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RESEARCH

Aerobic exercise and aromatase inhibitor–associated musculoskeletal symptoms: results of a randomized clinical trial

Catherine M. Bender[1] · Susan M. Sereika[1] · Amanda L. Gentry[1] · Yehui Zhu[2] · Monica Wagner[3] · Cheryl Cuglewski[1] · Jennie Duquette[1] · George Grove[4] · Meredith Cummings[1] · Myeong-ga Cho[1] · Adam M. Brufsky[5] · Emilia J. Diego[5] · Priscilla F. McAuliffe[5] · Anna L. Marsland[4] · Yvette P. Conley[1] · Kirk I. Erickson[6]

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Abstract

Purpose Women receiving aromatase inhibitors (AIs) for breast cancer frequently experience musculoskeletal symptoms (AIMS) including joint pain, stiffness, and muscle weakness. Aerobic exercise may reduce AIMS, but the evidence is inconclusive. This investigation examined whether aerobic exercise reduces pain in women with breast cancer.

Methods Pain was a secondary outcome of a randomized controlled trial where postmenopausal women with breast cancer receiving AIs ($N=136$) with or without pain were randomized to 6 months of moderate-intensity aerobic exercise ($n=70$) or usual care ($n=66$). The primary (Brief Pain Inventory severity, interference and worst pain) and secondary (SF-36 Bodily Pain and Breast Cancer Prevention Trial Symptom Checklist Musculoskeletal Pain) pain outcomes were assessed at pre-randomization (T1) and post-intervention (T2). Linear mixed modeling with linear contrasts was used to examine the effect of group assignment on outcomes.

Results Participants were a median = 4.7 months post-breast cancer diagnosis at T1. Group-by-time interactions were observed for pain severity ($\bar{x}=0.848$, 95% confidence interval (CI) = 0.233–1.464), pain interference ($\bar{x}=0.997$, 95% CI = 0.448–1.547), and worst pain ($\bar{x}=1.371$, 95% CI = 0.273–2.461) with significant increases in pain severity, interference, and worst pain in controls, small effect sizes, and no significant changes in the exercise group. We also found that a greater percentage of women in the control group had a clinically significant increase (≥ 2 points) in worst pain ($p=0.024$) and pain severity ($p=0.029$).

Conclusion Our results suggest that aerobic exercise prevents pain increase and may reduce pain prevalence when initiated early in AI therapy. The trial was registered at Clinical Trials.gov (NCT 02793921) on May 20, 2016.

Key findings Moderate-intensity aerobic exercise may prevent increases in pain and reduce pain when initiated early in AI therapy in postmenopausal women with breast cancer. Lack of exercise may be associated with increased over-the-counter pain medication use.

Keywords Musculoskeletal symptoms · Aromatase inhibitors · Postmenopause

Introduction

Five years of aromatase inhibitor (AI) therapy has been associated with improved survival outcomes in postmenopausal women with early-stage, hormone receptor positive breast cancer [1]. However, 50% of women report new-onset or worsening joint pain with AI therapy [2].

While the risk for AI-associated musculoskeletal symptoms (AIMS) persists throughout the standard 5-year AI course, [3] joint pain typically emerges soon after therapy initiation. The median time for pain to emerge is 6 weeks post-initiation while average reports of peak pain are at 6 months [4–6]. Pain is associated with poor AI therapy adherence and premature discontinuation in 31 to 73% of women [4–7]. Pain is the primary reason for discontinuation within the first 4.5 months of therapy [8].

While the mechanisms of AIMS are not clear, it is clear that multiple factors contribute to the problem including hormonal changes [9]. In postmenopausal women with breast cancer, AI use leads to additional, precipitous estrogen deprivation and molecular changes producing inflammatory effects and modulation of nociception processing

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which may exacerbate musculoskeletal symptoms [10]. Estrogen deprivation is among the strongest predictors of pain [10]. Women with more recent menses cessation (< 5 years) may be more susceptible to pain with the added precipitous estrogen drop with AI therapy [11]. There is also evidence suggesting that higher body mass index (BMI), previous taxane chemotherapy, and disease stage are associated with pain, but the pattern of these findings remains inconsistent [12].

Exercise may reduce pain in women with breast cancer, but the evidence is unclear [13–20]. Recent reviews have demonstrated inconclusive and conflicting results related to the potential benefits of exercise [13, 14, 16, 18–21]. Irwin et al. [17] found reduced pain with 12 months of aerobic exercise + strength training in women with breast cancer who were an average of 1.9 years post-AI therapy initiation [17]. However, the efficacy of aerobic exercise initiated earlier in the AI therapy course, when pain typically arises, is unknown. The purpose of this analysis of a secondary outcome from a randomized control trial (RCT) was to examine whether, compared to usual care, 6 months of moderate-intensity aerobic exercise reduces pain in postmenopausal women with early-stage breast cancer receiving AI therapy. We hypothesized that, compared to usual care, aerobic exercise, initiated early in the AI therapy course, would be associated with a reduction in pain severity, pain interference, and worst pain in postmenopausal women with breast cancer.

Methods

The Exercise Program for Cognition in Cancer (EPICC) Trial was an RCT in which women with breast cancer were randomized to receive 6 months of moderate intensity aerobic exercise or usual care. The primary outcome of EPICC was neurocognitive function. Pain was among the secondary outcomes of EPICC in which we also assessed the direct effects of exercise on symptoms such as pain that co-occurred with neurocognitive function. Assessments occurred at pre-randomization (T1) and after the completion of the exercise intervention or a comparable follow-up for controls (post-intervention, T2). The trial was approved by the University of Pittsburgh and St. Clair Health Institutional Review Boards and registered at Clinical Trials.gov (NCT 02793921). All participants provided written informed consent.

Participants

EPICC trial participants included postmenopausal women with stage 0–IIIa hormone receptive + breast cancer who were < 80 years old, English-speaking, had a minimum of 8 years of education and within 2 years of their diagnosis. Women were excluded if they received chemotherapy for a prior cancer, had evidence of distant metastasis, were hospitalized for psychiatric illness within 2 years, had any medical condition precluding exercise, had persistent breast cancer surgery complications (e.g., seroma requiring aspiration, wound dehiscence, infection, prolonged drain output, lymphedema), used an assisted walking device, or had a history of neurological illness, substance abuse, falls, or balance problems. The original enrollment criteria included women newly diagnosed with breast cancer, at pre-AI therapy, with an estimated, age-based VO_{2max} in the upper 50th percentile. To enhance enrollment, particularly post-COVID, we expanded the criteria to include women within 2 years of completing primary therapy and we dropped the VO_{2max}, requirement because very few women reached that threshold. Participants for this analysis of the EPICC secondary pain outcomes were limited to women receiving AI therapy. Participants' reports of pain were not a criterion for enrollment.

Procedure

Women were recruited from oncology clinics of the UPMC Hillman Cancer Center Breast Cancer Program and the Breast Care Center of St. Clair Health. At T1, demographic and clinical characteristics, concomitant medications, physical activity (Actigraphy), cardiorespiratory fitness, and pain were assessed. Following T1, participants were randomized to the exercise intervention or control arms. All participants maintained a weekly log of their exercise via an automated REDCap [22] survey. The T2 assessments occurred within 2 weeks of intervention completion and at a comparable time in controls.

Outcomes

Three primary pain outcomes were measured via the Brief Pain Inventory (BPI); they include pain severity, worst pain, and pain interference scores [23]. The BPI is an 11-item self-report measure with higher scores indicating greater pain. Pain severity, the sensory component of pain, was measured with the average of the scores on the four BPI pain severity items. Pain at its worst was measured with the score on the BPI item, *pain at its worst in the last 24 h.* Pain interference, the reactive component of pain or the extent that pain interferes with everyday function, was measured with the average of the scores on the seven BPI interference items [23]. Secondary pain outcomes included the Musculoskeletal Pain subscale of the Breast Cancer Prevention Trial Symptom Checklist (BCPT) [24, 25], and the Bodily Pain subscale of the Medical Outcome Study SF-36 [26]. The BCPT is a self-report measure of occurrence and burden associated

with endocrine therapy–related symptoms [24]. Its musculoskeletal pain subscale contains five items with responses from 0 (not at all) to 4 (extremely). The score is the sum of those items [25]. The SF-36 Bodily Pain subscale consists of two items rated on a Likert scale, scaled to a 0 to 100 score. Higher scores indicate greater pain [26]. Participants were given the option of completing the patient-reported outcomes via paper and pencil or REDCap.

Descriptors and covariates

Demographic and clinical characteristics (tumor, therapy, medical history) were extracted from the electronic health record. Covariates, including disease stage, chemotherapy use (yes/no), days since AI therapy initiation, years since menopause, and prescribed and over-the-counter pain medications (yes/no), were collected via the electronic health record. BMI was assessed during the cardiorespiratory fitness test.

Cardiorespiratory fitness

Cardiorespiratory fitness was measured using a sub-maximal graded exercise test [27]. This method was chosen because of the concern that maximal exercise testing can be challenging in at-risk or impaired populations. At the time of the inception of this trial, there was minimal safety information related to the use of the maximal exercise test in women with breast cancer. Therefore, the submaximal testing was chosen because it is considered a reliable and desirable approach for reducing risks. After a brief warm-up, the submaximal graded test was conducted using a modified Balke protocol during which the participant walked on a motor-driven treadmill at a constant speed between 2.0 and 4.0 miles per hour with 1% increments of incline each minute. Test speed was determined by the ability of the participant in consultation with the exercise physiologist before the test began. Prior to the test, height in inches and weight in pounds were recorded and the participant was fitted with a facemask to collect inspired air. During the test, heart rate was continually monitored along with blood pressure and rating of perceived exertion (RPE) every 2 min. Exhaled air was collected via a facemask connected to a ParvoMedics TrueOne 2400 metabolic cart. The test continued until any of the following criteria were met: (1) the participant reached 85% of their age-based heart rate maximum (220-age), (2) a RPE $\geq$ 15 was achieved for participants whose heart rate response was blunted due to beta-blocker medication, (3) the participant reached volitional exhaustion, or (4) the medical monitoring team expressed safety concerns about test continuation. VO2 submax was defined relative to body weight in kilograms (ml/kg/min) achieved at 85% of the age-predicted maximal heart rate.

Intervention

The 6-month exercise intervention prescribed a minimum of 150 min of moderate-intensity aerobic exercise/week under supervised conditions (monitored by exercise trainers and physiologists) as suggested by the American College of Sports Medicine (ACSM) recommendations for cancer survivors [28]. ACSM-certified research staff with exercise training expertise supervised the sessions and monitored and recorded intervention adherence, intensity, and any adverse events (e.g., fainting, dizziness, cardiac abnormalities, stroke, fracture). Vital sign checks and 5–10-min warm-ups/cool-downs were performed pre- and post-each exercise session by an exercise trainer. Based upon the T1 level of conditioning, exercise duration gradually increased during the first four weeks with the goal of reaching 45–60 min of exercise 3 days/week between weeks.

During exercise sessions, exercise intensity was measured continuously using a Polar H10 heart rate monitor, and RPEs were recorded at 15-min intervals using the BORG scale [29]. Participants were asked to rate their level of perceived exertion during each exercise session with the goal to be in the 13–15 range. The RPE value and heart rate were both taken into consideration when determining if the participant was working in the prescribed moderate-intensity level. Participants were encouraged to maintain a moderate-level intensity, equivalent to 60–75% of their age-predicted maximal heart rate. This aerobic exercise duration, frequency, and intensity were maintained through the remainder of the intervention and were monitored and recorded throughout the intervention.

The sessions were delivered by research staff at the Brain Aging and Cognitive Health (BACH) Lab of the University of Pittsburgh, Greater Pittsburgh YMCAs, and the Greater Pittsburgh Jewish Community Center. Participants chose their exercise mode, (treadmills, elliptical machines, stationary bicycles, or indoor walking tracks). In March 2020, COVID-19 stay-at-home restrictions commenced, and in-person supervised exercise sessions ceased. During this time, participants were instructed to exercise in their homes or remote settings. The trainers supervised sessions remotely via Zoom or phone calls. Once COVID-19 restrictions ceased, participants chose between resuming in-person exercise and continuing remotely with monitoring via Zoom. Trial investigators and research staff performing assessments were blinded to group membership. The interventionists were not blinded.

Adherence to the exercise intervention

Research staff trained in exercise physiology, exercise training, and safety monitored and recorded session attendance, intensity, minutes of activity, and adverse events data related to this supervised exercise intervention. Exercise intensity was measured continuously via a Polar heart rate monitor and every 15 min via an RPE using the unmodified BORG scale. Participants were asked to record home-based exercise (e.g., walking) including the intensity of the exercise, and any notes they considered relevant. For this study, adherence was the average weekly minutes of structured moderate-to-vigorous exercise divided by the prescribed 150 min per week and based on heart rate or the RPE Borg scale was used in the calculation of adherence, regardless of whether this happened under supervised or unsupervised (home-based) conditions. Further, only self-reported structured aerobic exercise (and not activity—e.g., home chores, resistance exercise) was included in the calculation of adherence.

Usual care

Women randomized to the usual care control condition were instructed to continue their usual activities for 6 months. They did not attend any exercise sessions. However, these participants wore Actigraph monitoring devices at the same timepoints as the intervention group to ensure that they were not significantly altering their behaviors during the measurement period. No information about the health benefits of exercise was provided to the control group. Exercise was neither withheld nor restricted in this group.

Statistical analyses

The original sample size for the EPICC trial was determined for the primary outcome, neurocognitive function. However, for this analysis, with the total sample size of 136 for those EPICC trial participants who were prescribed AI therapy (exercise group $n=70$; control group $n=66$), the a priori smallest detectable effect size in terms of the standardized mean differences in the mean changes from T1 to T2 for the three primary outcomes (BPI pain severity, worst pain, and pain interference) between the exercise and control groups (d) with at least 80% statistical power was $d=0.561$ for the Bonferroni-adjusted test-wise significance level of 0.0167 (two-tailed) and otherwise $d=0.484$ at a significance level of 0.05 (two-tailed) when applying linear contrasts from linear mixed modeling.

Prior to the primary analyses, data were screened by group for data anomalies (e.g., outliers, missing data, group imbalances), and descriptive statistics were calculated by treatment groups for key participant descriptors at T1 and the primary and secondary pain outcomes at T1 and T2. Using an intention-to-treat (ITT) approach, linear mixed modeling with linear contrasts was used to examine the effect of group assignment on pain outcomes and cardiorespiratory fitness over time. Assuming data were missing at random, full information maximum likelihood was used to handle missing data at T2. The Bonferroni-adjusted test-wise significance level was set at 0.0167 (=0.05/3) (two-tailed) for the three primary pain outcomes to reduce risk of type-1 error; for the secondary pain outcomes, cardiorespiratory fitness, actigraphy-based physical activity, and the categorical analyses described below, the level of significance was set at 0.05 (two-tailed). Results were considered trends for $0.05 \le p < 0.10$.

We also applied categorical analytic approaches (X^2) to explore differences between groups in the proportions of pain transitions from T1 to T2. Using established pain categories [30], BPI worst pain scores were categorized into four groups: no pain (0), mild pain (1–4), moderate pain (5–6), and severe pain (7–10). We then examined the transition across these categories from T1 to T2 using with contingency table and chi-square analyses. Additionally, to explore clinically meaningful changes in pain, we categorized BPI worst pain, pain severity, and pain interference scores into three groups: not clinically meaningful change (< 2-point), clinically meaningful increase (≥ 2-point increase), and clinically meaningful decrease (≥ 2-point decrease) [30, 31].

We also explored whether there were differences in pain medication use between groups using mixed-effects logistic regression and whether there were differences between groups in the percentage of women who experienced clinically meaningful changes in pain as indicated by a ≥ 2-point change in BPI worst pain, pain severity, and pain interference scores [30, 31].

Covariates, including disease stage, chemotherapy use, time on AI therapy, years since menopause, BMI, and pain medication use, were considered to adjust for possible group imbalances and/or variables related to the dependent variables [11, 12]. The identified covariates were added to the base model that included the key design effects of the group and time main effects and group-by-time interaction effect. This was accomplished by first adding one covariate at a time, then adding all covariates simultaneously (i.e., the full multivariate model), and lastly including only those covariates that were statistically significant at 0.05 (i.e., the parsimonious adjusted model). We also explored the effect of exercise intervention adherence, calculated as the average minutes of structured exercise/week divided by the prescribed 150 min/week and expressed as a percentage, for the exercise group. Some participants achieved on average > 150 min/week; these adherence values were computed as > 100%. Adherence was treated both as a continuous variable, where adherence was set at zero for controls and the

calculated adherence value was used for the exercise group, and as categorical variables, where each of the cut points of 80%, 90%, and 100% was applied to the continuous adherence variable for the exercise group and compared to the control condition. In both instances, interactions between the adherence variable and time were included in the model.

Results

The EPICC trial enrollment, randomization, and follow-up have been previously detailed [32]. Of the 153 women who were randomized to the EPICC trial exercise intervention ($n=77$) or control ($n=76$) arms, 17 were not receiving AI therapy and thus were not included in this analysis (Fig. 1). Hence, 136 participants met the criteria for this analysis, 70 participants in the exercise group, and 66 in the control group.

Table 1 summarizes the T1 sample demographic and clinical characteristics. Participants were well educated, predominantly White, and obese. No adverse events were experienced over the course of this trial. Participants overwhelmingly (95%) completed the patient-reported outcomes via REDCap. At T1, treatment and control groups were similar regarding primary and secondary pain outcomes ($p<0.05$). In particular, treatment and control groups were similar regarding their experience of worst pain in the past 24 h ($X^2=1.82$, df = 3, $p=0.611$), with about one-third ($n=46$, 33.8%) reporting no pain and those with pain ($n=90$, 66.2%) mostly experiencing mild levels (0 to 4) [33] for the BPI worst pain ($n=50$, 55.6%).

Cardiorespiratory fitness and physical activity

No differences in changes in cardiorespiratory fitness were observed from T1 to T2 between the groups (interaction

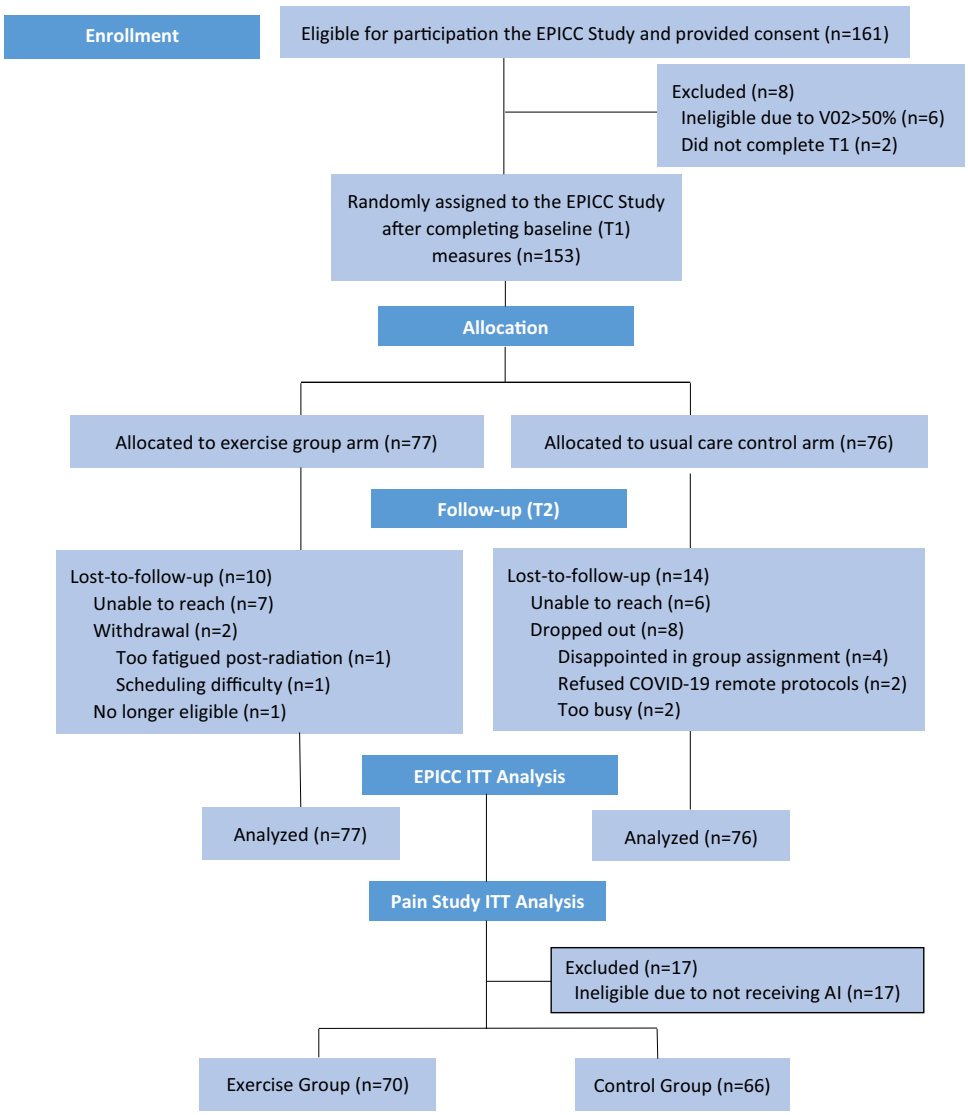

Fig. 1 CONSORT diagram for original EPICC trial analysis and for secondary pain study analysis

Table 1 Pre-randomization (T1) demographic and clinical characteristics ($N = 136$)

	Exercise group (n=70) Mean (SD)	Control group (n=66) Mean (SD)
Demographic characteristics		
Age (years)	61.8 (9.15)	63.3 (7.44)
Education (years)	16.25 (2.806)	15.78 (2.43)
Race (%)		
White	88.7	89.7
African American/Black	8.5	6.6
Native American	0	0
Asian	0	0.7
Other	2.8	2.9
Clinical characteristics		
BMI (kg/m^2)	30.2 (7.15)	31.8 (6.03)
Years since menopause	11.9 (7.42)	14.5 (8.34)
Cardiorespiratory fitness:		
VO2 (ml/kg/minute)	17.2 (3.91)	17.1 (2.84)
Average moderate physical activity (minutes/day via actigraphy)	30.4 (24.6)	29.6 (27.6)
Average moderate-vigorous physical activity (minutes/day via actigraphy)	32.3 (25.0)	31.2 (26.6)
Days on AI therapy	105.9 (184.14)	102.0 (191.29)
Disease stage (%)		
DCIS	18.3	10.8
I	56.3	72.3
IIa	15.5	13.8
IIb	7.0	0.0
IIIa	2.8	3.1
Surgery (%)		
Total or simple	13.7	11.6
Breast conserving	19.6	11.6
Breast conserving +	34.3	50.5
Sentinel node biopsy		
Breast conserving +	3.9	1.1
Axillary node dissection		
Revision	3.9	5.3
Other	24.5	20.0
Chemotherapy (%)		
Yes	16.9	13.6
No	83.1	86.4
Radiation therapy (%)		
Yes	83.1	83.1
No	16.9	16.9
Use of pain medications (%)		
Yes	43.7	29.2
No	56.3	70.8

effect = −0.527, $p = 0.250$). However, we found small improvements in cardiorespiratory fitness from T1 to T2 (time effect = 1.241, $p = 0.0001$), with improvements in each group.

We found no significant differences in the mean changes in moderate intensity physical activity levels (interaction effect = 0.062, $p = 0.987$) or moderate to vigorous intensity physical activity levels (interaction effect = −0.659, p = 0.854) from T1 to T2. Additionally, no significant changes from T1 to T2 were observed for either moderate intensity physical activity (time effect = 3.389, $p = 0.176$) or moderate to vigorous intensity physical activity levels (time effect = 3.586, $p = 0.143$).

Table 2 Group-specific descriptive statistics for primary and secondary pain outcomes at T1 and T2

	Exercise Group		Control Group	
	T1 Mean (SD), Min—Max	T2 Mean (SD), Min–Max	T1 Mean (SD), Min–Max	T2 Mean (SD), Min–Max
Primary pain outcomes				
BPI pain severity	1.91 (1.94), 0–8.00	1.65 (1.55), 0–5.75	1.63 (1.82), 0–7.00	2.27 (1.82), 0–6.75
BPI interference	1.26 (1.75), 0–6.57	0.91 (1.59), 0–6.29	0.94 (1.40), 0–6.00 2.45	1.69 (1.75), 0–6.57
BPI worst pain in the past 24 h	3.07 (3.04), 0–10	2.80 (2.76), 0–9	(2.56), 0–8	3.57 (2.80), 0–10
Secondary pain outcomes				
BCPT Musculoskeletal Pain Subscale	4.41 (3.46), 0–17	4.68 (3.46), 0–15	4.42 (3.46), 0–14	4.84 (3.32), 0–14
SF-36 Bodily Pain Subscale	68.34 (18.08), 41–100	71.90 (18.75), 31–100	70.64 (21.05), 22–100	69.60 (20.87), 32–100
Clinically meaningful changes	***n***	%	***n***	%
BPI pain severity				
Not clinically meaningful change	42	68.9	36	67.9
Clinically meaningful increase	9	14.8	14	26.4
Clinically meaningful decrease	10	16.4	3	5.7
BPI interference				
Not clinically meaningful change	51	85.0	38	71.7
Clinically meaningful increase	5	8.3	11	20.8
Clinically meaningful decrease	4	6.7	4	7.5
BPI worst pain in the past 24 h				
Not clinically meaningful change	27	44.3	24	45.3
Clinically meaningful increase	15	24.6	21	39.6
Clinically meaningful decrease	19	31.1	8	15.1
BPI worst pain transition				
Score				
No change in pain score	15	25.0	18	33.3
Pain score increase	19	31.7	26	48.1
Pain score decrease	26	43.3	10	18.5
Category				
No change in pain categories	36	60.0	40	74.1
No pain to pain	13	21.3	11	20.8
Mild pain (1–4)	8	61.5	7	63.6
Moderate pain (5–6)	3	23.1	3	27.3
Severe pain (7–10)	2	15.4	1	9.1
Pain to no pain	11	18.0	3	5.7
From mild pain (1–4)	9	81.8	2	66.7
From moderate pain (5–6)	1	9.1	1	33.3
From severe pain (7–10)	1	9.1	0	0

BPI Brief Pain Inventory, *BCPT* Breast Cancer Prevention Trial Checklist, *SF-36* Medical Outcome Study Short Form-36, *SD* standard deviation, *Min* minimum, *Max* maximum

Effect of the exercise intervention on pain

Table 2 reports the group-specific descriptive statistics for the primary and secondary pain outcomes at T1 and T2. Based on linear mixed modeling with linear contrasts for the efficacy analysis of our primary pain outcomes, we found significant group-by-time interactions for BPI pain severity ($p = 0.007$), pain interference ($p = 0.0005$), and worst pain ($p = 0.015$) (see Table 3); the effects were small (Cohen's $d = 0.07$, 0.11, and 0.05 respectively). Examining these interaction effects more closely, controls experienced a significant increase in pain severity ($t = 3.08$, $p = 0.003$), worst pain ($t = 2.93$, $p = 0.004$), and pain interference ($t = 3.89$, $p < 0.001$) from T1 to T2, whereas the exercise group experienced no statistically significant change in these pain outcomes over time. Compared to the exercise group, the control group experienced greater pain interference ($t = 2.30$, $p = 0.023$), and a trend for greater pain severity ($t = 1.73$, $p = 0.086$) at T2. No significant main or interaction effects were found for our secondary pain outcomes, the BCPT Musculoskeletal Pain, or SF-36 Bodily Pain subscales.

Exploring transitions from T1 to T2 regarding worst pain, we found differences between groups in the proportion of participants who reported no change, or an increase or decrease in pain during the past 24 h ($X^2 = 8.180$, df = 2, $p = 0.017$) with more exercise participants reporting a decrease in pain and more women in the control group reporting an increase in pain. We found no differences between groups in women who reported changes from no pain at T1 to any pain at T2 ($X^2 = 0.235$, df = 2, $p = 0.889$).

Table 3 Least squares means with standard errors and 95% confidence intervals for within and between-group differences in pain outcomes

Outcome	Least squares means and standard errors		Model within-group change	Model between-group differences in change	Model *F*-test, *p*-value
	T1 mean (SE)	T2 mean (SE)	Mean (95% CI)	Mean (95% CI)	
BPI pain severity					
Exercise group	1.911 (0.214)	1.756 (0.226)	−0.155 (−0.580, 0.270)	0.848 (0.233, 1.464)	$F_g = 0.26$, 0.609
Control group	1.639 (0.221)	2.322 (0.237)	0.693 (0.248, 1.139)		$F_t = 3.00$, 0.086
Full sample	1.770 (0.154)	2.039 (0.164)	0.269 (−0.038, 0.577)		$F_{gxt} = 7.45$, 0.007
BPI pain interference					
Exercise group	1.252 (0.197)	1.033 (0.206)	−0.219 (−0.599, 0.162)	0.997 (0.448, 1.547)	$F_g = 0.54$, 0.462
Control group	0.942 (0.202)	1.720 (0.216)	0.778 (0.382, 1.175)		$F_t = 4.07$, 0.046
Full sample	1.097 (0.141)	1.377 (0.149)	0.280 (0.005, 0.555)		$F_{gxt} = 12.92$, 0.0005
BPI pain at its worst in the last 24 h					
Exercise group	3.071 (0.334)	2.877 (0.356)	−0.194 (−0.952 0.564)	1.371 (0.273, 2.469)	$F_g = 0.03$, 0.869
Control group	2.455 (0.344)	3.632 (0.374)	1.177 (0.383, 1.971)		$F_t = 3.14$, 0.079
Full sample	2.763 (0.240)	3.255 (0.258)	0.492 (−0.057, 1.040)		$F_{gxt} = 6.11$, 0.015
BCPT Musculoskeletal Pain Subscale					
Exercise group	4.393 (0.415)	4.889 (0.432)	0.495 (−0.193, 1.183)	0.123 (−0.879, 1.124)	$F_g = 0.00$, 0.946
Control group	4.370 (0.442)	4.988 (0.457)	0.618 (−0.110, 1.345)		$F_t = 4.85$ 0.030
Full sample	4.382 (0.303)	4.938 (0.314)	0.556 (0.056, 1.057)		$F_{gxt} = 0.06$, 0.809
SF-36 Bodily Pain Subscale					
Exercise group	68.328 (2.231)	71.748 (2.388)	3.420 (−2.224, 9.064)	−5.191 (−12.355, 1.973)	$F_g = 0.00$, 0.984
Control group	70.987 (2.66)	69.216 (2.773)	−1.771 (−6.302, 2.759)		$F_t = 0.21$, 0.649
Full sample	69.657 (1.73)	70.482 (1.830)	0.824 (−2.758, 4.406)		$F_{gxt} = 2.06$, 0.154

BPI Brief Pain Inventory, *BCPT* Breast Cancer Prevention Trial Checklist, *SF-36* Medical Outcome Study Short Form-36, *SE* standard error, *CI* confidence interval, F_g group statistic, F_t time statistic, F_{gxt} group-by-time statistic

When we explored whether there were differences between groups in the proportions of women who reported changes from pain at T1 to no pain at T2, we found marginally significant differences between groups ($X^2 = 4.646$, df = 2, $p = 0.098$) with more women in the exercise group reporting a change from pain to no pain.

We also explored differences between groups in the percentage of women who experienced clinically meaningful changes in pain (≥ 2 points), [30, 31] and found that, compared to women in the exercise group (24.6%), a greater percentage of women in the control group (39.6%) had a clinically significant increase in worst pain ($p = 0.024$). Similarly, a greater percentage of women in the control group (26.4%) had a clinically significant increase in pain severity ($p = 0.029$) from T1 to T2, compared to the exercise group (14.8%). There was no between-group difference in the percentage with clinically meaningful change in pain interference ($p = 0.291$).

We also explored the effect of the exercise intervention on the use of pain medications. While women used of over-the-counter pain medications such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), none were prescribed narcotic analgesics. We found that 43.7% of the exercise group and 29.2% of the control group were taking pain medications at T1. At T2, 45.9% of the exercise group and 47.2% of the control group were taking pain medications. Based on unadjusted logistic mixed-effects modeling, we found a significant group-by-time interaction ($p = 0.029$) and a main effect for time ($p = 0.010$) for pain medication use (Fig. 2). From the linear contrasts for within-group change, we found a significant increase in the proportion of the control group using pain medications from T1 to T2 ($p = 0.001$), while the intervention group had no change in the proportion using pain medications ($p = 0.768$). These results were maintained even with covariate adjustment.

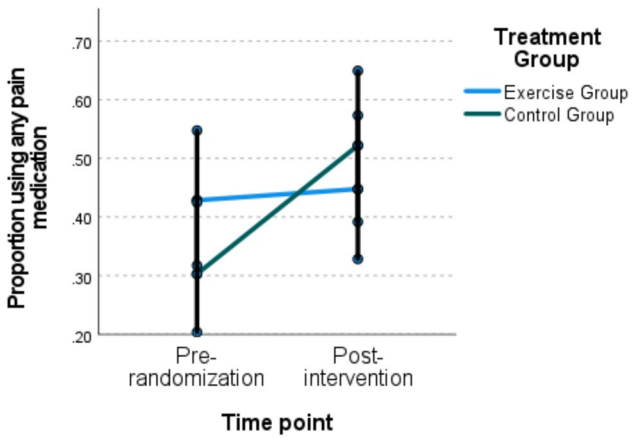

Fig. 2 Comparison of pain medication use between groups

Consideration of covariates

Regarding possible covariates, we found that BMI was positively associated with BPI pain interference ($p < 0.0001$), pain severity ($p = 0.012$), and worst pain ($p = 0.030$), BCPT Musculoskeletal Pain ($p = 0.008$), and SF-36 bodily pain ($p = 0.004$), but inclusion of BMI in the model did not change the ITT results of the effect of exercise on those pain outcomes. Use of pain medications was also positively associated with BPI pain severity ($p < 0.0001$), pain interference ($p < 0.0001$), and worst pain ($p < 0.0001$), BCPT musculoskeletal pain ($p = 0.002$), and SF-36 bodily pain ($p < 0.0001$). When we controlled for the use of pain medications, the results only remained significant for BPI pain interference. None of the other potential covariates (disease stage, chemotherapy use, time on AI therapy, years since menopause) were significantly associated with the pain outcomes.

Adherence to the exercise intervention

For the exercise group, the mean adherence was 95.93 ± 58.58% (143.90 min/week of moderate-intensity exercise). Additionally, 67.1% were ≥ 80% adherent, 64.3% were ≥ 90% adherent, and 54.3% were ≥ 100% adherent. When considering adherence to the exercise intervention, higher exercise adherence was associated with decreases in pain severity ($p = 0.046$) and pain interference ($p = 0.006$) and a trend for pain at its worst ($p = 0.071$).

Discussion

For this analysis of a secondary outcome (pain) from our EPICC trial, we hypothesized that, compared to usual care, aerobic exercise, initiated early in the AI therapy course, would be associated with a reduction in pain severity, pain interference, and worst pain in postmenopausal women with breast cancer. Results of the linear mixed modeling analysis indicate significant group-by-time interactions for pain severity, pain interference, and worst pain with no change in pain severity, pain interference, or worst pain with 6 months of aerobic exercise for women with breast cancer receiving AI therapy, while women in our control group experienced a significant increase in these pain outcomes. These results of no change in our exercise group are similar to those reported by Irwin and colleagues [17]. Interestingly, when we explored whether there were differences between groups in women who experienced changes in pain via transition analyses, we found a trend for more women in the exercise group to report a change from pain at T1 to no pain at T2, while more women in the control group experienced a change from no pain at T1 to pain at

T2. In addition to differences in analytic approaches applied (categorical versus continuous), these mixed results may be explained by the fact that the EPICC trial was not designed to test the effects of aerobic exercise on pain with AI use and the extent of the change was not considered in these more categorical analyses. The results also suggest that the dose of aerobic exercise delivered in this trial may be effective at mitigating an increase in pain but that a different dose may be needed to reduce pain with AI therapy. The importance of aerobic exercise dose is strengthened by the fact that we found that better adherence to the intervention was associated with less pain. Future studies should determine the optimal dose, intensity, and duration of aerobic exercise needed to reduce pain, and should examine the influence of multimodal exercise such as aerobic plus strength training or other modes of exercise on pain. It will also be important to determine effective strategies to enhance adherence to exercise recommendations.

The results of our study are unique because participants initiated aerobic exercise relatively early in the course of AI therapy and we did not restrict enrollment to women who were reporting pain at T1. Previous studies examining the use of exercise for pain in women with breast cancer enrolled women later in the course of therapy (average 1.7 to 2.25 years) [15, 17, 34–36] and restricted enrollment to women already reporting moderate to severe pain [15, 17, 34–38] with an average BPI worst pain score of 5.9 at T1 [17, 36]. The average worst pain scores in both of our exercise and control groups fell in the mild category (0 to 4) for the BPI [33] at T1 ($\bar{x}$=3.07 and 2.45 respectively). And, while the increase in pain in our control group remained in the mild pain category ($\bar{x}$=3.57) at T2, there was no change in pain in our exercise group ($\bar{x}$ =2.80). It should be noted that because we did not restrict our enrollment to women experiencing pain, the T1 values are influenced by women who reported no pain at T1. Had we restricted our enrollment to women who were experiencing moderate or severe pain at T1, we may have observed more robust results with respect to the benefits of aerobic exercise. However, the pain experience of our sample is representative of the population of postmenopausal women with breast cancer early in the course of therapy. Two-thirds (66.2%) of the participants in both groups reported pain at T1. These percentages are similar to those reported by Kidwell and colleagues who reported that 63.8% of women reported pre-existing pain before beginning AI therapy [39]. While we did not find that time on AI therapy was a significant covariate of the effect of aerobic exercise on pain in women with breast cancer, women were on average 4.7 months post-diagnosis at enrollment. Moreover, the average time for the experience of peak pain is 6 months post-AI therapy initiation [4–6]. Whether the initiation of aerobic exercise early in the course of AI therapy prevents a progression to moderate or severe pain later in therapy remains unclear but is an important avenue for future research.

While the effect sizes that we observed were modest, the increase in pain severity and worst pain reported by women in our control group was clinically meaningful as indicated by a greater percentage of women in that group experiencing a ≥ 2-point increase [30, 31] in pain from T1 to T2 compared to women in our exercise group who experienced no change in pain. Women who were not engaging in aerobic exercise experienced a clinically meaningful increase in pain. Their average pain was still in the mild range for BPI worst pain, but, again, these results may have been influenced by the women reporting no pain at T1. Irwin et al. reported a 1.6-point decrease in pain in women who engaged in 12 months of aerobic exercise + strength training while the control group experienced a 0.2-point increase in pain ($p = 0.001$) [17]. Our results suggest that there may be benefits of engaging women in aerobic exercise earlier in the course of AI therapy before they begin to experience moderate to severe pain.

Our results also indicate that the benefits of early engagement in aerobic exercise extend to the use of over-the-counter pain medications. Irwin and colleagues did not find reduced over-the-counter pain medication use with aerobic exercise + strength training in women experiencing AI therapy-related pain [17]. It is important to note that our over-the-counter pain medication data lacked detail about the frequency of use of these "as needed" medications. However, while use of over-the-counter pain medications such as acetaminophen and NSAIDs are generally considered safe for cancer survivors, their long-term use is not recommended, particularly for older adults [12, 40]. Our trial was not designed to examine changes in medication use over time, but our results are promising and could suggest a safer, more tolerable pain management approach for women with breast cancer receiving AI therapy.

Limitations

While our trial includes several strengths including an RCT design and large sample size, the study is limited by the fact that it was not originally designed to examine pain as a primary outcome, and the sample is predominantly White and well-educated, limiting generalizability. Additional research is needed to confirm these results in a study designed to formally test the effects of aerobic exercise specifically for AI-associated pain in a more diverse sample of women with breast cancer. Our use of an intervention comprised of aerobic exercise alone may also be viewed as a limitation given the current recommendations for aerobic exercise + strength training [41]. However, at the initiation of this trial, there was minimal evidence to support the safety and use of any form of exercise for management of pain or other

treatment-associated symptoms in postmenopausal women with breast cancer. Our decision to test the effects of aerobic exercise alone as a first step was based upon this lack of evidence. Given the results of our trial and additional research that has since been published [19], future studies should examine the relative benefits of aerobic exercise + strength training and other exercise modalities such as high-intensity interval training for managing pain.

As with most studies investigating exercise and musculoskeletal symptoms in patients using AIs, our primary outcome was assessed using a generic pain measure, the Brief Pain Inventory [19]. Using a standardized tool like the BPI allows for easier comparison of our findings with those from similar studies. A modified version of the BPI specifically targeting AI-associated arthralgias has been used in a previous study by Kim and colleagues [42]. However, details about the modification are limited. Further, one of our secondary outcome measures was the Musculoskeletal Pain Subscale of the Breast Cancer Prevention Trial Symptom Checklist, a self-report measure of symptoms associated with endocrine therapy use. We did not find a significant interaction affect with that measure. In future studies, incorporating a more specific AI-related musculoskeletal pain assessment alongside the BPI could provide a more accurate and complete characterization of AIMS.

Additionally, we recognize that our use of a usual care control group may be a limitation. However, this trial was one of the first to examine whether aerobic exercise initiated early in the course of AI therapy influenced outcomes in postmenopausal women with breast cancer. Based upon our results, future studies should include an attention-control group. Further, we utilized an age-based maximal heart rate approach which has numerous strengths including that it is easily understandable, easily calculated, used across a significantly greater number of cohorts, and much more clinically meaningful. In contrast, we know that it might not be as accurate as heart rate reserve which is calculated on an individual-by-individual basis. Nonetheless, given that our results are derived from an intervention that determined intensity based on the "less-accurate" age-predicted maximal heart rate, we would anticipate that studies using heart rate reserve would show even larger effects than those reported here. Yet, if we had used heart rate reserve, the results would be arguably less clinically translatable.

Finally, our initial exclusion of potential participants, with an estimated, age-based VO_{2max} in the upper 50th percentile, may have led to selection bias. However, we excluded very few women based upon this criterion. Conversely, we found women to be sedentary with obesity at enrollment. It is noteworthy that we had no enrollment criterion limiting BMI, yet the average BMI of both of our study groups fell in the obese category, consistent with the breast cancer risk profile of postmenopausal women [43]. We found that BMI was positively associated with all of our primary and secondary pain outcomes although it did not change the results of the effect of exercise on those outcomes. This is consistent with the work of others [12].

Future studies should also examine whether improvements in pain are associated with better AI therapy adherence. AIMS is a primary reason why women with breast cancer discontinue AI therapy. Significant negative consequences are associated with premature AI therapy discontinuation and decline in adherence. Hershman [44] found lower estimated 10-year survival among women who discontinued AI therapy early (73.6%) versus women who continued therapy (80.7%) ($p < 0.001$). Of those who continued therapy, the 10-year survival was 81.7 and 77.8% ($p < 0.001$) in women who did and did not adhere to at least 80% of prescribed therapy respectively [44]. Whether better AI therapy adherence is an outcome of AIMS prevention or reduction with aerobic exercise is not known.

Conclusions

Our results suggest that aerobic exercise, initiated early in the course of AI therapy, may reduce pain and prevent increases in pain in women with breast cancer. Clinicians should consider recommending aerobic exercise for women with breast cancer as soon as they are medically cleared to engage in physical activity after cancer surgery. Moderate-intensity aerobic exercise is an easily adaptable, non-pharmaceutical approach for pain in women with breast cancer.

Author contribution C.M.B.: Conceptualization, Investigation, Funding acquisition, Supervision, Writing original draft, Methodology, Analysis, Validation, Writing—review and editing. S.M.S.: Conceptualization, Investigation, Funding acquisition, Methodology, Analysis, Writing original draft, Writing—review and editing. A.L.G.: Project administration, Methodology, Supervision, Writing original draft, Writing—review and editing Y.Z.: Conceptualization, Analysis, Writing—review and editing M.W.: Conceptualization, Writing—review and editing C.C.: Project administration, Writing—review and editing J.D.: Project administration, Writing—review and editing G.G.: Project administration, Supervision, Methodology, Writing—review and editing M.C.: Conceptualization, Analysis, Writing original draft, Writing—review and editing M-g.C.: Conceptualization, Analysis, Writing original draft, Writing—review and editing A.M.B.: Methodology, Writing—review and editing E.J.D.: Conceptualization, Methodology, Writing—review and editing P.M.: Methodology, Writing—review and editing A.L.M.: Conceptualization, Investigation, Funding acquisition, Writing—review and editing. Y.P.C.: Conceptualization, Investigation, Funding acquisition, Writing—review and editing. K.I.E.: Conceptualization, Investigation, Funding acquisition, Supervision, Methodology, Writing—review and editing.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Boards of the University of Pittsburgh (Approval #19080223) and St. Clair Health (Approval #1712001).

Consent to participate All participants provided written informed consent upon study enrollment.

Competing interests Adam Brufsky, Md, PhD has the following disclosures: •Consultant: Astrazeneca, Pfizer, Novartis, Lilly, Genentech/Roche, SeaGen, Daiichi Sankyo, Merck, Agendia, Sanofi, Puma, Myriad •Research Support: Agendia, Astrazeneca Kirk Erickson, PhD has the following disclosures: •Member of scientific advisory boards for MedRhythms, Inc. and NeoAuvra, Inc. There are no other author conflicts to declare.

Disclosures Adam Brufsky, Md, PhD, has the following disclosures:

• Consultant: Astrazeneca, Pfizer, Novartis, Lilly, Genentech/Roche, SeaGen, Daiichi Sankyo, Merck, Agendia, Sanofi, Puma, Myriad.
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• Member of scientific advisory boards for MedRhythms, Inc., and NeoAuvra, Inc.
There are no other author conflicts to declare.

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Authors and Affiliations

Catherine M. Bender[1] · Susan M. Sereika[1] · Amanda L. Gentry[1] · Yehui Zhu[2] · Monica Wagner[3] · Cheryl Cuglewski[1] · Jennie Duquette[1] · George Grove[4] · Meredith Cummings[1] · Myeong-ga Cho[1] · Adam M. Brufsky[5] · Emilia J. Diego[5] · Priscilla F. McAuliffe[5] · Anna L. Marsland[4] · Yvette P. Conley[1] · Kirk I. Erickson[6]

✉ Catherine M. Bender
cbe100@pitt.edu

Susan M. Sereika
ssereika@pitt.edu

Amanda L. Gentry
amg168@pitt.edu

Yehui Zhu
yzhu21@mgh.harvard.edu

Monica Wagner
maw269@case.edu

Cheryl Cuglewski
chc331@pitt.edu

Jennie Duquette
jed118@pitt.edu

George Grove
ggrove@pitt.edu

Meredith Cummings
mhc13@pitt.edu

Myeong-ga Cho
myc23@pitt.edu

Adam M. Brufsky
brufskyam@upmc.edu

Emilia J. Diego
diegoe@upmc.edu

Priscilla F. McAuliffe
mcauliffepf@upmc.edu

Anna L. Marsland
marsland@pitt.edu

Yvette P. Conley
yconley@pitt.edu

Kirk I. Erickson
kirk.erickson@adventhealth.com

[1] University of Pittsburgh School of Nursing, Pittsburgh, PA, USA

[2] Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[3] Case Western Reserve University Frances Payne Bolton School of Nursing, Cleveland, OH, USA

[4] Dietrich School of Arts and Sciences, University of Pittsburgh, Pittsburgh, PA, USA

[5] University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[6] Adventhealth, Orlando, FL, USA