Paced Respiration for Vasomotor and Other Menopausal Symptoms: A Randomized, Controlled Trial

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BACKGROUND: Paced respiration has been internationally recommended for vasomotor symptom management, despite limited empirical evidence.

OBJECTIVE: To evaluate efficacy of a paced respiration intervention against breathing control and usual care control for vasomotor and other menopausal symptoms.

DESIGN: A 16-week, 3-group, partially blinded, controlled trial with 2:2:1 randomization and stratification by group (breast cancer, no cancer), in a Midwestern city and surrounding area.

PARTICIPANTS: Two hundred and eighteen randomized women (96 breast cancer survivors, 122 menopausal women without cancer), recruited through community mailings and registries (29 % minority).

INTERVENTIONS: Training, home practice support, and instructions to use the breathing at the time of each hot flash were delivered via compact disc with printed booklet (paced respiration intervention) or digital videodisc with printed booklet (fast shallow breathing control). Usual care control received a letter regarding group assignment.

MAIN MEASURES: Hot flash frequency, severity, and bother (primary); hot flash interference in daily life, perceived control over hot flashes, and mood and sleep disturbances (secondary). Intervention performance, adherence, and adverse events were assessed.

KEY RESULTS: There were no significant group differences for primary outcomes at 8-weeks or 16-weeks post-randomization. Most intervention participants did not achieve 50 % reduction in vasomotor symptoms, despite demonstrated ability to correctly do paced respiration and daily practice. Statistically significant differences in secondary outcomes at 8 and 16 weeks were small, not likely to be clinically relevant, and as likely to favor intervention as breathing control.

CONCLUSIONS: Paced respiration is unlikely to provide clinical benefit for vasomotor or other menopausal symptoms in breast cancer survivors or menopausal women without cancer.

INTRODUCTION

Vasomotor symptoms (hot flashes, night sweats) are the cardinal symptoms of menopause and can be associated with disrupted mood and sleep. Although pharmacological therapies are often the mainstay of treatment,[1] women's preferences or comorbid conditions may preclude their use. Breast cancer survivors, in particular, are unable to take certain pharmacological therapies, due to potential interactions with anti-estrogen therapies.[2]

Paced respiration has been internationally recommended as a first line therapy for vasomotor symptoms.[3] Recommendations are to take slow deep abdominal breaths at the start of a hot flash, breathing in through the nose and out through the mouth.[4] However, this recommendation does not mirror tested research protocols. Small studies (n=14 to 33) tested the following protocol:[5–7] During eight, biweekly, one-hour laboratory sessions, participants were connected to monitoring equipment that measured and graphed chest and abdominal expansion. A research assistant instructed participants to breathe 6–8 times per minute while increasing chest expansions on the polygraph. In addition, participants were instructed to practice this at home for 15 min, twice daily. These protocols were significantly more efficacious than attention control[5–7] and reduced vasomotor symptoms by $\geq$ 50 % among healthy menopausal women,[5,6] a clinically meaningful change desired by symptomatic women.[8,9] However, it is not easily implemented in clinical practice. Larger scale studies have combined verbal or written instructions on paced respiration (with or without daily practice) with other cognitive, behavioral, or pharmacological therapies, but have not tested paced respiration alone for vasomotor symptoms.[10–12] There are no large scale studies testing the intensive laboratory-based protocol, none testing a portable and more

easily disseminated version of paced respiration training for vasomotor symptoms, and none testing current recommendations for application without daily practice. Thus, international recommendations appear to be based on insufficient empirical evidence.

The purpose of this study was to evaluate efficacy of a paced respiration intervention (daily practice, application at each hot flash) against attention control (fast, shallow breathing) and usual care. Primary outcomes were vasomotor symptoms (hot flash frequency, severity, and bother). Secondary outcomes were hot flash related interference in daily life, perceived control over hot flashes, and mood and sleep disturbances.

METHODS

Design Overview

This was a 16-week, 3-group, partially-blinded, randomized controlled trial with assessments at baseline and at 8-weeks and 16-weeks post-randomization. The intervention group took part in a 2-week post-randomization visit to confirm learning and performance of paced respiration. The institutional review board and cancer center scientific review committee approved the study. Participants provided written, informed consent and authorization to use health information. Consents described a comparison of two breathing methods against usual care to maintain blinding of participants and data collectors. Recruitment occurred April 1, 2009 to February 1, 2011. Study visits occurred May 7, 2009 to June 30, 2011.

Setting and Participants

Recruitment transpired primarily through mass mailings to purchased lists of community-dwelling women and registry participants (tumor registries, Dr. Susan Love Research Foundation's Love/Avon Army of Women registry) and via breast cancer and high-risk clinics in the Midwest. Eligible participants were adult women: reporting two or more hot flashes per 24-hour day of moderate or greater severity (≥ 4 using 0 to 10 point numeric rating scale); desiring treatment; with peri-menopausal or post-menopausal status; in good general physical and mental health; without self-reported breathing difficulties; being metropolitan statistical area residents (60 mile radius) or willing to commute to the study site; and who were English literate. Hot flash frequency and severity were assessed via self-report at initial telephone screening, and confirmed via prospective electronic diaries at baseline. Breast cancer survivors were > 4 weeks post-completion of surgery, radiation, and/or chemotherapy for non-metastatic breast cancer, and had no other cancer history. The non-cancer group had no history of any cancer. Women taking hot flash treatments were not excluded, but had to

agree to continue these treatments for the study duration and use (yes/no) was evaluated as a covariate.

Data Collection

Mailings directed interested women to phone a research office. Trained staff determined eligibility, reviewed study requirements, and addressed questions before mailing study materials. Interested women signed a consent and authorization form and returned them by mail. Women who did not return items were telephoned to query interest and address questions.

Trained and blinded data collectors arranged and conducted the 30-minute, private visits. At baseline, they taught women to use electronic hot flash diaries for ≥ 24 h to ≤ 7 days (time determined by participant choice), verified completion of paper questionnaires, and measured height and weight. Once electronic diaries were returned in person or via prepaid mailers, baseline hot flashes were reviewed to confirm eligibility. Visits at 8 and 16 weeks occurred similarly. Compensation ($25) occurred at each visit.

Participants and blinded data collectors were told that a random subset of participants would participate in an extra visit, 2 weeks after randomization, for quality assurance. Such visits were conducted by other, non-blinded staff and only with intervention participants. The goal was to obtain physiological recordings of breath rate to verify correct performance of paced respiration. Staff referred participants with questions or problems back to their study materials and thus, did not act as in-person interventionists. This quality assurance monitoring continued as part of the 8-week and 16-week visits.

Randomization and Intervention

Randomization occurred in a 2:2:1 fashion in blocks of ten, with stratification by group (cancer, non-cancer). Biostatisticians furnished a password protected, electronic randomization list to the project manager responsible for randomization.

The paced respiration intervention group received a compact disc with paper booklet. The booklet reinforced instructions on the first audio track for how to accomplish a target breath rate of 6–8 breaths per minute, practice twice per day for 15 min, and apply the breathing at the onset of each hot flash. Women were instructed to do slow, deep, abdominal breathing in through the nose and out through the mouth as per international recommendations.[4] They were also instructed to practice twice per day for 15 min as per the small, laboratory-based studies.[5,6] The second and third tracks contained specially composed, digitally recorded music to help entrain the breath rate and structure the length of practice. Details of this intervention are contained in another manuscript (submitted).

The breathing control group received a digital videodisc with paper booklet. The booklet reinforced voice-over and video

demonstration to practice twice per day and to apply the fast shallow breathing at the onset of each flash. A previously published report provides additional details and data indicating this program was a suitable attention control.[13]

The usual care group received an investigator-signed letter explaining they were not selected to receive any study materials during the 16-week follow-up. These participants received paced respiration materials by mail after study completion.

Outcomes and Follow-up

Primary outcomes were hot flash frequency, severity, and bother (vasomotor symptoms), prospectively recorded in real time via an electronic diary at baseline and at 8 and 16weeks. Participants pressed buttons on a small device (Biolog™ ESR, UFI, Morro Bay, CA) to record each hot flash, and rate severity and bother, from 0 (not at all) to 10 (extremely). After diary data were downloaded, frequency, severity, and bother were calculated as 24-hour averages at each time point. Higher scores indicated worse outcomes (greater frequency, severity, bother).

Secondary outcomes were assessed with well-validated, standardized questionnaires at baseline and at 8 and 16 weeks: the Hot Flash Related Daily Interference Scale (HFRDIS),[14] Perceived Control over Hot Flashes Index (PCI),[15,16] Positive and Negative Affect Scale (PANAS),[17,18] Profile of Mood States-short form (POMS-SF),[19,20] and Pittsburgh Sleep Quality Index (PSQI).[21] Lower scores on the PCI, PANAS positive affect subscale, and POMS-SF vigor subscale indicated worse outcomes (less control, less positive affect, less vigor). For all others, higher scores indicated worse outcomes (greater interference, greater negative affect, greater mood disturbance, greater sleep problems).

Demographics, menopausal status, prior breath training experience, and breast cancer disease and treatment variables were assessed to describe the sample. Menopausal status was assessed through self-reported menstrual and gynecological history. Adverse events were monitored through participant self-reports.

To assess adherence, intervention participants demonstrated 15 min of paced respiration at 2, 8, and 16 weeks, while wearing an electronic monitoring strap placed around their diaphragm by non-blinded assessors (Model 1132 Pneumotrace II™, UFI, Morro Bay, CA). The strap's piezo electric sensors recorded expansion and contraction with inhalation and exhalation. After 15 min, the strap was removed. Downloaded data generated minute-by-minute breath rates for each time point. Home practice was recorded on a calendar.[22]

Statistical Analysis

The required sample size was based on data collected from 60 participants (minimum of two hot flashes per day and average severity ratings ≥ 4): 24-hour hot flash frequency ($M=6.42$, SD $=4.54$); 24-hour hot flash severity ($M=5.15$, SD=1.68); 24-

hour hot flash bother ($M=4.56$, SD=1.77). Power analysis for 16-week pairwise comparisons between the intervention and two control groups on the primary outcomes was done using an estimated 50 % reduction in hot flashes with intervention versus 25 % reduction with control. A ≥ 50 % reduction in hot flashes was seen in prior laboratory-based studies of paced respiration,[5] and appears to be a minimally clinically important difference.[8,9] A 25 % reduction is a typical placebo response. Under these assumptions with two strata and 2:2:1 randomization, 193 participants were needed to achieve 80 % power to detect a difference between groups with alpha of 0.05 for the primary outcomes, using a type I error rate control similar to the well-known Bonferroni procedure. Total enrollment was estimated at 213 to allow for attrition.

All analyses are based on all randomized subjects, regardless of adherence. Hot flash frequency was the total number of hot flashes and night sweats divided by the total diary recording time to produce an average over 24 hours. Severity and bother were also averaged over 24 hours. If no hot flashes were recorded, frequency, severity, and bother were set to zero.

We used frequency tables, including p-values from analysis of variance (ANOVA), for continuous baseline covariates and from Fisher's exact tests for categorical baseline covariates to compare randomized groups. Analyses for primary and secondary outcomes at 8 and 16 weeks were based on analysis of covariance (ANCOVA) to compare group differences adjusting for corresponding baseline outcomes. Pairwise comparisons between intervention and breathing control groups at 8 and 16 weeks were also based on ANCOVA. We did not adjust for multiple comparisons since all outcomes were hypothesis driven.

There were three different methods to handle missing data: all completed cases data analysis, last observation carry forward, and multiple imputations. The completed cases analysis (presented below) used all cases with baseline and 8-week data for the 8-week analysis and all cases with baseline and 16-week data for the 16-week analysis. The multiple imputations procedure was based on SAS 9.3, which imputes missing data five times using regression on variables significantly associated with all three primary outcomes of hot flash frequency, severity and bother (i.e. body mass index, income, smoking, hot flash therapies). All methods led to the same conclusions with only slight differences in p-values. Results did not vary by strata (cancer, no cancer) or by use of hot flash therapies (no, yes). We did not adjust for use of aromatase inhibitors (AI) or selective estrogen receptor modulators (SERM), type of hot flash treatment, or any other covariates in Table 1, because no imbalance was noted due to randomization.

RESULTS

There were 218 women (96 breast cancer survivors and 122 menopausal women) randomized (Fig. 1) with no significant differences at baseline in demographic, clinical, or

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Table 1. Baseline Characteristics by Group

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	Paced respiration intervention (*n*=88)	Breathing control (*n*=86)	Usual care control (*n*=44)	*p*
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	
Age	53.44 (6.84)	51.93 (6.81)	53.52 (5.68)	0.25
Body mass index	29.06 (7.50)	29.97 (6.94)	27.62 (4.95)	0.18
Years of education	15.01 (2.34)	15.05 (2.36)	15.05 (2.16)	0.99
Concurrent medications	2.32 (2.09)	2.30 (1.98)	2.41 (1.98)	0.96
Comorbid conditions	1.83 (1.24)	1.73 (1.26)	1.61 (1.26)	0.64
Past hot flash therapies tried	2.08 (1.74)	2.20 (1.65)	1.84 (1.63)	0.52
Current hot flash therapies	0.45 (0.69)	0.60 (0.76)	0.61 (0.75)	0.29
Years since last menses	6.87 (7.55)	7.17 (6.96)	7.00 (7.88)	0.97
Electronic hot flash diary days	3.73 (2.56)	4.02 (2.56)	3.95 (2.49)	0.74
24-hour hot flash frequency	7.02 (4.32)	6.43 (3.96)	7.31 (4.04)	0.46
24-hour hot flash severity	4.50 (1.60)	5.23 (1.58)	5.40 (1.26)	0.41
Ethnicity	*n* (%)	*n* (%)	*n* (%)	0.11
Latina	3 (3 %)	0 (0 %)	0 (0 %)	
Non-Latina	85 (97 %)	86 (100 %)	44 (100 %)	
Race				0.89
White/Caucasian	61 (69 %)	62 (72 %)	32 (73 %)	
Other	27 (31 %)	24 (28 %)	12 (27 %)	
Marital				0.99
Married/living with partner	56 (64 %)	55 (64 %)	29 (66 %)	
Single, widowed	28 (32 %)	28 (33 %)	13 (30 %)	
Other	4 (5 %)	3 (3 %)	2 (5 %)	
Employment				0.51
Full time	58 (66 %)	53 (62 %)	28 (64 %)	
Part time	9 (10 %)	13 (15 %)	9 (20 %)	
Not employed	21 (24 %)	20 (23 %)	7 (16 %)	
Difficulty paying for basics				0.28
None	68 (77 %)	56 (65 %)	35 (80 %)	
Some	16 (18 %)	23 (27 %)	8 (18 %)	
A lot	4 (5 %)	7 (8 %)	1 (2 %)	
Smoker				0.74
Never	59 (67 %)	53 (62 %)	29 (66 %)	
Ever (former, current)	29 (33 %)	33 (38 %)	15 (34 %)	
Menopausal status				0.29
Early peri/late peri	3 (4 %)	1 (1 %)	2 (5 %)	
Early post	6 (7 %)	14 (17 %)	6 (15 %)	
Late post	73 (89 %)	68 (82 %)	33 (80 %)	

Table 1. (continued)

	Paced respiration intervention (*n*=88)	Breathing control (*n*=86)	Usual care control (*n*=44)	*p*
Current hot flash therapies				0.77
None	58 (66 %)	47 (55 %)	24 (55 %)	
Prescription medication	21 (24 %)	25 (29 %)	13 (30 %)	
Over-the-counter product	6 (7 %)	9 (10 %)	5 (11 %)	
Both	3 (3 %)	5 (6 %)	2 (5 %)	
Use of SERM or AI				0.55
No, not currently	65 (74 %)	64 (74 %)	29 (66 %)	
Yes, currently	23 (26 %)	22 (26 %)	15 (34 %)	
Strata				0.97
Breast cancer survivor	38 (43 %)	38 (44 %)	20 (45 %)	
Menopausal woman	50 (57 %)	48 (56 %)	24 (55 %)	

Current hot flash therapies included the following: prescription medications [selective serotonin reuptake inhibitors (n= 44), hormone therapy (n= 4), gabapentin (n= 3), clonidine (n= 2), or a combination of these medications (n= 6)]; over-the counter products [combination product (e.g., soy with multivitamins and black cohosh, n= 8), flax seed oil (n= 6), women's menopause multivitamin (n= 4), or black cohosh (n= 2)]; or both [a combination of the listed prescription medications and over-the-counter products (n= 10)]
SERM selective estrogen receptor modulator, AI aromatase inhibitor

breast cancer variables (Table 1). Breast cancer participants were stage II or less (90 %), a mean of 5 years post-diagnosis (SD=5), and had received chemotherapy (53 %) and/or radiation therapy (67 %).

Vasomotor Frequency, Severity, and Bother

Figure 2 shows unadjusted mean vasomotor symptom frequency across time. Figure 2A and 2B depict severity and bother over time (appendix available online). After adjusting for baseline, there were no statistically significant differences among randomized groups at 8 or 16 weeks (*p*> 0.09). Paced respiration was not significantly more efficacious than breathing control or usual care for vasomotor symptoms (p's>0.05) or in producing a 50 % reduction in hot flashes. Percentages achieving 50 % reduction in hot flashes from baseline to 8 weeks and sustaining at 16 weeks were: 38 % intervention, 29 % breathing control, and 22 % usual care control. Table 2 shows unadjusted means by group and time for primary outcomes. Table 3 (appendix available online) includes data for secondary outcomes. Figure 3 (appendix available online) depicts effect sizes and 95 % confidence intervals for comparisons between intervention and breathing control.

Hot Flash Interference, Perceived Control, and Mood and Sleep Disturbances

There were few statistically significant differences in secondary outcomes at 8 and 16 weeks, but these small group differences are not likely to be clinically significant (appendix available online). At 8 weeks, significant differences were seen between paced respiration and breathing control for PSQI global scores only. From baseline to 8 weeks, PSQI global scores improved 0.61 points in the paced respiration intervention group and worsened by 1.06 points in the breathing control group (*p*=0.20). At 16 weeks, significant differences were seen for PANAS negative affect, PSQI sleep duration, and PSQI sleep medications, but affect and sleep duration favored breathing control. From baseline to 16 weeks, negative affect increased (worsened) 0.91 points with intervention and decreased (improved) 1.84 points in breathing control (*p*=0.03). Similarly, sleep duration difficulty worsened 0.07 points with intervention and improved 0.20 points in breathing control (*p*=0.40). In contrast, from baseline to 16 weeks, use of sleep medications decreased with intervention by 0.14 points and increased with breathing control by 0.14 points (*p*=0.03).

Adherence and Adverse Events

Most intervention participants achieved and sustained paced respiration across time points. At each time point, mean (standard deviation) breath rates were: 2 weeks, 7.35 (2.45); 8 weeks, 6.61 (1.60); and 16 weeks, 6.97 (1.92). Percentages of participants achieving eight or fewer breaths per minute at each time point were: 2 weeks, 75 %; 8 weeks, 84 %; and 16 weeks, 75 %. In addition, during the 16 weeks, the mean number of intervention practice sessions per participant was 109.83 (SD=67.76), or approximately once per day (16 weeks × 7 days per week=112). Similarly, during the 16 weeks, the mean number of breathing control practice sessions per participant was 133.93 (SD=78.27), or approximately once per day. No adverse events were reported.
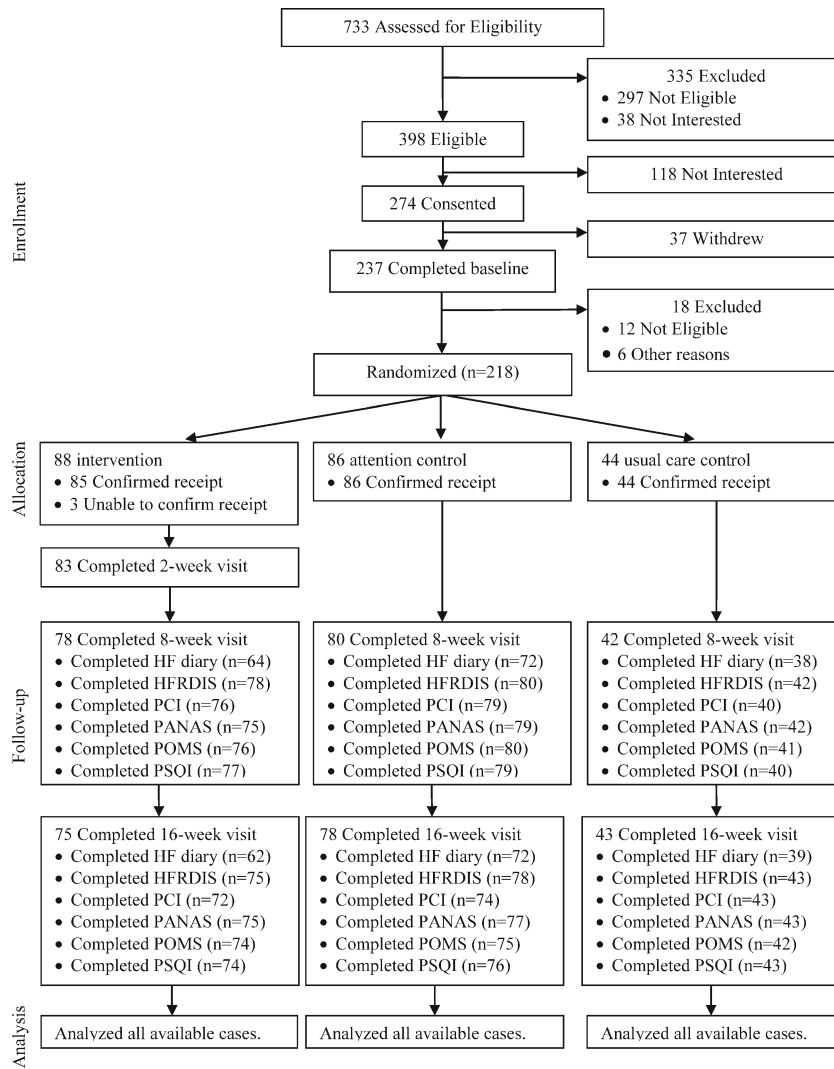
Figure 1. Participant flow diagram for primary and secondary outcomes. Legend: Accrual diagram showing attrition. *HF* hot flash, *HFRDIS* Hot Flash Related Daily Interference, *PCI* Perceived Control Index, *PANAS* Positive and Negative Affect Scale, *POMS* Profile of Mood Disturbance Scale, *PSQI* Pittsburgh Sleep Quality Index.
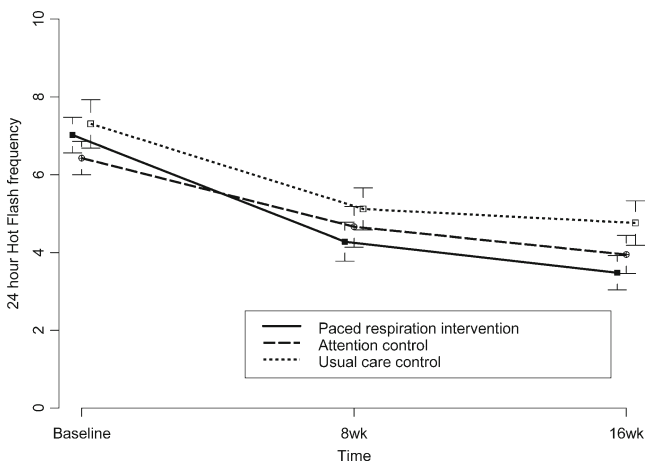

Figure 2. 24-hour average hot flash frequency by group over time. Legend: Data points are unadjusted means and standard errors with 95 % confidence interval error bars. Frequency was 24-hour average. No significant differences at 8 or 16 weeks.

DISCUSSION

Paced respiration is unlikely to provide clinical benefit for vasomotor or other menopausal symptoms in breast cancer survivors or menopausal women without cancer. It was not significantly more efficacious than attention control or usual care control for primary outcomes and most secondary outcomes. Although some minor benefits for paced respiration were seen for sleep, the observed small differences are not likely to be clinically meaningful, may have been due to nighttime sleep's natural variability, and statistical significance may have been spurious, since other outcomes were shown to favor breathing control. These negative study findings provide important evidence against international recommendations for paced respiration to alleviate vasomotor symptoms.

Negative study findings cannot be attributed to poor learning or lack of ability. Most intervention participants demonstrated their learned ability to perform and sustain paced respiration at

Table 2. Primary Outcomes by Group and Time with Comparison Between Intervention and Breathing Control: Unadjusted Means and (Standard Deviation)

	Paced respiration intervention n=88	Breathing control n=86	Usual care control n=44	p
Hot flash frequency				
Baseline	7.02 (4.32)	6.43 (3.96)	7.31 (4.04)	
				0.18
8 weeks	4.28 (4.04)	4.66 (4.40)	5.12 (3.35)	
				0.09
16 weeks	3.48 (3.45)	3.95 (4.19)	4.76 (3.54)	
Hot flash severity				
Baseline	4.50 (1.60)	5.23 (1.58)	5.40 (1.26)	
8 weeks	4.50 (2.06)	4.75 (1.86)	5.20 (1.41)	0.82
16 weeks	4.33 (2.06)	4.65 (2.07)	5.20 (1.89)	0.88
Hot flash bother				
Baseline	4.52 (1.72)	4.78 (1.72)	4.69 (1.32)	
8 weeks	4.02 (1.94)	4.48 (2.11)	4.78 (1.41)	0.39
16 weeks	3.89 (1.93)	4.22 (2.19)	4.76 (1.73)	0.94

the target breath rate at each time point using the CD-based materials. This suggests that the previously tested, more structured, laboratory-based intervention may not be necessary for teaching women how to do paced respiration.[5–7]

Negative study findings may be due to daily rather than twice daily practice, but even daily practice is not part of international recommendations. International recommendations are to apply at the onset of each flash only, even though prior laboratory studies involved twice-daily, at-home practice sessions.[5–7] Twice daily practice may be impractical with women's busy lives. It is also possible that women did not practice twice daily because they did not perceive the practice as beneficial, in which case, practice rates may simply be another indicator of poor efficacy.

The major problem in any study of this nature is our limited understanding of vasomotor symptom etiology, which severely hampers efforts to create or identify appropriate interventions. Paced respiration was previously hypothesized to be efficacious due to its ability to decrease sympathetic activation, but this hypothesis remains unsupported.[6]

There were some study limitations. Participants, who were compensated volunteers, could have led to some sample bias. The 16-week intervention duration was relatively short. However, because our intervention was less intense than the previously tested laboratory-based protocol, we extended our study from the 8-week length of prior studies to 16 weeks to allow enough time to identify any benefits. Finally, although prior studies used sternal skin conductance monitoring as a physiological measure of vasomotor symptoms,[5–7] components for the Biolog™ hot flash monitoring system were unavailable and/or problem-

atic during the years of this study.[23] It would have been interesting to evaluate response via physiologically-recorded hot flashes.

Strengths were inclusion of an attention control and the stratified sample. The control was rationally structured to do the opposite of the active intervention to avoid symptom alleviation. Without the control, the intervention would have looked more promising in relation to usual care. With its inclusion, we were able to show that paced respiration is no more beneficial than fast, shallow breathing. In addition, efficacy findings were similar across two groups of women and, therefore, are more informative to practitioners.

Clinical implications include the following. First, if patients request information or advice concerning paced respiration, clinicians should be prepared to discuss the relative lack of empirical support for this therapy. Second, recommendations for the use of paced respiration as a first line hot flash therapy should be viewed skeptically in light of our study findings. Greater benefit is likely to be seen with other more proven interventions, such as hormones, selective serotonin re-uptake inhibitors, or other emerging non-pharmacological therapies. Third, clinicians who regularly use printed or electronic patient education materials should ensure that information concerning paced respiration is updated to reflect currently available evidence.

In conclusion, paced respiration was not more efficacious than fast, shallow breathing or usual care in providing clinical benefit for vasomotor or other menopausal symptoms in this sample of breast cancer survivors and menopausal women without cancer.

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