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Long-term follow-up of acupuncture and hormone therapy on hot flushes in women with breast cancer: a prospective, randomized, controlled multicenter trial

Authors: J. Frisk^{ab} S. Carlhäll^a A. -C. Källström^b L. Lindh-Åstrand^a A. Malmström^c M. Hammar^a

Affiliations: ^a Division of Obstetrics and Gynaecology, Department of Molecular and Clinical Medicine, Faculty of Health Sciences,

^b Department of Surgery, County Council Östergötland, Sweden

^c Department of Oncology, University Hospital of Linköping,

Abstract

Objective To evaluate the effects of electro-acupuncture (EA) and hormone therapy (HT) on vasomotor symptoms in women with a history of breast cancer.

Methods Forty-five women were randomized to EA ($n = 27$) for 12 weeks or HT ($n = 18$) for 24 months. The number of and distress caused by hot flushes were registered daily before, during and up to 24 months after start of treatment.

Results In 19 women who completed 12 weeks of EA, the median number of hot flushes/24 h decreased from 9.6 (interquartile range (IQR) 6.6-9.9) at baseline to 4.3 (IQR 1.0-7.1) at 12 weeks of treatment ($p < 0.001$). At 12 months after start of treatment, 14 women with only the initial 12 weeks of EA had a median number of flushes/24 h of 4.9 (IQR 1.8-7.3), and at 24 months seven women with no other treatment than EA had 2.1 (IQR 1.6-2.8) flushes/24 h. Another five women had a decreased number of flushes after having additional EA. The 18 women with HT had a baseline median number of flushes/24 h of 6.6 (IQR 4.0-8.9), and 0.0 (IQR 0.0-1.6; $p = 0.001$) at 12 weeks.

Conclusion Electro-acupuncture is a possible treatment of vasomotor symptoms for women with breast cancer and should be further studied for this group of women.

Keywords: Acupuncture; Breast Neoplasms; Hot Flushes; Hormone Replacement Therapy; Menopause

Introduction

Most menopausal women suffer from vasomotor symptoms with hot flushes and sweating, which may interfere with daytime activities, sleep and quality of life [1-3]. Hot flushes are more common, severe, and last longer in women with breast cancer than in healthy postmenopausal women [4-7]. Adjuvant therapy like tamoxifen may increase both frequency and intensity of flushes [8-10]. Hormone therapy (HT) with estrogen combined with progestagens effectively decreases hot flushes and thereby improves night sleep and quality of life [11]. Prospective studies have, however, shown that HT increases the risk of cardiovascular events in older women and in women with cardiovascular disease [12, 13]. Long-term HT increases the risk of developing breast cancer [12, 14]. Retrospective studies

have, however, been unable to show increased recurrence rate with HT [15, 16], although selection bias may contribute to the results.

The incidence of breast cancer world-wide rose 30-40% from the 1970s to the 1990s. In Sweden, the incidence increased by 32% from 1986 to 141.3/100 000 women in 2005 [17]. Mortality is, however, stable or decreasing [18]. The rising number of breast cancer survivors, combined with their high prevalence of vasomotor symptoms, has raised the demand for non-hormonal treatments of menopausal symptoms for these women.

The HABITS study (Hormonal replacement therapy after breast cancer - is it safe?) aims to analyze prospectively if women with breast cancer would benefit from HT or any non-hormonal alternative, and to determine whether HT would affect the risk of recurrence or survival [19]. Several non-hormonal treatments have been suggested [20-22], but none appears as effective as HT. Acupuncture has been associated with a decreased number and intensity of hot flushes in menopausal women, both with and without breast cancer [23-27]. The decrease was not as pronounced as with HT, but more than described for placebo treatment [11, 22, 28]. No prospective study has reported the decrease over more than 6 months, whereas a retrospective study reported effects of acupuncture completed with self-acupuncture over several years [29]. Acupuncture has been tried because it seems to increase central β -endorphin activity [30] which may make thermoregulation more stable and in turn decrease vasomotor symptoms [23, 31, 32]. Acupuncture has not yet been sufficiently compared with placebo. Although placebo needles exist [33-35], they are probably not completely non-effective, and induce neuronal stimulation [36, 37]. Moreover, a placebo needle was not available when this study was designed.

Acupuncture treatment of climacteric symptoms has, to our knowledge, mainly been studied in short trials with one single university unit involved and has not been compared with HT in women with breast cancer. The present study aimed to assess the long-term effect of acupuncture and HT on vasomotor symptoms in women with a treated breast cancer.

Material and Methods

Patients

This randomized, controlled study was part of an international, multicenter study, HABITS [19], involving patients from three centers in Sweden. The inclusion was between April 1998 and December 2002. The women were referred from breast surgeons or oncologists because they suffered from breast cancer and vasomotor symptoms severe enough to merit therapy. At the screening visit to a gynecologist, all women underwent a physical and gynecological examination. The inclusion criteria were: previously completed treatment for breast cancer *in situ*, T1 and T2 tumors with four or fewer lymph nodes positive for metastasis, T3 tumors [38] without metastasis, no clinical or mammographic signs of recurrence, and vasomotor symptoms needing treatment according to the woman herself. A verified postmenopausal hormonal status was not demanded.

The exclusion criteria were: ongoing treatment for breast cancer other than tamoxifen/torimefen, other malignancies, metachronous breast cancer, thromboembolic disease, ongoing liver disease, porphyria or cerebrovascular lesion and, added in 2001, active cardiovascular disease.

The computer-generated randomization in blocks of eight for the HABITS study occurred at the University of Uppsala [19]. A total of 219 women were randomized to HT and 215 to non-hormonal treatment. In our substudy, all 45 women in our region were invited to take part, eight from Kalmar, 25 from Linköping and 12 from Norrköping. In all, 27 women were randomized to non-hormonal and 18 to hormonal treatment; the groups were uneven because the three centers did not fill each of their blocks. All women accepted either HT or electro-stimulated acupuncture (EA), which was the suggested non-hormonal alternative. The specific type of HT used was, according to the protocol, decided locally by the gynecologist. One woman offered EA could not start due to practical reasons, one changed to HT before starting EA, and two did not fill in any log books or other data and did not show up at the follow-up visits. In all, 23 women, who actually started EA and registered log books before and during treatment, were analyzed in the EA group, and 18 in the HT group (Figure 1). Baseline data are shown in Table 1.

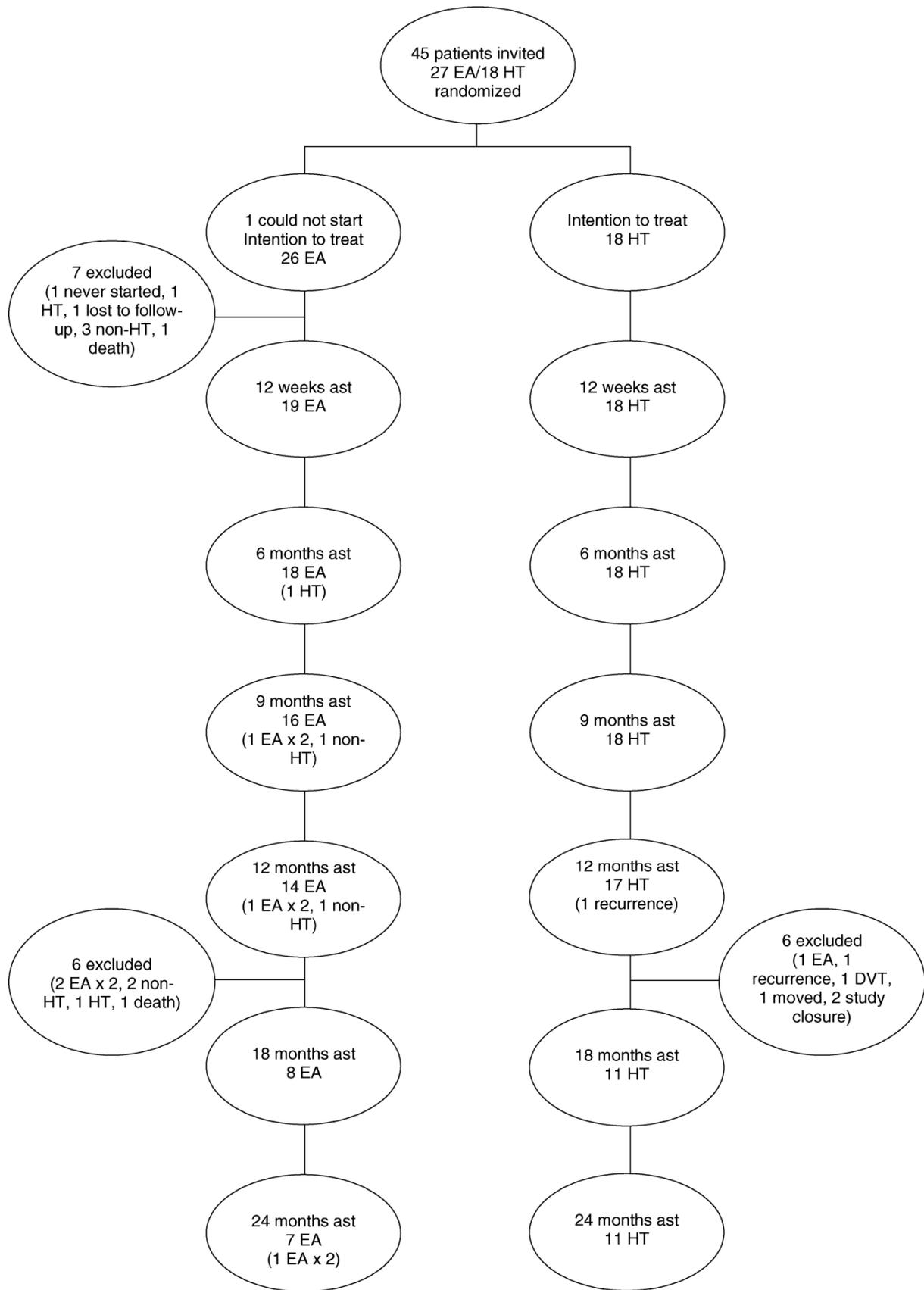


Figure 1. Chart diagram showing the inclusion of patients with breast cancer and vasomotor symptoms in the study of electro-acupuncture and hormone therapy of vasomotor symptoms. ast, after start of treatment; DVT, deep venous thrombosis

Table 1: Demographic data at baseline (means or numbers) for 41 women with climacteric symptoms and breast cancer. There were no significant differences between the groups

	Electro-acupuncture (n = 23)	Hormone therapy (n = 18)
Age (years)	56.5	53.4
Cancer diagnosis (years since)	4.5	4.2
Menopause (years)	6.5	7.4
Body mass index (kg/cm ²)	23.1	24.5
Smokers (yes)	5	3
Ongoing tamoxifen treatment (yes)	4	4
Change of tamoxifen treatment during the time included (yes)	0	0

Treatment

Hormone therapy

Women less than 2 years after menopause were given a sequential estrogen/progestagen combination; if they were more than 2 years after menopause, they were given continuous combined estrogen/progestagen. If hysterectomized, the women received unopposed estrogen. Tibolone was not allowed. According to the protocol, HT should be used for 24 months and then be stopped. Due to a safety analysis of the HABITS study [19], showing increased recurrence risk in the HT group, all women were recommended to stop HT. Consequently, two women in our study stopped HT after 1 year.

Electro-acupuncture

In the EA group, treatment was given as previously described [23] by a physiotherapist for 30 min twice a week for the first 2 weeks, and once a week for 10 weeks. Six physiotherapists, educated and experienced in acupuncture, administered the EA, both at hospitals and private practices. They were instructed orally and in writing about the acupuncture points and not to discuss expected or experienced effects with the patients.

Monitoring

The patients were monitored with daily entries made in a log book, recording the numbers of hot flushes during day and night, and how disturbing they were (range 0 = no distress to 10 = worst possible distress) [23, 24]. The log books were filled in daily for 1-3 weeks before treatment, continuously during the first 12 weeks of treatment and thereafter for 1 week per month, altogether 24 months. The measuring points were baseline, the 12th week of treatment, and 1 week at 6, 9, 12, 18 and 24 months after start of treatment.

The baseline average number of hot flushes and degree of distress by flushes/24 h were calculated based on the log-book recordings during days 8-15 before the start of therapy. The slightly modified version [39] of the Kupperman's Index (KI) [40], filled in by the woman herself, was used to assess climacteric symptoms at the screening visit, and at the visits at 12 weeks, and 6, 9, 12, 18 and 24 months after start of treatment. The highest total score possible was 51.

Statistics

Analyses were made using the SPSS version 12.0.1. Missing data were completed in the log books and for the KI, by taking the mean of the previous and the following measurements for that specific patient (log book data in eight cases (3%), when including women with another period of acupuncture in 12 cases (5%), KI data in three cases (1%), when including women with another period of acupuncture in 6 cases (3%)).

Changes in flushes and KI were analyzed within and between both treatment groups using the analysis of variance (ANOVA) for repeated measures. The Wilcoxon signed rank sum test was used for paired comparisons within each group. The value of p for statistical significance was taken as 0.05.

Ethics

This study was approved by the Ethics Committee at the University of Linköping and performed according to the Declaration of Helsinki. The patients were informed about the study, both in writing and orally, before they gave their informed consent.

Results

Significant changes were seen in numbers of and distress by flushes in both groups at all measuring points. In the EA group, the flushes returned to some degree, and five women asked for additional treatment after 12 months (Figure 1). Both treatments had a persistent, significant effect over time, but with significant differences between groups (ANOVA), in favor of HT regarding number of flushes/24 h, distress caused by flushes and KI ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively) at 12 months after start of treatment.

Electro-acupuncture

Four of the 23 women starting EA never completed the 12 weeks of acupuncture (Figure 1). Three changed to other non-hormonal therapies due to insufficient effect, and one had breast cancer recurrence after 4 weeks of EA and passed away a few weeks later.

Sixteen of the 19 women (84%) asked for no other treatment than 12 weeks of EA during 1 year, and 7/19 (37%) during 24 months. Five of these 19 women had EA a second time within the 24-month study, and their number of flushes tended to decrease (from a median 5.0/24 h; interquartile range, IQR 4.6-6.7 to 2.3/24 h; IQR 2.2-5.3) after the second acupuncture treatment period. By the end of the study, 12/23 (52%) had asked for no other treatment than EA for 24 months. No adverse events possibly related to EA were registered.

Hormone therapy

Eleven out of 18 women completed 24 months of HT. Seven women were excluded for recurrence of cancer ($n = 2$), deep venous thrombosis ($n = 1$), premature ending of HT because of the safety analysis ($n = 2$), moved ($n = 1$), change to EA ($n = 1$) (Figure 1).

Numbers of hot flushes/24 h

Nineteen women completed 12 weeks of EA and their number of flushes was significantly decreased ($p < 0.001$) throughout the 24 months (Table 2). By including the five women who had a second period of EA, 12 women completed 24 months without any other kind of treatment than EA, with a median decrease in number of flushes from 9.6 (IQR 6.6-9.9; $n = 19$) at baseline to 4.3 (IQR 1.0-7.1; $n = 19$; $p < 0.001$) after 12 weeks from start of treatment, to 4.8 (IQR 1.9-6.8; $n = 16$; $p = 0.003$) at 12 months from start of treatment and to 2.9 (IQR 1.7-3.3; $n = 12$; $p = 0.003$) at 24 months from start of treatment.

Table 2: Median numbers and mean changes in numbers of hot flushes/24 h in the electro-acupuncture group

Time from baseline (months)	n	Median (IQR 25-75 percentile)	p*	Mean decrease (95% CI)**
0	19	9.6 (6.6-9.9)		
3	19	4.3 (1.0-7.1)	0.000	4.5 (2.5-6.5)
6	18	3.6 (1.6-6.9)	0.000	4.4 (2.4-6.4)
9	16	3.5 (1.4-6.9)	0.002	4.5 (2.1-6.9)
12	14	4.9 (1.8-7.3)	0.009	3.7 (1.1-6.2)
18	8	2.1 (0.9-4.0)	0.012	5.8 (1.8-9.8)
24	7	2.1 (1.6-2.8)	0.018	6.4 (2.3-10.5)

*Significance value of mean decrease, based on pair-wise comparisons with Wilcoxon's test;
**mean decrease denotes the decrease from baseline in the individual women who were followed to a certain time point.

IQR, interquartile range; CI, confidence interval

In the HT group ($n = 18$), their median number of flushes/24 h was decreased from 6.6 (IQR 4.0-8.9) at baseline to 0.0 (IQR 0.0-1.6) at 3 months follow-up ($p = 0.001$) without further changes.

Distress caused by hot flushes

In the EA group, the median distress caused by flushes decreased from 5.5 (IQR 4.2-6.9) at baseline to 2.4 (IQR 0.9-4.0; $n = 19$; $p < 0.001$) at 12 weeks from start of treatment, to 3.9 (IQR 2.3-5.0; $n = 14$; $p = 0.026$) at 12 months from start of treatment and to 2.3 (IQR 0.9-3.3; $n = 7$; $p = 0.018$) at 24 months after start of treatment. The HT group ($n = 18$) showed a decrease in distress caused by flushes from a median of 5.0 (IQR 1.5-7.9) at baseline to 0.00 (IQR 0.00-1.0) after 3 months of treatment ($p = 0.001$) without further changes.

The Kupperman Index score

ANOVA repeated measures analysis showed that treatment in both groups had a persistent, significant effect over time, with HT having the stronger effect (at 12 months, $p = 0.002$; at 24 months, $p = 0.039$; Table 3 and 4).

Table 3: Median scores and mean changes in Kupperman's Index in the electro-acupuncture group

Time from baseline (months)	n	Median (IQR 25-75 percentile)	p*	Mean decrease (95% CI)**
0	19	24.0 (19.3-29.3)		
3	19	12.0 (9.0-17.0)	0.000	12.9 (8.8-17.1)
6	18	13.5 (6.7-18.2)	0.000	11.8 (8.3-15.4)
9	16	14.0 (8.2-22.0)	0.002	9.8 (4.8-14.8)
12	14	13.0 (10.0-17.5)	0.002	11.4 (6.5-16.2)
18	8	12.5 (8.0-16.7)	0.035	12.8 (2.7-22.8)
24	7	8.0 (2.0-12.0)	0.018	18.1 (9.5-26.8)

*Significance value of mean decrease, based on pair-wise comparisons with Wilcoxon's test;
 **mean decrease denotes the decrease from baseline in the individual women who were followed to a certain time point
 IQR, interquartile range; CI, confidence interval

Table 4: Median scores and mean changes in Kupperman's Index in the hormone therapy group

Time from baseline (months)	n	Median (IQR 25-75 percentile)	p*	Mean decrease (95% CI)**
0	18	23.0 (15.5-27.7)		
3	18	6.0 (3.0-9.2)	0.000	13.8 (9.0-18.5)
6	18	6.5 (3.0-9.0)	0.001	13.9 (8.2-19.6)
9	18	7.5 (3.0-14.0)	0.001	12.9 (7.3-18.5)
12	17	6.0 (2.0-8.5)	0.000	15.0 (10.5-19.5)
18	11	7.0 (0.0-7.0)	0.008	14.1 (7.2-21.0)
24	11	4.0 (1.0-6.0)	0.007	15.9 (8.4-23.4)

*Significance value of mean decrease, based on pair-wise comparisons with Wilcoxon's test;
 **mean decrease denotes the decrease from baseline in the individual women who were followed to a certain time point
 IQR, interquartile range; CI, confidence interval

Discussion

In this prospective, randomized, multicenter, controlled study we found that 16 out of 19 women who had no other treatment than 12 weeks of EA received relief from their vasomotor symptoms over a period of 1 year. Twelve women out of the 19 needed no other treatment

than EA over the 24-month period. Five of those 19 women had another, shorter period of EA during the 2 years, and needed no further treatment after that.

Four women in the EA group reported no or very little effect of acupuncture during the 12 weeks of treatment. This is in line with earlier observations [29, 41], showing that about one out of five women could be regarded as 'resistant' to the mode of acupuncture given.

Thus, in our study, EA relieved vasomotor symptoms in most women with breast cancer, albeit the symptoms tended to come back during the 21-month follow-up. One question is whether this is caused by the treatment as such or by less specific placebo- or procedure-related effects; this should be evaluated with a proper placebo model. Placebo needles have been developed but probably cause neuronal stimulation [33, 34]. We are not aware of any study that has used the placebo acupuncture needle on hot flushes in women with breast cancer; when the present study was designed, no such needle was available. In our study, the long-lasting and profound effects on the vasomotor symptoms for up to 2 years contradict placebo effects which usually do not persist for more than 3 months. Furthermore, we have shown, in an earlier study, physiological effects of acupuncture treatment on vasomotor symptoms, with decreased urinary excretion of the vasodilating, sweat-inducing peptide CGRP during successful therapy²³. It could also be argued that the decrease in flushes after 2 years is a physiological reduction over time, something that is not possible to exclude without an untreated control group, which we considered unethical in this group of patients.

Although EA seems to be a promising alternative, HT is more effective than EA in decreasing the numbers of flushes and the distress they cause. However, the HABITS study found higher recurrence rate of breast cancer in the HT group than in the non-hormonal group [19]. Although another Swedish study was unable to show increased risk of recurrence in the HT group [42], HT should probably not be the first alternative in women with a history of breast cancer.

Only one woman of 27 randomized to non-hormonal therapy chose to have another kind of non-hormonal treatment instead of trying acupuncture. The reason for her not to receive EA was lack of practical travel arrangements. Thus, women do not seem reluctant to try acupuncture.

To our knowledge, this is the first prospective study that has tried to assess long-term effects of acupuncture treatment for vasomotor symptoms in an 'everyday' setting involving, for example, different physiotherapists at different locations. Although it is a study of limited size, the results are positive and support previous reports that acupuncture is an alternative to HT for relieving vasomotor symptoms. Almost 85% of the women who suffered from climacteric symptoms, to the extent that they were willing to accept HT despite their breast cancer, were satisfied with 12 weeks of acupuncture as the sole therapy for 1 year, and 63% for 2 years.

The survival rate from breast cancer has been increasing for at least the past 25 years [18], and menopausal symptoms are common in these surviving women. This, however small, study suggests that EA is a safe alternative that may help many women with breast cancer through a distressing time and that it merits further evaluation. A prospective, randomized, placebo-controlled study on acupuncture and its effect on vasomotor symptoms in menopausal women is desired, ideally with a placebo acupuncture needle without physiological effects.

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Conflict of interest Nil.

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