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Breast Cancer

Randomized Controlled Trial of a Home-Based Walking Program to Reduce Moderate to Severe Aromatase Inhibitor-Associated Arthralgia in Breast Cancer Survivors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Aromatase inhibitor • Arthralgia • Exercise

Abstract

Background. In postmenopausal women diagnosed with breast cancer (BC), most BC tumors are hormone receptor positive and guidelines recommend adjuvant endocrine therapy that includes an aromatase inhibitor (AI). This study investigates the impact of a 6-week, home-based, self-directed walking program on the commonly reported side effect of AI-associated arthralgia (AIAA).

Materials and Methods. In this phase II trial, consented BC patients were randomized to walking Intervention ($n = 31$) or Wait List Control (WLC; $n = 31$). Eligibility criteria included: stage 0–III BC, on AI for at least 4 weeks, $\geq$3 on a 5-point scale inquiring about joint symptom intensity "at its worst," and exercising $\leq$150 minutes per week. Outcomes were self-reported joint symptoms and psychosocial measures. Analyses comparing Intervention and WLC groups were conducted on an intention-to-treat basis to assess intervention impact at 6 weeks (postintervention) and at 6-months follow-up. Adjusted means were calculated to assess differences in two groups.

Results. In our final sample ($n = 62$), mean age was 64 years, 74% were white, and 63% had a body mass index of 30 or higher. At postintervention, Intervention group participants reported significantly increased walking minutes per week, reduced stiffness, less difficulty with activities of daily living (ADL), and less perceived helplessness in managing joint symptoms. At 6-months follow-up (postwalking period in both Intervention and WLC), walking minutes per week had decreased significantly; however, improvements in stiffness and difficulty with ADLs were maintained.

Conclusion. This study adds to the growing evidence base suggesting exercise as a safe alternative or adjunct to medications for the management of AIAA. ***The Oncologist*** 2017;22:1238–1248

Implications for Practice: Breast cancer survivors whose adjuvant endocrine treatment includes an aromatase inhibitor (AI) often experience the side effect of AI-associated arthralgia (AIAA). This study investigates the impact of a 6-week, home-based, self-directed walking program in the management of AIAA. Compared with Wait List Control, women in the Intervention group reported significantly increased walking minutes per week, reduced stiffness, less difficulty with activities of daily living, and less perceived helplessness in managing joint symptoms. This study adds to the growing evidence base suggesting exercise as a safe alternative or adjunct to medications for the management of AIAA.

Introduction

Most new cases of breast cancer are diagnosed in postmenopausal women, and in 70%–80% of these women, their tumors are hormone receptor positive (HR+), for which national guidelines recommend adjuvant endocrine therapy that includes an aromatase inhibitor (AI) [1, 2]. Joint symptoms of pain, stiffness, and achiness (arthralgia) are commonly reported side effects of AI treatment, affecting an estimated 33%–74% of breast cancer patients on AI therapy seen in clinical practice, and rated moderate to severe by as many as 70% of women who report them [3, 4]. For most breast cancer survivors experiencing AI-associated arthralgia (AIAA), pharmacological remedies such as analgesics and antidepressants provide little or no joint symptom relief [6]. There is a need to identify effective, easy-to-use, sustainable, and safe alternative or adjunctive approaches to AIAA management, so that they are able to remain on AI therapy while having as pain-free a life as possible.

We investigated whether an evidence-based walking program developed by Callahan and colleagues, which is effective

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in reducing joint symptoms in adults with arthritis (Arthritis Foundation's Walk With Ease [WWE]) [7], could have similar benefits for women experiencing AIAA. We have reported elsewhere about our adaptation of the WWE program for breast cancer survivors on AI therapy through interviews and pilot testing (WWE-Breast Cancer [WWE-BC]) [8–10]. Here, we present findings from a 6-week randomized phase II "proof of concept" study designed to evaluate the effect of WWE-BC between baseline and 6 weeks (end of intervention) and at 6-months follow-up. The specific focus of our study is breast cancer survivors reporting moderate to severe AIAA. Primary outcomes were patient-reported and included the following: (a) engagement in walking (minutes per week), (b) joint pain/symptoms, and (c) adherence to AI therapy. Secondary outcomes were as follows: (a) self-efficacy to engage in physical activity and manage joint pain/symptoms, (b) psychosocial measures of quality of life, and (c) satisfaction with WWE-BC. We also report feasibility (recruitment), tolerability (retention), and safety (adverse events).

Materials and Methods

Participants

The study sample was identified through a review of the appointment schedule for women being seen in breast cancer clinics at a university-affiliated tertiary care hospital. The recruitment period was February 2014 through August 2015. Oncology providers of patients identified as potential study participants were approached to ascertain the patient's appropriateness for the intervention study and current status of AI treatment compliance. To be eligible for the study, patients had to be adherent to their AI prescription for at least 4 weeks, age 21 or older, and not undergoing chemotherapy or radiation treatment during the study period. Patients approved by their provider were then screened in person by study staff. To identify patients with moderate to severe AIAA, eligibility was limited to patients who scored 3 or higher on a 5-point scale inquiring about joint pain, stiffness, or achiness intensity "at its worst" in the past 7 days (PROMIS Pain Intensity—Short Form 3a) [11]. Patients were also asked how many days a week they engaged in physical activity for exercise or pleasure and how many minutes per day they did so. For study eligibility, patients had to be exercising below the guideline-recommended level of 150 minutes per week [12]. Patients who met both pain and physical activity criteria were then invited to review informed consent forms and provide written consent to participate in the study. The intervention study protocol was approved by the UNC Lineberger Comprehensive Cancer Center Protocol Review Committee and the UNC Institutional Review Board. The study was registered with clinicaltrials.gov (NCT01900418).

Intervention

Walk With Ease-Breast Cancer has been described in detail elsewhere [8, 9]. The evidence base for WWE was established in group-based classes and as a self-directed physical activity program for adults with arthritis [7]. Walk With Ease includes a WWE workbook that encourages participants to walk for at least 150 minutes per week. For our phase II proof of concept study, consented patients were randomized to Intervention or Wait List Control (WLC).

The intervention period was 6 weeks (as tested in the original WWE study [7]), during which study participants were asked to walk on their own or with others at a pace that was safe, comfortable, and sustainable at the guideline-recommended level of 150 minutes per week. Participants received a copy of the Arthritis Foundation's Walk With Ease workbook [13] with strategies for starting and sustaining a daily walking program. Participants also received a 4-page brochure developed by the research team titled "Walk With Ease for women with a breast cancer diagnosis" containing brief topics such as "Why walk," "Joint pain and some cancer treatments," quotes from women who had completed the walking program in a prior pilot study [8], "How to get started," and a summary of the "UNC Pilot Study." In addition, participants received a printed physical activity log to record daily minutes of walking for leisure, pleasure or recreation. There was no contact with study participants during the 6-week intervention period. The WLC group was asked to await further contact from the research team at 6 weeks after study enrollment/baseline, at which time they received the same materials and instructions as the Intervention group and were encouraged to walk 150 minutes per week.

Questionnaires

At baseline, consented patients received a printed questionnaire with a self-addressed stamped return envelope and were asked to mail in the completed questionnaire within 1 week of recruitment. Up to three email and telephone follow-ups were conducted weekly to encourage baseline retention in the study through the completion of the baseline questionnaire. At 6 weeks from baseline, the Intervention group was mailed a 6-week questionnaire with a self-addressed stamped envelope for returning the questionnaire. The questionnaire included "Program Satisfaction" questions and a request to include their walking diary in the return envelope. At this 6-week time point, WLC participants were also mailed the 6-week questionnaire, but without the satisfaction questions. At that time, the WLC participants were provided instructions and materials and encouraged to start the walking program. Six weeks later, the WLC group received a second 6-week questionnaire that included the satisfaction questions and a request to return the walking diary in the self-addressed stamped envelope provided by the study team. Both Intervention and WLC groups were mailed a 6-months follow-up questionnaire, 6 months after they had completed the walking program.

Measures

Measures included in the questionnaires are summarized in Table 1. All measures pertain to patient-reported outcomes and are validated and commonly used in cancer or rheumatology research. Self-reported symptom measures included (a) separate Visual Analog Scales (VAS) for pain, stiffness, and fatigue [14] and (b) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [15] subscales for pain, stiffness, and function/difficulties with activities of daily living. Psychosocial measures included (a) Functional Assessment of Cancer Therapy-General (FACT-G) [16] subscales for physical, social/family, functional and emotional well-being and (b) Rheumatology Attitudes Index (RAI) [17], a measure of perceived control over rheumatology symptoms. Efficacy for pain self-management was measured using the Arthritis Self-Efficacy

Table 1. Measures

Domain	Explanation
Self-reported walking	
Walking (on average) . . . days per week . . . minutes per day	Days times minutes/day = minutes/week
Self-reported joint symptoms	
VAS Pain: how much pain/achiness/discomfort have you had in and around your joints over the past week?	0 = no pain to 10 = pain as bad as it could be. Score ≥4 is associated with premature AI discontinuation [29].
Stiffness: How much of a problem has stiffness been for you over the past week?	0 = no stiffness to 10 = stiffness as bad as it could be.
Fatigue: How much of a problem has unusual fatigue or tiredness been for you over the past week?	0 = fatigue is no problem to 10 = fatigue is a major problem. Severe fatigue is defined as ≥4 [30].
WOMAC Pain subscale Stiffness subscale Function/difficulties with activities of daily living	Higher score = greater pain, range 0–20 Higher score = greater stiffness, range 0–8 Higher score = greater difficulties, range 0–68
Total joint pain locations on a body chart	Range 1–10 locations
Psychosocial measures	
FACT-G Physical well-being Social/family well-being Functional well-being Emotional well-being	Lower score = greater symptoms, range 0–28 Lower score = less support, range 0–28 Lower score = lower function, range 0–28 Lower score = more emotional concerns, range 0–24
RAI	Higher score = greater perceived helplessness Range 1–5
Efficacy for pain self-management	
ASE Pain Symptoms	Lower score = lower self-efficacy Range 1–10 Range 1–10
Efficacy and outcome expectations for physical activity	
OEE	Higher score = negative outcome expectations Range 1–5
SEPA	Higher score = higher confidence in being physically active Range 1–5

Abbreviations: ASE, arthritis self-efficacy scale; FACT-G, functional assessment of cancer therapy-general; OEE, outcome expectations from exercise; RAI, rheumatology attitudes index; SEPA, self-efficacy for physical activity; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

Scale (ASE) subscales for pain and symptoms [18]. Additional psychosocial measures pertained to efficacy and outcome expectations for physical activity: Outcome Expectations from Exercise [19] and Self-Efficacy for Physical Activity [20] scales.

Study participants were also asked to provide demographic information (age, race, ethnicity, education, marital status, height, weight), self-assessed general health (1 = excellent to 5 = poor), and breast cancer stage and treatment. With regard to AI adherence during the study period, the study participants were asked to report how often they (a) forgot to take their AI therapy as prescribed and (b) chose not to take the AI therapy as prescribed, with response options from 1 = never forgot/never chose not to take the AI to 5 = very often forgot/often chose not to take the AI as prescribed. Participants were queried about physical activity through the following items: (a) How many days a week do you go for a walk for at least 10 minutes, for any reason, in and around your neighborhood or elsewhere? and (b) How much time (minutes) do you usually spend when you go for a walk in and around your neighborhood or elsewhere? Responses to both questions were multiplied to ascertain total minutes of walking per week.

Statistical Analysis

Analyses were conducted on an intention-to-treat (ITT) basis. During recruitment, three participants who were randomized to receive the intervention were inadvertently assigned to the WLC group instead, and three others who were randomized to the WLC group were inadvertently assigned to receive the intervention. One of the mis-randomized WLC participants did not complete the 6-week follow-up questionnaire, leaving 5 mis-randomized study participants. The mis-randomizations were unintentional and were found to be non-differential when comparing baseline demographic characteristics with those who were correctly randomized. Further, the mis-randomized participants still received a protocol-defined regimen (the walking intervention). We therefore decided to go forward with the ITT analyses, with all participants analyzed according to the group

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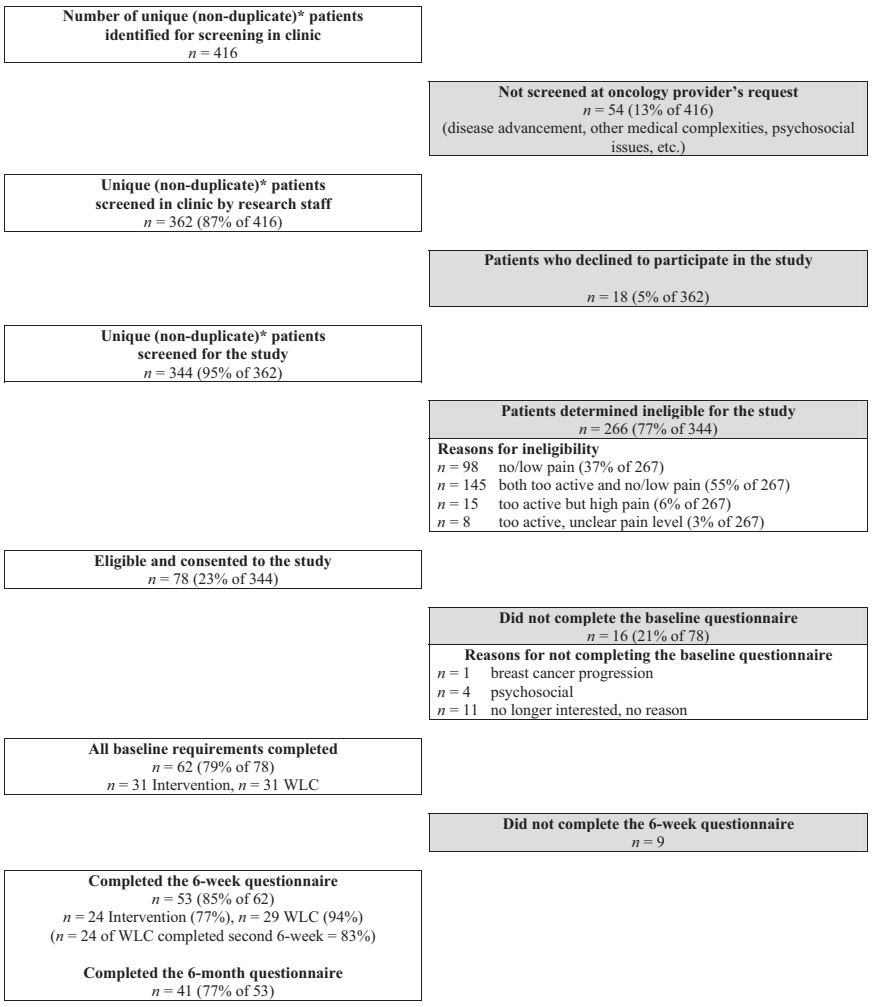

Figure 1. STROBE. *, Unique patients were screened 2–3 times to see if their joint symptoms or physical activity level had changed over time. Abbreviation: WLC, wait list control.

to which they were assigned regardless of the inadvertent randomization errors.

Baseline descriptive statistics were computed for participant demographic characteristics, joint symptom, psychosocial and efficacy measures, and other items inquiring about breast cancer diagnosis and treatments, AI adherence, self-reported health, and physical activity using means with standard deviation (SD) for continuous variables and percentages for categorical variables. Independent chi-square tests and Student's *t* tests were used to compare categorical and continuous participant characteristics, respectively.

For longitudinal analyses, least squares mean estimates were calculated with 95% confidence intervals at baseline and 6-week follow-up for the Intervention and WLC groups separately. Differences in mean psychosocial responses from the baseline to the 6-weeks follow-up were then compared between two groups. Adjusted means were calculated for the primary and secondary outcomes at baseline, postintervention follow-up (6 weeks), and at the end of the study (6-months follow-up) for the total sample and the differences between the end of intervention (6 weeks for Intervention group and 12 weeks for WLC group) and 6-months follow-up in both groups. Covariates included age, race, education, body mass index (BMI; kg/m^2), and breast cancer stage. We used mixed models to account for any autocorrelation within individual study participants.

As estimates for a future power calculation for larger sample randomized controlled trials, we calculated effect size expressed as Cohen's *d* [21] as the difference between the mean change scores from baseline to 6 weeks for the Intervention and WLC groups divided by the pooled baseline SD with adjustment for small sample size [22]. To interpret effect sizes, we used Cohen's "rules of thumb": small = 0.20, medium- = 0.50, and large = 0.80 [21].

As a proof of concept study, statistical significance was not our highest priority. However, we calculated a priori that a sample size of 60 participants would have an 80% power to detect an effect size of 0.37 or greater for the measures of VAS pain, stiffness, and fatigue. In the parent WWE study [7], our observed effect sizes for self-directed participants were 0.36, 0.40, and 0.21, respectively. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html).

Results

Recruitment, Retention, and Safety

The total number of patients identified for screening was 416 (Fig. 1); this figure does not include multiple contacts with

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Table 2. Baseline characteristics of Intervention and Wait List Control groups

Characteristic	Total *n* (%)	Intervention *n* (%)	Wait List Control *n* (%)	*p* value[a]
Demographics				
Age at baseline, years	63.8 ± 8.3	63.3 ± 6.9	64.4 ± 9.7	.59
Education, ≤high school	14 (23%)	6 (19%)	8 (27%)	.46
Body mass index, ≥30 kg/m^2	7 (11%)	3 (9%)	4 (13%)	.95
White race	46 (74%)	23 (72%)	23 (77%)	.67
General health				.15
Excellent	2 (3%)	2 (7%)	0 (0%)	
Very good	16 (27%)	6 (19%)	10 (35%)	
Good	32 (53%)	16 (52%)	16 (55%)	
Good-to-fair	1 (2%)	0 (0%)	1 (3%)	
Fair	9 (15%)	7 (23%)	2 (7%)	
Breast cancer clinical characteristics				
Breast cancer stage				.42
I	25 (40%)	10 (31%)	15 (50%)	
II	20 (32%)	11 (34%)	9 (30%)	
III	7 (11%)	5 (16%)	2 (7%)	
IV	10 (16%)	6 (19%)	4 (13%)	
Total years after diagnosis	2.8 ± 2.5	2.7 ± 2.9	2.8 ± 2	.91
Radiation	43 (74%)	21 (70%)	22 (79%)	.46
Chemotherapy	35 (65%)	18 (62%)	17 (68%)	.65
Lumpectomy	31 (84%)	13 (72%)	18 (95%)	.06
Mastectomy	24 (57%)	11 (52%)	13 (62%)	.53
Ever taken tamoxifen	16 (29%)	11 (41%)	5 (17%)	.05
Currently taking exemestane	12 (25%)	7 (30%)	5 (19%)	.36
Currently taking anastrozole	27 (52%)	13 (54%)	14 (50%)	.76
Currently taking Letrozole	30 (53%)	16 (53%)	14 (52%)	.91
Hysterectomy	31 (50%)	14 (44%)	17 (57%)	.31
Taking vitamin D supplement	47 (80%)	28 (90%)	19 (68%)	.03
Forgetting/choosing not to take AI				.04
Never forget	44 (79%)	25 (89%)	19 (68%)	
Forget once a week	11 (20%)	2 (7%)	9 (32%)	
Forget twice a week	1 (2%)	1 (4%)	0 (0%)	
Never choose not to take AI	54 (100%)	27 (100%)	27 (100%)	1.0
Self-reported joint pain				
WOMAC, pain[a]	6.9 ± 3.4	7.2 ± 3.6	6.7 ± 3.1	.50
WOMAC, stiffness[a]	4.0 ± 1.6	4.4 ± 1.9	3.7 ± 1.3	.07
WOMAC, difficulty[a]	22.2 ± 10.6	24.6 ± 10.5	20.0 ± 10.4	.11
WOMAC, total score[a]	33 ± 14.4	36.2 ± 14.9	30.5 ± 13.8	.17
Pain, VAS[a]	5.2 ± 2.3	5.3 ± 2.5	5.1 ± 2.0	.79
Fatigue, VAS[a]	4.3 ± 2.8	4.2 ± 3.1	4.3 ± 2.5	.94
Stiffness, VAS[a]	4.9 ± 2.4	4.8 ± 2.5	4.9 ± 2.4	.89
Pain points, total[a]	4.5 ± 2.0	4.7 ± 2.1	4.3 ± 1.9	.45
Psychosocial measures				
Pain ASE[b]	6.3 ± 2.3	5.7 ± 2.4	6.8 ± 2.1	.06
Symptom ASE[b]	6.7 ± 2.2	6.2 ± 2.4	7.1 ± 1.7	.10
OEE[c]	2.2 ± 0.6	2.1 ± 0.7	2.2 ± 0.6	.73
SEPA[d]	2.6 ± 0.9	2.5 ± 0.8	2.6 ± 0.9	.74
FACT-G, physical[e]	20.9 ± 4.7	20.8 ± 4.7	21.1 ± 4.9	.81

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Table 2. (continued)

Characteristic	Total *n* (%)	Intervention *n* (%)	Wait List Control *n* (%)	*p* value[a]
FACT-G, social/family[e]	21.2 ± 5.9	21.0 ± 6.1	21.5 ± 5.7	.74
FACT-G, functional[e]	18.6 ± 5.6	17.3 ± 6.7	19.9 ± 3.8	.07
FACT-G, emotional[e]	18.9 ± 4.7	18.4 ± 5.0	19.3 ± 4.3	.46
RAI score[f]	2.3 ± 0.9	2.4 ± 1.0	2.2 ± 0.9	.39
Walking				
Walking time, min/wk	35.5 ± 50.4	32.2 ± 49.7	39.0 ± 51.7	.61

Result of Student's *t* test (continuous variables) or chi-square test (categorical variables) for determining if the Intervention and Wait List Control means are significantly different.
[a]Higher scores indicate greater symptom severity.
[b]Lower scores indicate lower self-efficacy in managing pain and symptoms.
[c]Higher scores indicate negative outcome expectations from exercise.
[d]Higher scores indicate higher confidence in being physically active.
[e]Lower scores indicate worse well-being.
[f]Higher scores indicate greater perceived helplessness.
Abbreviatons: ASE, arthritis self-efficacy scale; FACT-G, functional assessment of cancer therapy-general; OEE, outcome expectations from exercise; RAI, rheumatology attitudes index; SEPA, self-efficacy for physical activity; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

potential study participants. Of these patients, 54 were eliminated from further consideration based on oncology provider concerns—disease advancement, other medical complexities, or psychosocial issues on the day they were in clinic). Of the patients approached by research staff, 18 declined to be considered for the study. Of the remaining 344 patients screened in person by research staff, 266 (77%) were determined ineligible for reasons of low/no pain and/or engagement in high levels of physical activity. This left 78 patients who were consented into the study, of which 62 (79% of 78) completed the baseline questionnaire—11 patients were no longer interested in the study, 4 had psychosocial reasons (such as losing a job or taking care of an ailing husband), and 1 had cancer progression. Thirty-one patients who completed the baseline questionnaire were randomized to Intervention and 31 patients to WLC. Nine participants did not complete the 6-week questionnaire, leaving 53 (85% of 62) for the ITT analysis—24 Intervention and 29 WLC. At 6-months postintervention, 41 (77% of 53) completed the 6-months questionnaire. No adverse events related to the intervention were reported.

Study Participants

An overview of baseline characteristics of Intervention and WLC groups is presented in Table 2. Self-assessed general health was rated very good/excellent by 30% of participants, while the remainder rated their general health as fair, good, and between fair and good. Participants averaged just under 3 years since breast cancer diagnosis. Average amount of time on AI was 1.7 years (SD 1.43), ranging from .17 to 7 years. Seventy-nine percent of participants reported "never" forgetting to take their AI therapy, 20% reported forgetting to take their AI about once a week, and 2% reported forgetting to take their AI twice a week. At baseline, significantly more Intervention participants than WLC participants had ever taken tamoxifen ($p = .05$), taken vitamin D supplement ($p = .03$), and never forgot to take their AI ($p = .4$).

At baseline, WOMAC scores (higher scores signifying greater pain) were moderate for Pain (6.9 on a scale of 0–20), mid-range for Stiffness (4.0 on a scale of 0–8), and moderate for Difficulty with Activities of Daily Living (22.2 on a scale of 0–68). Visual Analog Scales (range 0–10) were in the mid-range for Pain (5.2), Stiffness (4.9), and Fatigue (4.3). Mean number of pain points (identified on a graphic of a human) was 4.5 out of 10. Overall psychosocial quality of life as measured by FACT-G subscales (scale of 0–28, with higher scores signifying higher quality of life) was moderately high: Physical Well-Being (20.9), Social/Family Well-Being (21.2), Functional Well-Being (18.6), and Emotional Well-Being (18.9). Perceived helplessness in coping with joint symptoms (RAI score, range 1–5, with higher scores indicating greater perceived helplessness) was moderate (2.3). Efficacy for self-management of arthritis symptoms (range 1–10, with higher scores signifying higher self-efficacy) was moderately high for ASE Pain (6.3) and ASE Symptoms (6.7). Outcome Expectations from Exercise (range 1–5, with lower scores signifying higher expectations) were positive (2.2), and Self-Efficacy for Physical Activity (range 1–5, with higher scores signifying higher confidence in being physically active) were mid-range (2.6). Average minutes walking per week was 35.5.

Intervention Impact at 6 Weeks

A summary of the mean change scores for Intervention and WLC groups between baseline and end-of-intervention (6 weeks) is presented in Table 3, adjusted for baseline age, BMI, race, education, and breast cancer stage. Measures indicating significant improvement in the Intervention group included increased walking minutes per week ($p < .01$) and improved WOMAC Stiffness core ($p < .05$), WOMAC Difficulty with Activities of Daily Living/Function ($p < .01$), WOMAC Total score ($p < .01$), and RAI perceived helplessness score ($p < .01$). Cohen's *d* effect sizes were large for walking minutes/week ($d = 1.17$) and medium or approaching medium for WOMAC Stiffness ($d = 0.45$), WOMAC Difficulty/Function ($d = 0.58$), WOMAC Total ($d = 0.53$), and RAI Score ($d = 0.44$). When the WLC group completed the walking intervention (after their wait period, at weeks 7 through 12), the beneficial effects of walking were similar to those observed in the Intervention group (weeks 1 through 6; data not presented).

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Table 3. Covariate-adjusted[a] means (SD) for baseline and 6-week follow-up measures—postwalking for Intervention group, no walking for Wait List Control group

Outcome	Time point	Intervention	Wait List Control	Effect size
Walking				
Walking time, min/wk	Baseline mean (SD)	32.49 (55.12)	39.38 (55.02)	
	6-week mean (SD)	108.7 (55.32)	49.89 (54.92)	
	Change (95% CI)	76.22 (51.33, 101.1)[c]	10.52 (–12.08, 33.12)	1.17 (0.54, 1.81)
Self-reported arthritis symptoms				
WOMAC, pain[d]	Baseline mean (SD)	7.22 (3.34)	6.57 (3.32)	
	6-week mean (SD)	6.82 (3.42)	6.65 (3.32)	
	Change (95% CI)	−0.4 (–1.91, 1.1)	0.08 (–1.31, 1.46)	0.14 (–0.41, 0.70)
WOMAC, stiffness[d]	Baseline mean (SD)	4.43 (1.66)	3.66 (1.65)	
	6-week mean (SD)	3.49 (1.72)	3.48 (1.65)	
	Change (95% CI)	–0.94 (–1.78, −0.11)[b]	−0.18 (–0.94, 0.57)	0.45 (–0.11, 1.02)
WOMAC, difficulty[d]	Baseline mean (SD)	24.39 (10.42)	19.84 (10.43)	
	6-week mean (SD)	17.69 (10.6)	19.35 (10.28)	
	Change (95% CI)	–6.69 (–11.35, −2.04)[c]	−0.49 (–4.51, 3.53)	0.58 (–0.05, 1.22)
WOMAC, total score[d]	Baseline mean (SD)	35.99 (14.11)	30.41 (14.25)	
	6-week mean (SD)	27.24 (14.55)	29.29 (14)	
	Change (95% CI)	–8.75 (–15.01, −2.5)[c]	−1.13 (–6.44, 4.19)	0.53 (–0.10, 1.16)
Pain, VAS[d]	Baseline mean (SD)	5.22 (2.43)	4.95 (2.43)	
	6-week mean (SD)	4.47 (2.53)	4.82 (2.44)	
	Change (95% CI)	−0.75 (–1.93, 0.44)	−0.12 (–1.24, 0.99)	0.25 (–0.37, 0.87)
Fatigue, VAS[d]	Baseline mean (SD)	4.2 (2.81)	4.32 (2.82)	
	6-week mean (SD)	4.83 (2.87)	4.77 (2.82)	
	Change (95% CI)	0.63 (–0.56, 1.82)	0.45 (–0.63, 1.53)	0.06 (–0.53, 0.65)
Stiffness, VAS[d]	Baseline mean (SD)	4.76 (2.48)	4.99 (2.49)	
	6-week mean (SD)	4.52 (2.58)	5.17 (2.48)	
	Change (95% CI)	−0.24 (–1.53, 1.05)	0.18 (–1.02, 1.38)	0.17 (–0.45, 0.78)
Psychosocial measures				
Pain ASE[d]	Baseline mean (SD)	5.73 (2.13)	6.87 (2.13)	
	6-week mean (SD)	5.26 (2.11)	6.98 (2.11)	
	Change (95% CI)	−0.46 (–1.32, 0.4)	0.12 (–0.67, 0.91)	0.27 (–0.29, 0.83)
Symptom ASE[d]	Baseline mean (SD)	6.25 (2.09)	7.17 (2.07)	
	6-week mean (SD)	5.71 (2.08)	7.15 (2.07)	
	Change (95% CI)	−0.53 (–1.43, 0.36)	−0.02 (–0.86, 0.82)	0.24 (–0.31, 0.80)
OEE[e]	Baseline mean (SD)	2.09 (0.61)	2.2 (0.61)	
	6-week mean (SD)	2.13 (0.59)	2.26 (0.6)	
	Change (95% CI)	0.04 (–0.18, 0.26)	0.06 (–0.15, 0.26)	0.03 (–0.53, 0.59)
SEPA[f]	Baseline mean (SD)	2.57 (0.82)	2.56 (0.82)	
	6-week mean (SD)	2.88 (0.83)	2.73 (0.82)	

(continued)

Table 3. (continued)

Outcome	Time point	Intervention	Wait List Control	Effect size
	Change (95% CI)	0.3 (–0.09, 0.7)	0.17 (–0.19, 0.53)	0.16 (–0.41, 0.74)
FACT-G, physical well-being[g]	Baseline mean (SD)	20.9 (4.7)	20.73 (4.67)	
	6-week mean (SD)	21.26 (4.62)	21.06 (4.63)	
	Change (95% CI)	0.36 (–1.5, 2.22)	0.33 (–1.4, 2.06)	0.01 (–0.55, 0.56)
FACT-G, social/family well-being[g]	Baseline mean (SD)	21.14 (5.58)	21.48 (5.54)	
	6-week mean (SD)	20.64 (5.28)	21.89 (5.45)	
	Change (95% CI)	−0.51 (–2.25, 1.24)	0.41 (–1.2, 2.02)	0.16 (–0.39, 0.72)
FACT-G, functional well-being[g]	Baseline mean (SD)	17.55 (5.51)	19.74 (5.47)	
	6-week mean (SD)	18.42 (5.13)	18.98 (5.37)	
	Change (95% CI)	0.87 (–0.65, 2.39)	−0.76 (–2.15, 0.64)	0.29 (–0.27, 0.85)
FACT-G, emotional well-being[g]	Baseline mean (SD)	18.84 (4.21)	19.07 (4.18)	
	6-week mean (SD)	18.67 (4.05)	19.11 (4.14)	
	Change (95% CI)	−0.17 (–1.72, 1.38)	0.05 (–1.36, 1.46)	0.05 (–0.51, 0.61)
FACT-G total score[g]	Baseline mean (SD)	78.42 (15.34)	80.95 (15.24)	
	6-week mean (SD)	79.9 (14.36)	81.02 (15)	
	Change (95% CI)	1.48 (–3.32, 6.27)	0.07 (–4.28, 4.42)	0.09 (–0.47, 0.65)
RAI score[h]	Baseline mean (SD)	2.34 (0.94)	2.16 (0.93)	
	6-week mean (SD)	1.92 (0.87)	2.15 (0.91)	
	Change (95% CI)	–0.43 (–0.68, −0.17)[c]	−0.01 (–0.25, 0.23)	0.44 (–0.12, 1.00)

[a]Adjusted for baseline age, BMI, race, education, and breast cancer stage.
[b]$p < .05$.
[c]$p < .01$.
[d]Higher scores indicate greater symptom severity.
Lower scores indicate lower self-efficacy in managing pain and symptoms.
[e]Higher scores indicate negative outcome expectations from exercise.
[f]Higher scores indicate higher confidence in being physically active.
[g]Lower scores indicate worse well-being.
[h]Higher scores indicate greater perceived helplessness.
Abbreviations: ASE, arthritis self-efficacy scale; CI, confidence interval; FACT-G, functional assessment of cancer therapy-general; OEE, outcome expectations from exercise; RAI, rheumatology attitudes index; SEPA, self-efficacy for physical activity; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

Six-Months Follow-Up

A summary of findings at 6-months follow-up is presented in Table 4. Total walking minutes per week decreased significantly from postintervention to 6-months follow-up ($p < .01$), illustrating the challenge of sustaining behavioral interventions in the absence of continued active intervention. Rheumatology Attitudes Index perceived helplessness scores returned to baseline values ($p < .01$). However, improvements seen in WOMAC Stiffness, Difficulty/Function, and Total scores were largely maintained at 6 months, suggesting longer-lasting impact.

Satisfaction with WWE-BC

In response to the question "I benefitted from doing the WWE program," all who responded ($n = 36$) said they agreed or strongly agreed with this statement, including participants in WLC after they had completed the walking intervention. There was similar agreement/strong agreement (100%) with the statement "The WWE program motivated me to become more physically active" ($n = 37$) and with the statement "I would recommend the WWE program to a friend or family member" (97%). Regarding the statement "I think the WWE program is an appropriate amount of time (6 weeks) to see benefits from the program", 83% agreed/strongly agreed while 17% disagreed or strongly disagreed ($n = 31$). Eighty-three percent thought the WWE workbook was very helpful or somewhat helpful with reaching their walking goals ($n = 30$).

Discussion

We conducted a "proof of concept" study to evaluate the impact of an evidence-based self-directed walking program on joint symptoms in breast cancer survivors experiencing moderate to severe AIAA. Study participants significantly increased their walking minutes per week during the 6-week walking period, and walking was associated with significant improvements in

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Table 4. Covariate-adjusted[a] means (SD) for postintervention to 6-month follow-up measures to assess whether outcomes seen postintervention were maintained at 6 months

Outcome	Mean (SD) at baseline	Mean (SD) at postintervention	Mean (SD) at 6 months	Mean change (95% CI) from postintervention to 6 months
Walking				
Walking time, min/wk	36.29 (59.96)	101.14 (68.41)	66.15 (85.5)	−34.99 (–58.86, −11.12)[b]
Self-reported arthritis symptoms				
WOMAC, pain[c]	6.92 (3.51)	6.09 (3.81)	6.76 (4.67)	0.67 (−0.45, 1.78)
WOMAC, stiffness[c]	4.07 (1.76)	3.12 (1.91)	3.27 (2.4)	0.14 (−0.47, 0.75)
WOMAC, difficulty[c]	22.07 (10.57)	17.71 (11.63)	18.23 (14.61)	0.52 (−3.46, 4.5)
WOMAC, total score[c]	33.21 (14.86)	26.63 (15.89)	27.56 (19.81)	0.92 (−4.43, 6.28)
Pain, VAS[c]	5.14 (2.58)	4.33 (2.83)	4.49 (3.54)	0.16 (−0.86, 1.18)
Fatigue, VAS[c]	4.32 (3.02)	4.4 (3.35)	4.09 (3.88)	−0.31 (−1.28, 0.65)
Stiffness, VAS[c]	4.85 (2.48)	4.33 (2.68)	4.32 (3.42)	−0.01 (−0.98, 0.96)
Psychosocial measures				
Pain ASE[d]	6.31 (2.24)	5.99 (2.49)	6.53 (3)	0.53 (−0.19, 1.26)
Symptom ASE[d]	6.72 (2.17)	6.28 (2.42)	6.64 (3.24)	0.36 (−0.52, 1.24)
OEE[e]	2.15 (0.65)	2.15 (0.74)	2.08 (0.91)	−0.07 (−0.31, 0.16)
SEPA[f]	2.55 (0.89)	2.85 (0.88)	2.9 (1.19)	0.04 (−0.26, 0.34)
FACT-G, physical[g]	20.82 (4.87)	21.71 (5.42)	21.06 (6.46)	−0.65 (−2.18, 0.87)
FACT-G, social/family[g]	21.23 (5.83)	20.84 (6.34)	20.86 (7.35)	0.01 (−1.58, 1.61)
FACT-G, functional[g]	18.59 (5.69)	18.96 (6.21)	19.42 (7.22)	0.46 (−1.12, 2.04)
FACT-G, emotional[g]	18.89 (4.43)	18.55 (5)	18.58 (5.99)	0.03 (−1.45, 1.51)
FACT-G total score[g]	79.49 (16.17)	80.49 (17.79)	79.66 (20.66)	−0.82 (−5.48, 3.83)
RAI score[h]	2.26 (0.96)	1.95 (1.07)	2.29 (1.14)	0.34 (0.11, 0.56)[b]

[a]Adjusted for baseline age, BMI, race, education, and breast cancer stage.
[b]$p < .01$.
[c]Higher scores indicate greater symptom severity.
[d]Lower scores indicate lower self-efficacy in managing pain and symptoms.
[e]Higher scores indicate negative outcome expectations from exercise.
[f]Higher scores indicate higher confidence in being physically active.
[g]Lower scores indicate worse well-being.
[h]Higher scores indicate greater perceived helplessness.
Abbreviations: ASE, arthritis self-efficacy scale; CI, confidence interval; FACT-G, functional assessment of cancer therapy-general; OEE, outcome expectations from exercise; RAI, rheumatology attitudes index; SD, standard deviation; SEPA, self-efficacy for physical activity; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

WOMAC Stiffness, Difficulty with Activities of Daily Living/Function scales, WOMAC Total score, and perceived helplessness in managing their joint symptoms (RAI). When the 10 study participants with stage IV breast cancer were excluded from the analysis, the FACT-G measures showed even greater improvement for Intervention compared with WLC postintervention.

These findings are promising and warrant further exploration in a large-sample trial. Our findings corroborate those reported in an earlier pilot study of WWE-BC that assessed the feasibility of the home-based walking program in breast cancer survivors age 65 and older, which suggested intervention benefits for reducing joint stiffness [8]. At 6-months follow-up, the minutes/week that participants walked declined to preintervention levels and a return to baseline values was seen for most psychosocial and efficacy measures. However, it is notable that WOMAC Stiffness, Difficulty/Function, and Total scores remained at the improved levels seen immediately postintervention.

Our findings join a small but growing number of studies evaluating the potential benefits of physical activity in managing AIAA. Of these studies, the largest to date, by Irwin and colleagues, was a randomized controlled trial in breast cancer survivors reporting less than 90 minutes a week of aerobic exercise, no strength training, and scoring $\geq$3 for worst joint pain (scale 0–10) [23, 24]. Participants in that study ($n = 121$) were randomized to usual care or an exercise intervention that included twice-weekly supervised resistance training and home-based aerobic exercise, with increasing intensity over time. At end of intervention (12 months), the intervention group reported at 29% decrease in "worst" joint pain scores, while the usual care group reported a 3% increase ($p < .001$). Similarly, pain severity and pain interference scores declined significantly in the intervention compared with usual care group ($p < .001$). The authors did not find a dose-response effect of exercise; more exercise was not associated with greater improvement in joint symptoms. Other small scale studies of exercise to reduce AIAA have explored aquatic exercise [25], Nordic walking [26], and an 8-week home-based aerobic and resistance exercise program [27], and all have reported promising benefits. Recent meta-analyses of AIAA management interventions rated the

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overall evidence regarding exercise to reduce AIAA as moderate and that further studies are needed [6, 28].

A strength of our study is that, similar to the Irwin study [23, 24], it is focused specifically on women experiencing moderate to severe AIAA. This subset of breast cancer survivors is in greatest need of effective ways to manage their joint symptoms, because they are at risk of suboptimal adherence and discontinuation and poor quality of life. A further strength is that we used a simple, scalable intervention that is evidence-based in reducing arthritis and joint symptoms [7] and offers web-based support for adults wanting to pursue a more active lifestyle (http://www.arthritis.org/living-with-arthritis/tools-resources/walk-with-ease/) [13]. Our findings suggest that almost any level of increased physical activity may reduce AIAA and that home-based physical activity can be done at a time, place, and pace to accommodate the wide variety of lifestyles of breast cancer survivors. And, while our study was focused on women with moderate to severe joint symptoms, survivors experiencing milder AIAA symptoms may experience similar benefits.

Our study has some limitations. We have noted earlier that there was some unintentional mis-randomization; however, sensitivity analysis did not change the overall results of our study. The findings were the same regardless of whether the analysis was according to original random assignment or mis-randomization. Our final sample is over-represented with women with more than a high school education; however, the proportion of nonwhite women (28% Intervention and 23% WLC) is representative of the racial mix of the state where the study was conducted. Recruitment was challenging in light of the dual requirements for moderate to severe joint symptoms and below guideline recommended levels of physical activity. As we screened survivors for study eligibility, many women reported high levels of exercise despite substantial joint pain. We did not collect information on the type or intensity of exercise that these women engaged in, only the number of minutes per week. As in all behavioral intervention studies, there is always the self-selection bias of women who are willing and able to participate in this type of study, which affects generalizability to the general population of female breast cancer survivors.

A second limitation was the shortness of our intervention period—6 weeks, as tested in the original WWE study [7]; a longer intervention period may have produced stronger and more lasting benefits for reducing joint symptoms and deserves further investigation in a large sample trial. A future study might also include intermittent contact with study participants to encourage their engagement in walking, such as contacts via telephone, text messages, or email. Further, although we screened for new or recently-intensified joint symptoms, we cannot rule out the possibility that some of the joint symptom improvements were at least partially for arthritis pain and stiffness, which are common in postmenopausal women.

Conclusion

Further studies are warranted; however, the combined evidence of diverse studies cited above suggests that physical activity can be offered to women on AI therapy as a safe alternative or adjunct to medications for the management of AIAA. Guidelines in general recommend 150 minutes a week for adults diagnosed with cancer [12], and this level of physical activity could be an appropriate target for breast cancer survivors seeking to manage their AIAA. Our interviews with breast cancer survivors suggest that the message of exercise for the management of AIAA would be well-received at the time AI therapy is initiated, rather than waiting until joint symptoms have started or intensified [10]. The breast cancer diagnosis can present a "teachable moment" where patient-oncology provider conversations about physical activity can focus on physical well-being and mental health as well as the potential for symptom self-management.

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Disclosures

The authors indicated no financial relationships.

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