if the medication has been taking for more than 4 weeks prior to study entry AND the dose of the medication is going to be kept consistently during the study.

Age: 18 years or older
Gender: Female

Participation Details
Estimated time commitment: 20 sessions over 10 weeks
What may participants be asked to do?
If you decide to participate, you will be involved in the study for about 20 weeks. Participants will be randomly assigned to one of two groups – an immediate acupuncture group or a delayed acupuncture group.

- The immediate acupuncture group will receive 20 acupuncture sessions over the first 10 weeks after joining the study.
- The delayed acupuncture group will receive 10 acupuncture treatments after a 10-week waiting period.
- All acupuncture treatments will be adminstered by Zakim Center staff acupuncturists trained on the study.

We will collect various measures throughout the study.

- Medical history & questionnaires. Participants will be asked to complete questionnaires, a medication log, and a hot flash diary at various time points throughout the study.
- Blood tests. There are two study-associated blood draws.
- One at Baseline and one at Week 10. Activity tracker. Participants will be asked to wear an activity tracker watch for a full week at Baseline, Week 10, and Week 20.

Does your project involve any of the following activities?

- Survey
- Personal health tracking
- Blood draw
- Office visit

Travel Requirements

- Accessible by public transportation
- Parking available
- Parking reimbursed

Where will participants need to go?
Zakim Center for Integrative Therapies and Healthy Living, 450 Brookline Ave, SW140, Boston, MA 02215

Benefits and Compensation
What will participants receive?

- Participants may receive up to 20 acupuncture sessions, depending on their randomization group.
- Participants will receive a voucher to cover parking after each acupuncture treatment session or study-related visit.
- Participants will receive a $10 gift card at Week 10 in exchange for the completion of all study-related surveys and logs required from Baseline to Week 10.
- Participants will receive an additional $10 gift card at Week 20 in exchange for the completion of all study-related surveys and logs required from Week 10 to Week 20.

Select all that apply: Gift card
Dollar Amount (up to): $20.00

Appendix XII. Options for Treatment Location

Hot Flash Study – Options for Treatment Location

1) **Name:** Zakim Center
   Location: 450 Brookline Ave 1st floor of Dana-Farber's Dana/Shields Warren Building SW 140, Boston, MA 02215
   Phone number: (617) 244-2833
   Available Time: M-F, clinic hours vary

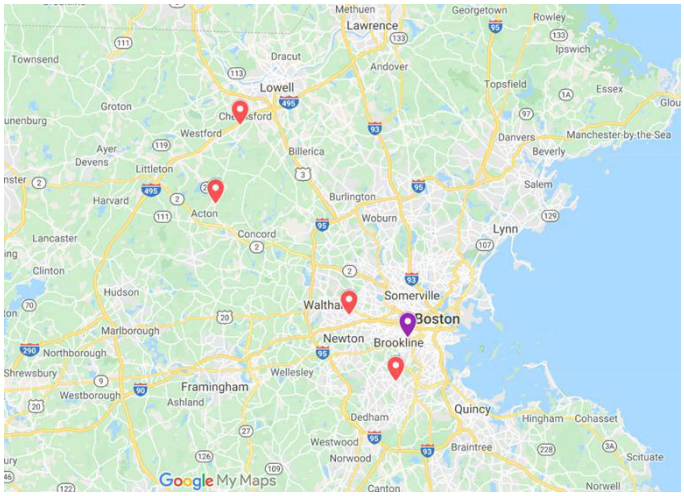
2) **Name:** Weidong Lu clinic
   Location: 55 Chapel Street, Suite 004, Newton, MA 02458
   Phone number: (617) 244-2833
   Available Time: Thursday 9am-5:00pm, Saturday 9am-5pm

3) **Name:** Dongyan Yu clinic
   Location: 271 Great Road, Suite 2, Acton, MA 01720
   Phone number: (978) 257-7891
   Available Time: Tuesday 8am-5:00-pm, Thursday 8am-5pm, Saturday by appointment

4) **Name:** Zhiping Li clinic
   Location: 48 Cummings HWY, Roslindale, MA 02131
   Phone: (617) 323-7809
   Available Time: Monday through Saturday 10am-5 pm, except on Tuesdays

5) **Name:** Joy Yue Zhang clinic
   Location: 175 Littleton Rd. Unit 6, Westford, MA 01886
   Phone: (978) 692-8889
   Available Time: Monday, Tuesday, Friday 8am-6pm; Thursday 12pm-6pm

Hot Flash Study Participating Private Clinic Locations



Appendix XIII. Sleep Diary

Protocol #: 18-371 **Participant ID: _____**

Weekly Sleep Diary (Please complete upon awakening)

	Sample	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	04 / 05 / 19 MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY	___/___/___ MM DD YY
1. What time did you get into bed to try to go to sleep?	10:15 p.m.							
2. How long did it take you to fall asleep?	55 min							
3a. How many times did you wake up, not counting your final awakening?	6 times							
3b. In total, how long did these awakenings last?	2 hours 5min							
4. What time was your final awakening?	6:35 a.m.							
5a. How many times did you nap or doze?	2 times							
5b. In total, how long did you nap or doze?	1 hour 10 min							
6. Did you have any hot flash(es) that interfered with your sleep? If yes, how many?	( ) No (x) Yes (x) 1-2 ( ) 3-4 ( ) 5 or more							

Adopted from the Consensus Sleep Diary
Carney et al. *Sleep* 2012

Appendix XIV. Insomnia Severity Index

Insomnia Severity Index

For each question, please mark the number that best describes your answer. Please rate the CURRENT (i.e. LAST MONTH) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with you CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think you sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

Appendix XV. Opt Out Card for Patient Recruitment Mailing

ID Number_____

If you do not wish to participate, please check the box below and return this card by mail.

☐ I choose not to participate in this study. I do not wish to be contacted by this study in the future. I understand that this will not affect my care at Dana-Farber Cancer Institute.

Thank you.

ID Number_____

If you do not wish to participate, please check the box below and return this card by mail.

☐ I choose not to participate in this study. I do not wish to be contacted by this study in the future. I understand that this will not affect my care at Dana-Farber Cancer Institute.

Thank you.

ID Number_____

If you do not wish to participate, please check the box below and return this card by mail.

☐ I choose not to participate in this study. I do not wish to be contacted by this study in the future. I understand that this will not affect my care at Dana-Farber Cancer Institute.

Thank you.

ID Number_____

If you do not wish to participate, please check the box below and return this card by mail.

☐ I choose not to participate in this study. I do not wish to be contacted by this study in the future. I understand that this will not affect my care at Dana-Farber Cancer Institute.

Thank you.

Kelsey Maymon
Dana-Farber Cancer Institute
450 Brookline Ave, SW560
Boston, MA 02215

Kelsey Maymon
Dana-Farber Cancer Institute
450 Brookline Ave, SW560
Boston, MA 02215

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Boston, MA 02215

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Dana-Farber Cancer Institute
450 Brookline Ave, SW560
Boston, MA 02215

Appendix XVI: Plain Language Summary

Clinical Research Results
Plain Language Summary

Study Name: Acupuncture for Hot Flashes Study

This study was done to learn more about the effect of acupuncture on hot flash-related menopausal symptoms in women with estrogen receptor-positive (ER+) breast cancer who were being treated with hormonal medications (HM) in the United States of America (USA), China, and South Korea.

Thank you to all the participants in this study. We can make progress in managing the side effects of breast cancer treatment through dedicated volunteers who join research studies like this one. We are very grateful.

It is important to note that this is a summary of the overall results of the clinical trial.
Individual participants might have had different results. Other trials might also have different results.

1. Why Was This Trial Done?

Hormonal medications (HM) reduce the chance of cancer recurrence and death in patients with ER+ breast cancer, but may have multiple side effects, including hot flashes.

This trial was done to find out:

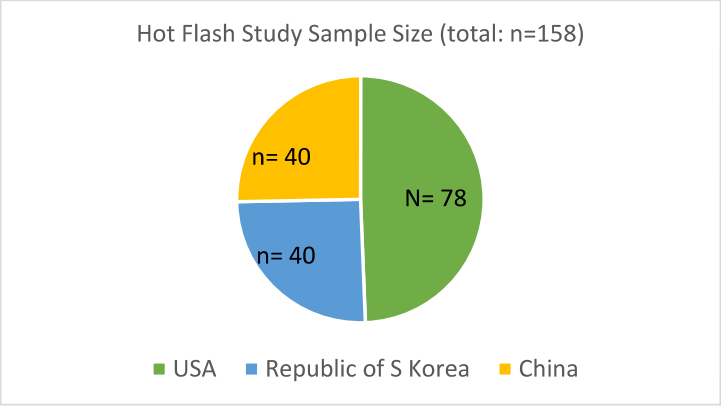
1) whether acupuncture would decrease the number and severity of hot flashes in breast cancer survivors taking HM in the USA, China, and South Korea,
2) whether acupuncture could improve the quality of life in these same participants.

2. Who Took Part?

A total of 158 participants took part in the study.

Participants in this study:

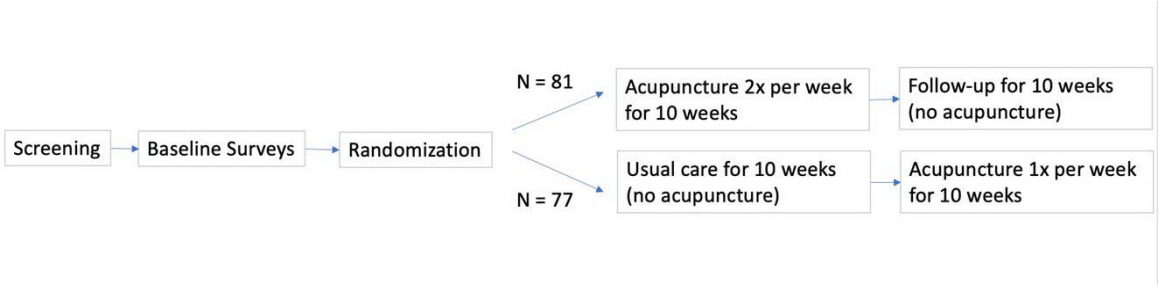
- had estrogen receptor-positive (ER+) breast cancer,
- had completed primary chemotherapy and surgery,
- were being treated with hormonal medications (HM) and
- reported getting hot flashes for at least 4 weeks, with at least 14 hot flashes per week.



3. What Treatment Was Studied?

The study treatment was acupuncture given 2 times per week, for 10 weeks, compared to no acupuncture for 10 weeks. The study looked at whether there was a change between baseline and week 10 in the number and severity of hot flashes and other symptoms and then compared the two study groups.

Participants in the study were randomly assigned to one of the two study groups to decrease differences between the groups. The study flow is described here:



In weeks 10 to 20, the two study groups switched treatments. Participants who received no acupuncture for the first 10 weeks then received acupuncture once per week for 10 weeks. This was called the "delayed acupuncture" group. Participants who received acupuncture for the first 10 weeks did not receive acupuncture between weeks 10 and 20.

Three surveys were used to find out if acupuncture had an effect:

- the Endocrine Symptom Subscale (ESS) was used to assess hormonal symptoms,
- the Hot Flash Score (HFS) was used to measure the number and severity of hot flashes,
- The FACT-B measured disease-specific quality of life in patients with breast cancer.

4. What Were The Results?

Overall, this study found significant decreases in hot flashes and hormonal symptoms after 10 weeks of acupuncture given 2 times per week.

When a result is significant, it means the result was unlikely to have happened by chance.

At week 10, more participants in the acupuncture group (64%) had improvements in the number and severity of hot flashes, compared with the control group (18%).

Also, more participants (54%) experienced a general improvement in all hormonal symptoms in the acupuncture group vs the control group (26%).

The study also found that breast cancer-specific quality of life was significantly improved at week 10 in the acupuncture group.

Participants in the delayed acupuncture group (who started acupuncture at week 10 and received 10 weekly sessions) also reported significant improvements in hormonal symptoms from week 10 to week 20.

Overall, these findings show that many participants felt acupuncture decreased the number and severity of hot flashes, and improved their quality of life.

5. What Were The Side Effects?

There were no acupuncture-related side effects reported by participants.

6. How Has This Trial Helped?

This study found that acupuncture could help reduce the side effects of hormonal medications, which might help patients keep taking them.

Future research could look at whether improving hot flashes and other hormonal symptoms leads to more people completing cancer treatment and whether it ultimately improves cancer-related outcomes in women with breast cancer.

8. Where Can I Learn More About This Trial?

You can find more information about this trial at the links below:

- On www.clinicaltrials.gov: NCT03783546
- In the following publication(s):
    - https://pubmed.ncbi.nlm.nih.gov/35998768/
    - Link to results publication if it is published when we send this to participants

If you have questions about the trial or your experience, please speak to your treating provider.

Thank you again for your participation. We could not do this work without you.

These are the Dana-Farber Cancer Institute protocol IDs: 18-371 and 21-483

This study was supported by a grant of the Comprehensive and Integrative Medicine R&D project through the Comprehensive and Integrative Medicine Institute (CIMI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant Numbers: HI20C1753) and through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea.

Appendix XVII: Return of Results Experience Survey

Acupuncture for Hot Flashes Study Summary
Participant Experience Survey

[will be programmed into REDCap]

Hello!

You are being asked to complete this survey because we recently sent you the study results summary for the Acupuncture for Hot Flashes Study that you participated in. Thank you so much for being a study participant!

The purpose of this survey is to collect your opinions on the experience of receiving the study results summary. In case helpful, we have included a link here.

The survey is anonymous so we will not know if the responses came from you. We store our survey data on a password protected server. This survey should take about 10 minutes for you to complete.

We very much appreciate you taking the time to give us feedback!

For each question, please check the most appropriate response.

1. What is your age?
    a. 18-30
    b. 31-50
    c. 51-70
    d. 71 and older

2. What is your race?
    a. American Indian or Alaska Native
    b. Asian
    c. Black or African American
    d. Native Hawaiian or other Pacific Islander
    e. White
    f. Other
    g. Prefer not to answer

3. How would you rate your general knowledge about breast cancer?
    a. Very informed
    b. Somewhat informed

c. Not very informed
d. Not at all informed

4. How would you rate your general knowledge about acupuncture?
   a. Very informed
   b. Somewhat informed
   c. Not very informed
   d. Not at all informed

5. How would you rate your general knowledge about clinical trials (also called human research studies or clinical research studies)?
   a. Very informed
   b. Somewhat informed
   c. Not very informed
   d. Not at all informed

6. Do you recall which study group you were randomly assigned to?
   a. Yes – immediate acupuncture arm.
   b. Yes – delayed acupuncture arm.
   c. No – I'm not sure which arm I was assigned to.

7. The study summary told me everything I wanted to know.
   a. Strongly disagree
   b. Slightly disagree
   c. Neither
   d. Slightly agree
   e. Strongly agree

8. The information in the study summary was easy to understand.
   a. Strongly disagree
   b. Slightly disagree
   c. Neither
   d. Slightly agree
   e. Strongly agree

9. I am glad I found out the study results.
   a. Strongly disagree
   b. Slightly disagree
   c. Neither
   d. Slightly agree

e. Strongly agree

10. Finding out the study results was upsetting.
    a. Strongly disagree
    b. Slightly disagree
    c. Neither
    d. Slightly agree
    e. Strongly agree

11. In general, do you think researchers *should* share the overall results of a study (that is, summary results, not individual results or data) with study participants?
    a. Yes
    b. No
    c. I am not sure

    Please explain your answer:

    If YES, how do you think researchers should share the overall study results with participants? (please select up to three options)
    a. Email
    b. Website
    c. Letter mailed to home address
    d. In-person meeting
    e. Phone call
    f. Social media
    g. As long as results are shared, it doesn't matter how
    h. Other: please specify

Dana-Farber Cancer Institute

450 Brookline Avenue
Boston, MA 02215-5450

Dear [participant name],

We are reaching out to you from Dana-Farber Cancer Institute about the Acupuncture for Hot Flashes study, which you previously participated in. As a reminder, this study was done to learn more about the effect of acupuncture on hot flash-related symptoms in women with estrogen receptor-positive (ER+) breast cancer who were being treated with hormonal medications (HM).

We are reaching out to notify you that we have completed the primary analyses of the study and would like to share a summary of these results with you. We would also like to ask you to complete a 5-minute survey about the experience of receiving these results.

If you are interested in receiving these results, please call our study coordinator at [study coordinator phone number] or email at [study coordinator email].

Once you have confirmed that you are interested, we will email you a summary of the study results and a link to complete the survey.

If we do not hear back from you within a month, we will follow-up with a call to see if you are interested in receiving the study results and the experience survey.

Participation is voluntary and your decision will not affect your care at Dana-Farber Cancer Institute in anyway.

Thank you for your time and consideration,

Dr. Weidong Lu

Principal Investigator