Original Article

A Randomized Controlled Trial of Relaxation Training to Reduce Hot Flashes in Women with Primary Breast Cancer

Deborah R. Fenlon, PhD, RGN, Jessica L. Corner, PhD, RGN, and Joanne S. Haviland, MSc

School of Nursing & Midwifery (D.R.F., J.L.C.), University of Southampton, Southampton; Macmillan Cancer Support (J.L.C.), London; and Clinical Trials and Statistics Unit (J.S.H.), Institute of Cancer Research, Sutton, United Kingdom

Abstract

Hot flashes are experienced by about 52% of perimenopausal women. After breast cancer, this may increase to 70%. The use of hormone replacement therapy is not recommended in women who have had breast cancer; therefore, alternatives are required to help relieve hot flashes. This study was conducted to assess the efficacy of relaxation training in reducing the incidence of hot flashes in women with primary breast cancer. This was a randomized controlled trial of 150 women with primary breast cancer who experienced hot flashes. The intervention group received a single relaxation training session and was instructed to use practice tapes on a daily basis at home for one month; the control group received no intervention. Outcomes were incidence and severity of flashes using a diary and validated measures of anxiety and quality of life. The incidence and severity of hot flashes, as recorded by diaries, each significantly declined over one month ($P < 0.001$ and $P = 0.01$, respectively), compared with the control group. Distress caused by flashes also significantly declined in the treatment group over one month ($P = 0.01$), compared with the control group. There were no significant differences between the treatment group and the control group at three months and no changes in anxiety or quality-of-life measures. Relaxation may be a useful component of a program of measures to relieve hot flashes in women with primary breast cancer. J Pain Symptom Manage 2008;35:397–405.

Key Words

Breast cancer, hot flashes/flashes, relaxation

Introduction

Hot flashes are experienced by approximately 52% of perimenopausal women.[1] After breast cancer, this may increase to 70% of women.[2,3] Hormone replacement therapy is no longer preferred for the treatment of this problem generally,[4–6] and is contraindicated in women with breast cancer because of an

This work was funded by Cancer Research UK.

Address correspondence to: Deborah R. Fenlon, PhD, RGN, School of Nursing and Midwifery, University of Southampton, University Road, Highfield, Southampton SO17 1BJ, United Kingdom. E-mail: dfenlon@soton.ac.uk

Accepted for publication: May 10, 2007.

0885-3924/08/$—see front matter
doi:10.1016/j.jpainsymman.2007.05.014

increased risk of recurrence.[7] Increasingly, women have been turning to the use of complementary and alternative medicines[8,9] for menopausal problems and seeking other nonpharmacological strategies.

The cause of hot flashes is still unknown and appears to be due to a change in the hypothalamic control of temperature regulation. The variation in core body temperature that takes place before either sweating or shivering occurs is reduced in symptomatic postmenopausal women from $0.4°C \pm 0.18$ to $0.0°C \pm 0.06$, which means that women are more sensitive to small variations in temperature; a number of neurotransmitters have been postulated to be involved in this process, including serotonin,[10] beta-endorphins, and norepinephrine.[11,12]

There may be a link between postmenopausal changes and a norepinephrine-mediated cause of flashes, as estrogen levels affect the number of adrenergic receptors in the brain, which, in turn, modulate the amount of norepinephrine available.[12] The relaxation response directly influences central norepinephrine,[13] and it may be postulated that relaxation might have a favorable effect on flashes through the modulation of norepinephrine release.

Swartzman et al.[14] have demonstrated that women subjected to stress experience an increased number of flashes over a 24-hour period. The fact that stress potentiates, rather than precipitates, flashes suggests that there is not a direct sympathetic response to stress, but supports the view that the flash mechanism is mediated via a central mechanism and would be consistent with norepinephrine influences on the brain.

A number of small studies have provided evidence to support the use of relaxation to reduce flashes.[15–20] A recent work by Nedstrand et al.[21] comparing relaxation with estrogen replacement concluded that relaxation is a useful alternative treatment for vasomotor symptoms in postmenopausal women. However, these studies are all small and there is a need for a large-scale, randomized, controlled trial to investigate the use of relaxation to reduce hot flashes in postmenopausal women and, in particular, for women with breast cancer, for whom replacement estrogen is contraindicated. In this article, we report the results of such a trial.

Methods

We recruited 150 women from three breast cancer follow-up clinics in a specialist cancer hospital in the southeast of England. Inclusion criteria were postmenopausal women diagnosed with primary breast cancer and suffering from menopausal hot flashes. Any level of severity was accepted for inclusion in the trial as long as the women found the flashes to be troublesome. Postmenopausal was defined as six months without menstruation. This criterion may have included some women for whom menstruation returned at a later date, but was chosen as it included women with chemotherapy-induced menopause, which appears to be associated with particularly severe flashes. The women also were required to be able to complete written records in English. Women using estrogen therapy, aromatase inhibitors, or any other hormone therapies, except tamoxifen, were excluded. Those taking remedies or prescription medicines likely to have an impact on hot flashes, such as acupuncture, venlafaxine, progesterones, or clonidine, also were excluded. Remedies for which there is no evidence of efficacy, such as evening primrose oil, increased dietary soy, starflower oil, multivitamins, and reduced caffeine intake, were not exclusions. Ethical approval for the study was given by the local hospital ethics committee and written consent was obtained from the participants.

Women attending the clinics were asked if they were experiencing hot flashes and whether they were interested in a study to see if relaxation training could reduce their flashes. Following randomization, in those allocated to receive the intervention, an appointment for relaxation training was booked for the following week on completion of the baseline diary. Day 0 was taken as the day of relaxation training, and in the control group, Day 0 was the day after completion of the diary. We audited the number of women eligible for the study attending clinics over the course of one month. Of the 79 potentially eligible women 54 (68%) were experiencing hot flashes. Of those with flashes, 13 (24%) were taking other treatments for flashes and 20 (37%) said that flashes were not troublesome, leaving 21 (39%) women who were eligible for entry to the study. Of the eligible women, nine

(43%) entered the trial. Reasons given for not entering are given in the flow diagram (Fig. 1).

Intervention

Women randomized to the treatment arm of the study were seen by the occupational therapist for a single, hour-long, one-to-one session of training about relaxation. The training included the basics of stress management; written information about stress; and a session of relaxation using deep breathing techniques, muscle relaxation, and guided imagery (used to enhance the relaxation effect). An audiotape of the trainer's voice talking through the same relaxation session was given to the women to use at home. A second reinforcing

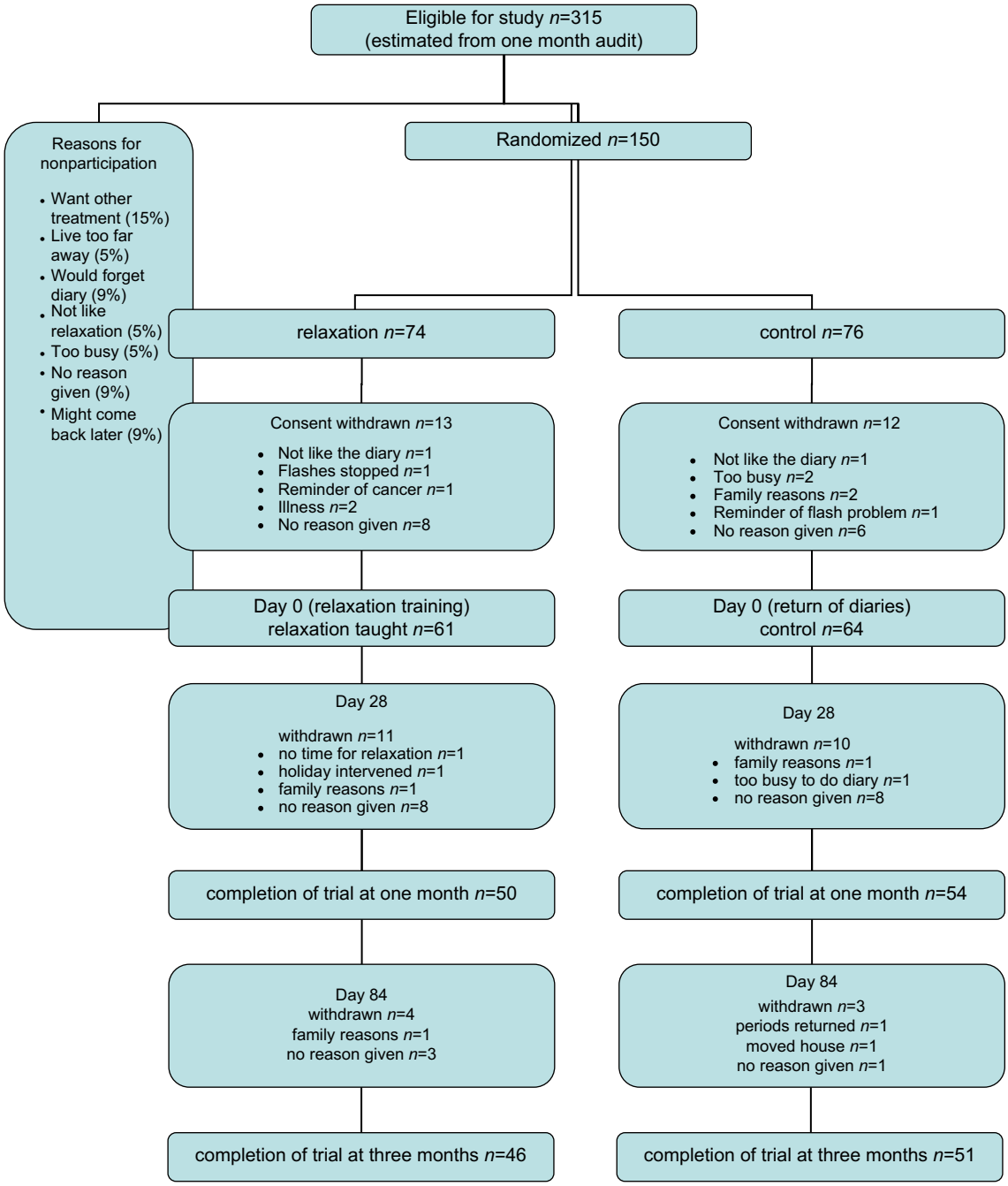

Fig. 1. Patient recruitment and follow up.

training session was offered to those who chose to take it up, but was accepted by only two women. The women were then asked to use the tape provided to undertake a 20-minute relaxation once per day for at least a month. No instruction was given regarding the use of the relaxation tapes after this time. Records of relaxation during the first month were returned by 69% women in the intervention group. Half of the women that returned these records practiced relaxation every day and the rest practiced at least every other day.

The baseline diary and questionnaires were given out by the recruiting research nurse, whereas the diary and questionnaires at one and three months were posted, with specific instructions as to when to complete them. One reminder phone call was made a week after the expected return of the diaries and questionnaires.

The care of women randomized to the control arm of the study was given attention with regards to their flashes, but otherwise were given no other intervention for their flashes. The attention consisted of spending time with a specialist nurse, discussing hot flashes and menopause management. This took the form of a general discussion on menopause management, including hot flashes, aging, vaginal dryness, and bone health. Women were advised about lifestyle measures to improve their health, such as diet, exercise, vaginal moisturizers, and stress reduction. They were asked not to commence any new therapies specifically for hot flashes during the course of the trial.

Outcomes

The incidence of flashes was measured using a diary, kept by the women, of every flash as it occurred over the period of one week. Diaries have been recommended for use in hot flash research by a number of researchers.[22,23] The women also gave a measure of the severity of each flash using predefined categories based on work by Finck et al.,[24] who defined hot flashes using interviews gathered from women with breast cancer. The definition described four domains of flashes: length of flash; physical manifestation; emotional response and behavioral response. For each of these domains, four levels of severity (graded 1–4) were described using the descriptors outlined by Finck et al.[24] to ensure that all women were using the same definitions of severity. The maximum possible score per flash was, therefore, 16. In the diary, a space was allocated for women to record if they found anything that helped their flashes.

The distress caused by flashes was measured using the Hunter menopause scale.[25] Women scored from zero to ten the level of distress due to flashes; the degree to which flashes were perceived as a problem; and the degree to which they were perceived to interfere with everyday life. We also gathered data on quality of life using the Functional Assessment of Cancer Therapy[26] with the endocrine subscale (FACT-ES),[27] and anxiety, which was measured using the Spielberger State/Trait Anxiety Index (STAI).[28] All measures were completed at baseline, and one and three months after relaxation training. One month was chosen as it was felt that this was when maximum benefit was likely to be gained from this intervention. Flashes were measured again at three months, as any intervention that is to be clinically relevant needs to be sustained over a period of months.

Sample Size

Sample size was based on pilot data[20] showing that eight women experienced a 30% reduction in flashes. Women were recruited to the pilot study in the same way as in the main study. This group of 16 women had a mean of five flashes per day. For 90% power and 5% significance to detect a reduction in incidence of flashes of 30%, 43 women were required in each arm of the trial (assuming a mean number of five flashes per day, SD 3; two-sided test). To allow for a 30% dropout rate, as found in the pilot study,[20] the intended accrual was 150 patients in total. This number agrees with that suggested by Sloan et al.,[23] reporting data from a number of studies on women with flashes, who state that at least 50 patients per treatment arm are required to provide sufficient power to detect a clinically meaningful change in hot flash activity.

Randomization

An independent trials office, accessed by telephone, was responsible for randomization of patients to relaxation training or to the control group. A computer-generated randomization

list was used. Stratification took place according to clinic site and whether the patient was over or under 50 years of age. The women were recruited by a specialist breast care nurse (DF), who did not have access to the randomization lists. Recruitment took place over a period of 15 months.

Statistical Methods

We summed the total number of flashes that occurred over the period of one week. Severity of each flash was the sum of the four domains of flashes. The mean severity per flash was used in the analysis to prevent conflation with incidence of flashes. Levels of distress using the Hunter menopause scale were given as a simple score from 0–10. We summarized the FACT-ES quality-of-life questionnaire by calculating total quality-of-life score, as described in the scoring manual.[29] State and trait anxiety were calculated according to the STAI manual.[30] We compared median scores for change in all outcome measures between the groups using the Mann–Whitney *U* test, because distributions of change scores were skewed. Analysis was undertaken on the basis of "intention to treat," with all randomized women contributing data included in the analysis. No imputation of missing data was done. As multiple tests were carried out on the data, a cutoff for statistical significance of $P < 0.01$ was used throughout.

Results

Participants and Follow Up

Of 150 women recruited to the trial, 104 women completed the trial to the primary endpoint at one month and 97 completed all three months. Reasons for noncompletion are shown in Fig. 1. The women ranged in age from 36 to 77 years and the majority were white, British, and married (Table 1). A

Table 1
Baseline Demographics and Clinical Characteristics

Characteristics	Category	Relaxation Group ($n = 76$) (%)	Control Group ($n = 74$) (%)
Age (median and interquartile range)		54.9 (51.9–59.0)	55.4 (51.6–60.3)
Marital status	No current partner	18 (24)	19 (26)
	Married/partner	54 (72)	50 (67)
	Missing data	4 (5)	0 (0)
Ethnic origin	Caucasian	71 (93)	72 (97)
	Other (including mixed race)	5 (6)	2 (2)
Time since diagnosis	Less than 2 years	20 (26)	33 (45)
	2–5 years	26 (34)	20 (27)
	Over 5 years	30 (39)	21 (28)
Time since last menstruation	Less than one year	8 (11)	10 (14)
	1–2 years	13 (17)	10 (14)
	2–5 years	19 (25)	15 (20)
	More than 5 years	36 (47)	39 (53)
Currently taking tamoxifen		45 (59)	38 (51)
Had chemotherapy		35 (46)	39 (53)
Had oophorectomy		3 (4)	13 (18)
Taking any other treatment or medication		29 (38)	29 (39)
Other remedies for hot flashes		11 (14)	17 (23)
Incidence and severity of flashes from diaries (median and interquartile range)			
Flashes per week		31.5 (20.00–45.00)	37.0 (20.00–81.00)
Severity per flash		4.7 (3.5–5.9)	4.7 (3.0–6.0)
Hunter menopause scale (median and interquartile range)			
Distress due to flashes		5.0 (2.0–6.0)	5.0 (4.0–7.0)
Problem caused by flashes		5.5 (4.0–7.3)	6.0 (4.0–7.8)
Interference to daily life by flashes		3.0 (2.0–6.0)	3.0 (1.3–6.0)
FACT-ES (mean and standard deviation)			
Total score		170 (152.8–178.3)	168.2 (149.3–183.0)
State-Trait Anxiety Index (mean and standard deviation)			
State anxiety		37 (30–44)	35 (27–48)
Trait anxiety		40.5 (34.2–48)	37 (31.7–47)

number of women were taking alternative remedies for hot flashes. These were equally distributed between the groups and were remedies for which there is no evidence of benefit, including evening primrose oil,[14] soy,[6] starflower oil,[2] multivitamins,[3] and reduced caffeine intake.[1] There were no significant differences in clinical characteristics or outcome measures between the groups at baseline, except for oophorectomy. The analysis was recalculated excluding all women with oophorectomy. This resulted in minor differences, which did not affect the overall conclusions. Although prompted, there were no records made in the diaries of new treatments for flashes being taken up during the course of the study. The mean wait time for relaxation training was two weeks.

Comparison Between Relaxation and Control

To test the effectiveness of relaxation, we compared the change in flashes over time between the two groups (Table 2). After one month, there was a median improvement of seven flashes per week (22% improvement) in the relaxation group; this was significant when compared with the change in the control group (<0.001) (Fig. 2). The severity of flashes also improved significantly when compared to the control group, which experienced no change ($P = 0.01$). Apparent improvements in both the number and severity of flashes in the relaxation group at three months were not significant ($P = 0.06$ and $P = 0.05$, respectively) (Fig. 3). When examining the impact of flashes on the women's lives over one month, the distress due to flashes was seen to improve ($P = 0.01$), whereas the improvement in the extent to which women thought flashes were a problem and how much flashes interfered with daily life did not reach statistical significance ($P = 0.06$ and $P = 0.09$, respectively). Relaxation did not appear to be more beneficial in different treatment or age groups, although the numbers in the study were insufficient to detect significant differences in subgroups. No statistically significant changes were seen in either state or trait anxiety on the STAI, nor on scores on the FACT-ES.

Discussion

The use of relaxation training reduced both the incidence and the severity of hot flashes and, possibly more importantly, the consequent distress in women with breast cancer one month after training with relaxation techniques. Although the median reduction of five per day to four per day may appear small, this may reflect a real benefit for some women,

Table 2
Median Scores for Change in Number, Severity, and Distress Due to Flashes, State and Trait Anxiety, and Quality of Life at One and Three Months After Treatment

Item	Relaxation Group (median)	Control Group (median)	Median Difference	95%CI for Median Difference	Mann–Whitney test, *P*-Value
One month after randomization ($n = 104$)	($n = 50$)	($n = 54$)			
Improvement in number of flashes per week	7	1	7	4, 11	<0.001*
Improvement in severity per flash	0.47	0	0.54	0.11, 1.01	0.01*
Improvement in distress due to flashes	1	0	1	0, 2	0.01*
Improvement in problem due to flashes	1	1	1	0, 1	0.06
Improvement in interference to daily life due to flashes	0	0	1	0, 1	0.09
Improvement in trait anxiety	0	2	−1	−4, 1	0.24
Improvement in state anxiety	−1	0	−1.0	−4.0, 2.0	0.51
Change in quality of life (FACT-ES)	−0.38	−0.33	0.12	−4.06, 4.65	0.94
Three months after randomization ($n = 97$)	($n = 46$)	($n = 51$)			
Improvement in number of flashes per week	11	4	5	0, 10	0.06
Improvement in severity per flash	0.55	0.08	0.56	0.02, 1.18	0.05
Improvement in distress due to flashes	0	0	0	−1, 1	0.66
Improvement in problem due to flashes	1	0.5	0	0, 1	0.21
Improvement in interference to daily life due to flashes	0	0	1	0, 1	0.11
Improvement in trait anxiety	1	1	1.0	−2.0, 3.0	0.72
Improvement in state anxiety	0	−2	2.0	−2.0, 5.0	0.31
Change in quality of life (FACT-ES)	−5.2	−3.5	−1.5	−7.0, 4.4	0.62

All negative numbers indicate the measure is becoming worse.
*Indicates statistical significance.

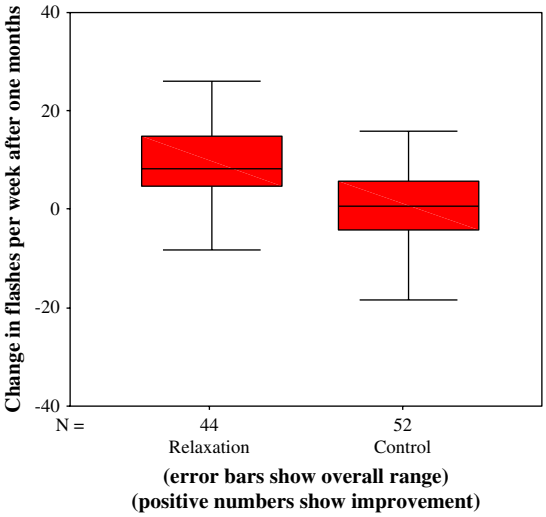

Fig. 2. Change in number of flashes (median and interquartile range) per week after one month.

especially as the severity was also reduced. The relevance of this for women is supported by the significant reduction in the level of distress reported due to flashes. It may be that the number of flashes alone is less important than the severity of the flash, or the combination of number and severity of flashes, in terms of the distress caused to the individual. The majority of those women who completed the study managed to practice relaxation on a frequent and regular basis, suggesting that this form of relaxation may be a useful technique that some women find acceptable to use for themselves, although it is possible that those

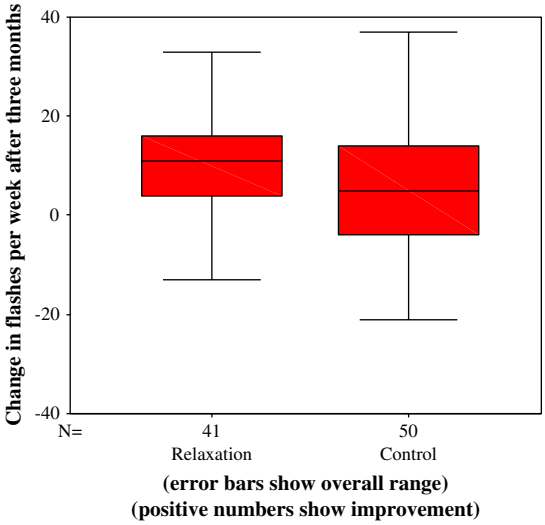

Fig. 3. Change in number of flashes (median and interquartile range) per week after three months.

women who did not find relaxation acceptable were among those who were not selected for the study.

There was an apparent imbalance in the baseline number of flashes, with the intervention group experiencing less than the control group, although this was not a statistically significant difference. These baseline differences may have contributed to obscure any benefit due to the intervention, which may suggest that the real benefit of relaxation is greater than demonstrated.

The reduction in incidence was apparently not sustained after three months. This may be due to the trial design. The women were asked to practice the relaxation session daily for one month and then it was left to them to decide whether or not to continue. Records of relaxation were also not maintained after this time. The reason for this decision was to maximize the intervention at the one-month time point, but the consequence may have been to weaken the findings at three months. The level of intervention was also minimal, being comprised of only a single training session, to emulate clinical reality where resources are scarce. More intensive training may result in a longer lasting effect.

There were no differences seen in quality of life, as measured by the FACT-ES, between the relaxation and control groups, either before or after intervention. As the FACT-ES measure was developed for women undergoing breast cancer treatment, it is heavily weighted toward the presence of treatment side effects and symptomatology and so may have been insufficiently sensitive to detect quality-of-life issues associated with flashes.

This sample comprised a population mainly of white British women in southeast England. Findings may not be generalizable to other populations. The sample was also biased towards those who had the midrange of severity of flashes. Women with mild flashes chose not to participate in the study and women with severe flashes were frequently taking other remedies for flashes, which excluded them from the trial. The wait time for relaxation training meant that baseline to Day 0 was a mean of two weeks longer in the treated group than the control group. However, as no significant change was seen in flash incidence in the control group over three months, this was not thought to influence the outcome.

Women were included in the study if they were more than six months without menstruation in order to include women experiencing a chemotherapy-induced menopause, which often is accompanied by particularly severe flashes. However, there was a risk that menstruation would return in some of these women. This happened in only one case, which was in the control arm. This woman had frequent and severe flashes, which ceased on the return of menstruation. It is possible that this case weakened the outcome of the study.

Although self-report measures of hot flashes have been shown to correspond well to laboratory monitoring methods of measuring flashes,[31] the use of diaries may introduce bias due to participant's willingness to please, or to the control group's disappointment at not being given active treatment. Furthermore, as there was no placebo, it could be suggested that the benefit was due to placebo response. Some authors report a placebo effect for trials with hot flashes.[23] Designing a placebo intervention for this kind of study is problematic, as there is no inactive form of relaxation training. It has been suggested that a major component of placebo is the attention that participants receive due to the therapeutic relationship between the participant and the researcher,[32] in this case an experienced breast care nurse. All the women spent time before randomization with the researcher who was recruiting women to the study. This recruitment interview involved assessing women's experience of flashes and discussion of management strategies, and the relationship was maintained through the trial by means of the maintenance of the diaries and follow-up phone calls and correspondence. In this way, it could be suggested that all the women obtained the benefits that would have been achieved from placebo. An alternative explanation might be that the control group did not achieve a placebo response due to disappointment in not getting the relaxation training. Future work would need to address the issue of the placebo effect.

Conclusions

This study showed a small, but significant reduction in the incidence, severity, and distress caused by hot flashes in women with breast cancer who underwent training in relaxation. Although doubts remain about the possibility of a placebo effect and the fact that this effect was small, there may be real benefits for some women who use relaxation for the relief of hot flashes. Future work might focus on finding ways to enhance this effect, identifying subgroups who might achieve greater benefit and exploring what women perceive to be the real benefits of this kind of approach to managing hot flashes.

Acknowledgments

The authors acknowledge the contribution of Jill Cooper, who provided the relaxation training.

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