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ORIGINAL REPORT

Randomized Exercise Trial of Aromatase Inhibitor–Induced Arthralgia in Breast Cancer Survivors

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A B S T R A C T

Purpose

Arthralgia occurs in up to 50% of breast cancer survivors treated with aromatase inhibitors (AIs) and is the most common reason for poor AI adherence. We conducted, in 121 breast cancer survivors receiving an AI and reporting arthralgia, a yearlong randomized trial of the impact of exercise versus usual care on arthralgia severity.

Patients and Methods

Eligibility criteria included receiving an AI for at least 6 months, reporting ≥ 3 of 10 for worst joint pain on the Brief Pain Inventory (BPI), and reporting < 90 minutes per week of aerobic exercise and no strength training. Participants were randomly assigned to exercise (150 minutes per week of aerobic exercise and supervised strength training twice per week) or usual care. The BPI, Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, and Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire were completed at baseline and at 3, 6, 9, and 12 months. Intervention effects were evaluated using mixed-model repeated measures analysis, with change at 12 months as the primary end point.

Results

Over 12 months, women randomly assigned to exercise (n = 61) attended 70% (± standard deviation [SD], 28%) of resistance training sessions and increased their exercise by 159 (± SD, 136) minutes per week. Worst joint pain scores decreased by 1.6 points (29%) at 12 months among women randomly assigned to exercise versus a 0.2-point increase (3%) among those receiving usual care (n = 60; $P < .001$). Pain severity and interference, as well as DASH and WOMAC pain scores, also decreased significantly at 12 months in women randomly assigned to exercise, compared with increases for those receiving usual care (all $P < .001$).

Conclusion

Exercise led to improvement in AI-induced arthralgia in previously inactive breast cancer survivors.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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INTRODUCTION

Guidelines recommend that postmenopausal women with hormone receptor–positive breast cancer receive an aromatase inhibitor (AI) as part of their breast cancer treatment.[1-4] However, adverse effects often result in poor AI adherence, with up to 50% of patients not taking AIs as prescribed and discontinuation rates of 20% within the first year of use.[5-7] Both nonadherence and early discontinuation of AIs have been shown to be independent predictors of mortality.[8]

Arthralgia, defined as pain or stiffness in the joints, is the most common reason for poor AI adherence and drug discontinuation[5-7] and is reported in up to 50% of patients with breast cancer within 6 months of starting AI therapy.[9,10] There are few data regarding effective treatment of AI-induced arthralgia.

Exercise may improve AI-induced arthralgia, because it has been shown to be beneficial for osteoarthritis.[11] Exercise may also have beneficial effects on disease-free survival and quality of life, which are also adversely affected by AI therapy.[12,13] To our knowledge, no trial has examined the effect of exercise on AI-associated arthralgia in breast cancer survivors. The purpose of the HOPE (Hormones and Physical Exercise) study was to examine the effect of an exercise intervention on severity of AI-induced arthralgia in women receiving AIs and experiencing arthralgia.

PATIENTS AND METHODS

Our study was a randomized trial comparing the impact of a 12-month exercise intervention versus usual care (control) on AI-induced arthralgia. All procedures, including written informed consent, were approved by the Yale School of Medicine Human Investigation Committee and Connecticut Department of Public Health Human Investigation Committee.

Participants and Recruitment

Breast cancer survivors were recruited between June 1, 2010, and December 30, 2012, from five hospitals in Connecticut through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center, a field arm of the Connecticut Tumor Registry. Eligible participants were physically inactive (< 90 minutes per week of physical activity in past 6 months and no strength training in past year), postmenopausal women diagnosed 0.5 to 4.0 years before enrollment with hormone receptor–positive stage I to III breast cancer who had been receiving an AI for at least 6 months. Participants had to have been experiencing arthralgia for at least 2 months that were at least mild in severity (ie, score of ≥ 3 of 10 for worst pain item of Brief Pain Inventory [BPI]).[14] Women were eligible if their arthralgia started after initiation of an AI or if they had preexisting joint pain that was exacerbated by AI use.

Primary Outcome Measures

Arthralgia. We assessed arthralgia via three different questionnaires completed at baseline and at 3, 6, 9, and 12 months.

BPI. The BPI is a 14-item questionnaire developed for use in patients with cancer that assesses worst pain, pain severity, and pain interference over the past week, reported on a scale of 0 to 10.[14] Worst pain is categorized as mild (score of 3 to 4), moderate (score of 5 to 7), or severe pain (score of 8 to 10). Pain severity is measured as the average of responses to questions on worst

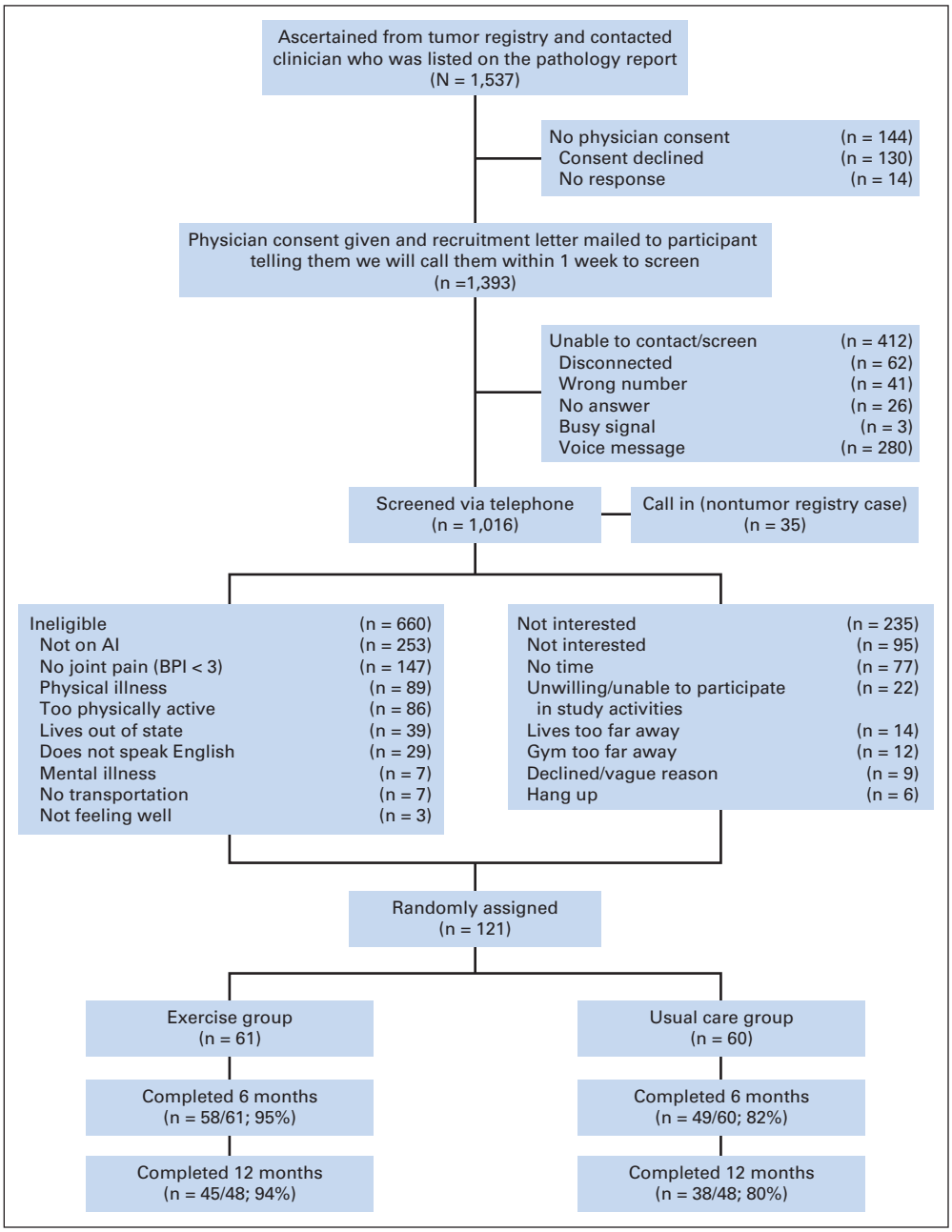

Fig 1. Flow of participants through Hormones and Physical Exercise study. AI, aromatase inhibitor; BPI, Brief Pain Index.

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pain, average pain, least pain, and pain right now. Pain interference is the average of seven interference items, such as walking, mood, and sleep. The BPI is the most common, valid, and reliable measure to assess joint pain in cancer survivors (Cronbach's α and test-retest reliability score > 0.80).[14] The BPI was modified to capture joint pain and stiffness by adding the term "joint pain/stiffness" rather than just the word "pain" throughout the questionnaire.

Western Ontario and McMaster Universities Osteoarthritis index. The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index measures lower-extremity joint symptoms in the past 7 days in three domains: pain, stiffness, and physical function.[15] Scores are normalized into a 0- to 100-point scale, with higher scores indicating worse pain, stiffness, and functional limitations. Internal consistency is good (Cronbach's $\alpha > 0.85$; test-retest reliability scores [ie, intraclass correlation coefficients] ranging from 0.58 to 0.92).[15]

Disabilities of the Arm, Shoulder and Hand questionnaire. The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a 30-item questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limbs.[16] It is a reliable and valid instrument, with high internal consistency (Cronbach's α, 0.91; test-retest reliability [intraclass correlation coefficient, 0.92]). A higher score indicates more upper-extremity disability.[16]

Grip strength. We assessed grip strength using a baseline bulb dynamometer at baseline and at 6 and 12 months. Each participant underwent three trials of squeezing a rubber ball with the dominant hand, with the pressure (in psi) averaged over three trials.

Table 1. Baseline Characteristics of Randomly Assigned Participants in HOPE Study (N = 121)

Characteristic	Exercise Group (%) Mean	Exercise Group (%) SD	Usual-Care Group (%) Mean	Usual-Care Group (%) SD	P
Age, years	62.0	7.0	60.5	7.0	.25
Race/ethnicity					.85
Non-Hispanic white	85		84		
Hispanic	2		5		
African American	10		7		
Asian/Pacific Islander	2		2		
American Indian	0		2		
Education					.25
High school graduate	10		15		
Some school after high school	33		42		
≥ College graduate	57		43		
Time since diagnosis, years	2.7	3.1	3.3	3.9	.30
Time since initiating AI therapy, years	1.9	2.9	1.8	1.3	.89
Disease stage					.70
0	1		0		
I	59		62		
II	30		32		
III	10		7		
Chemotherapy					.22
Yes	54		43		
No	46		57		
Radiation therapy					.65
Yes	82		75		
No	18		25		
BMI, kg/m^2	30.0	6.8	28.7	5.5	.27
Taking pain medication	52		42		
Physician-diagnosed arthritis	49		32		
Current glucosamine and chondroitin use	13		18		

Abbreviations: BMI, body-mass index; HOPE, Hormones and Physical Exercise; SD, standard deviation.

Secondary Outcome and Covariate Measures

Demographics and medical history. Medical record review and an interviewer-administered questionnaire were used to determine disease stage, surgery, adjuvant therapy, endocrine therapy, and comorbidities.

Pain medication. At baseline and at 6 and 12 months, participants completed a medicine-supplement questionnaire that asked about current over-the-counter or prescription medication use. Current use of glucosamine and chondroitin was also captured. Participants also completed the following pain medication question on the BPI: Are you taking any oral medications for pain/stiffness (yes or no)?

AI adherence. Participants recorded their daily AI use in a log reviewed monthly by telephone or in person with study staff. Reasons for missed doses were assessed by study staff.

Height and weight. Height (stadiometer) and weight (digital scale; no shoes) were measured at baseline and at 6 and 12 months. All measurements were taken twice and averaged.

Physical activity. At baseline (for screening purposes) and at 6 and 12 months, participants completed a physical activity questionnaire, assessing the past 6 months of activity, including the type, frequency, and duration of 20 activities.[17]

Table 2. Physical Activity, Cardiorespiratory Fitness, Muscular Strength, and Body Weight Changes and Adherence to Exercise in HOPE Study

Measure	Exercise Group Mean	Exercise Group SD	Usual-Care Group Mean	Usual-Care Group SD	P
Physical activity questionnaire, minutes per week					
Baseline	54.8	93.0	60.7	99.0	.74
12 months	222.1	118.6	103.6	104.7	< .001
Change	159	136	49	86	< .001
Percent reporting ≥ 150	70		6		
Percent reporting ≥ 120	74		15		
VO_2 max, ml/kg per minute					
Baseline	23.0	5.3	23.1	3.5	.88
12 months	24.6	5.5	23.0	4.7	.17
Change	1.5	2.1	−0.4	2.7	< .001
Percent change	6.5	3.7	−1.8	11.2	.0013
Body weight, kg					
Baseline	78.5	18.1	75.5	14.5	.32
Change	−2.1	4.3	0.1	3.6	.014
Percent change	−2.4	5.4	0.0	4.8	.037
Daily activity log*					
Aerobic exercise, minutes per week	119	78	NA		
Twice-per-week strength-training session attendance, %	70	28	NA		
One-repetition maximum, lbs					
Leg press			NA		
Baseline	156	58			
12 months	245	75			
Change	82	61			
Percent change	62	52			
Bench press					
Baseline	43	17			
12 months	60	19			
Change	16	11			
Percent change	42	32			

Abbreviations: HOPE, Hormones and Physical Exercise; NA, not applicable; SD, standard deviation; VO_2 max, maximal oxygen consumption.
*Daily activity logs were completed for each week of exercise intervention; if woman did not exercise that week, value of 0 was reported in her activity log.

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Cardiorespiratory fitness. Cardiorespiratory fitness was measured at baseline and at 12 months with a standard maximal oxygen consumption (VO_2 max) treadmill test.[18]

Exercise Intervention

The yearlong exercise intervention was a combination of a twice-per-week supervised resistance training program (under supervision of American College of Sports Medicine–certified cancer exercise trainer) at a local health club and a home-based aerobic exercise program of 150 minutes per week, in accordance with current exercise recommendations for cancer survivors.[19] Participants wore heart-rate monitors during each workout. After each exercise session, participants recorded the type, duration, and average heart rate during exercise in physical activity logs as a measure of exercise adherence.[20] Participants returned logs to the exercise trainers at the end of each week. Exercise trainers recorded attendance to the supervised sessions.

The aerobic exercise intervention consisted primarily of brisk walking (treadmill or outside), although participants could choose other aerobic exercise, such as stationary bicycling. Exercise started at 50% of maximal heart rate (determined from VO_2 max testing) and increased over the first month to 60% to 80% of maximal heart rate for the study duration. The strength-training protocol consisted of six exercises (ie, bench press, latissimus pull down, seated row, leg press, leg extension, and leg curl) performed for eight to 12 repetitions for three sets. Participants progressed up to three sets per exercise over the first month. After two sessions during which a participant lifted the same weight 12 times during each set, the weight was increased by the smallest possible increment.

Usual-Care Group

Women were instructed to continue with their usual activities. Participants were not discouraged from exercising on their own but were not given any exercise instruction until the end of the study. Women were telephoned monthly by research staff to determine AI adherence.

Both the exercise and usual-care groups were provided with an educational booklet prepared for the HOPE study, which addressed breast cancer topics such as lymphedema and fatigue. Topics were discussed monthly over the telephone (usual-care group) or at an exercise session (exercise group).

Statistical Analyses

Sample size was estimated at the design stage to detect a difference in the primary end point (ie, change in BPI score at 12 months). We powered our study with 60 patients per group to detect a difference of 1.5 (standard deviation [SD], 2.5) in the BPI worst pain change score with 90% power at a two-sided significance level of .05 based on results of the study by Hershman et al.[21] Participants were grouped according to the intention-to-treat principle. Permuted block randomization (at 1:1 ratio) with random block size was performed, stratified by joint pain before AI therapy and current bisphosphonate use (related to our secondary aim of bone mass). Intervention effects were evaluated by differences in mean changes at follow-up time points between exercise and usual-care groups using mixed-model repeated measures analysis. This approach is robust, because it includes all available data and accounts for correlations between repeated measures. Because the two study groups did not differ at baseline, analyses only adjusted for pain medication use (assessed via BPI) and baseline score for the respective arthralgia outcome measure. The inclusion of baseline arthralgia score as a covariate corresponds to the analysis of covariance approach, with efficiency to test group differences.[22] Group-by-time interaction was also included as a fixed effect. Post hoc comparisons at each time point were conducted with Bonferroni correction for multiple comparisons (0.013 was used as significance cutoff). Sensitivity analyses using a random-effects pattern mixture model approach were performed to evaluate the potential influence of study completion status and AI adherence on primary analyses.[23] Participants were divided into two groups on the basis of completion status at the 12-month visit. The corresponding dichotomous covariate, as well as its interaction with main effects of time, group, and group-by-time interaction, was included in the analysis. Completion status did not differ between groups ($P = .26$). No statistically significant joint effect was detected for any completion status–related term or by group-by-time interaction, indicating the estimated group effects were not dependent on completion

Table 3. Effect of Exercise Versus Usual Care on BPI-Assessed Pain at Baseline and Changes at 3, 6, 9, and 12 Months*

	Exercise Group		Usual-Care Group		Treatment Effect (control minus exercise)		
Outcome†	Change From Baseline	95% CI	Change From Baseline	95% CI	Change From Baseline	95% CI	*P*
Worst pain							
Baseline	5.6	5.2 to 6.2	5.9	5.4 to 6.3			.42
3 months	−1.2	−1.9 to −0.5	−0.1	−0.8 to 0.7	1.2	0.1 to 2.2	.03
6 months	−0.6	−1.2 to 0.0	−0.3	−0.9 to 0.4	0.3	−0.5 to 1.2	.45
9 months	−1.4	−2.2 to −0.6	−0.1	−0.9 to 0.7	1.3	0.2 to 2.5	.03
12 months	−1.6	−2.2 to −1.1	0.2	−0.5 to 0.8	1.8	0.9 to 2.6	< .001
Severity							
Baseline	4.0	3.6 to 4.4	4.2	3.7 to 4.7			.51
3 months	−1.0	−1.4 to −0.5	−0.2	−0.7 to 0.3	0.8	0.1 to 1.5	.03
6 months	−0.5	−0.9 to 0.0	−0.4	−0.9 to 0.1	0.1	−0.6 to 0.7	.87
9 months	−0.8	−1.4 to −0.2	−0.4	−0.9 to 0.2	0.4	−0.4 to 1.2	.31
12 months	−1.1	−1.6 to −0.6	0.3	−0.2 to 0.8	1.4	0.7 to 2.1	< .001
Interference							
Baseline	2.9	2.4 to 3.4	3.0	2.4 to 3.6			.64
3 months	−0.9	−1.5 to −0.3	−0.1	−0.8 to 0.6	0.8	−0.1 to 1.7	.09
6 months	−0.7	−1.2 to −0.3	−0.3	−0.8 to 0.2	0.4	−0.2 to 1.1	.20
9 months	−0.8	−1.4 to −0.2	−0.3	−0.9 to 0.3	0.5	−0.3 to 1.4	.22
12 months	−1.1	−1.6 to −0.5	0.4	−0.2 to 0.9	1.4	0.7 to 2.2	< .001

Abbreviation: BPI, Brief Pain Inventory.
*Adjusted for baseline value and pain medication use. Sample sizes for 3 and 6 months were 58 and 49 patients in exercise and usual-care groups, respectively; sample sizes for 9 and 12 months were 45 and 38 patients, respectively.
†BPI-assessed pain on scale of 0 to 10.

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status or AI adherence. Analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC). Statistical significance was set at $P < .05$ using two-sided tests.

RESULTS

A total of 1,537 estrogen receptor–positive breast cancer survivors were identified through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center (Fig 1). Screening telephone calls were completed with 1,016 women (66% of patients with breast cancer treated at five Connecticut hospitals). Of these 1,016 women screened, 253 had already stopped taking an AI because of adverse effects or had chosen not to take an AI because of potential adverse effects. An additional 407 women were ineligible, leaving 356 eligible women, with 121 eligible women (34%) randomly assigned. Given funding cuts, the last 25 of the 121 women recruited were enrolled into a 6-month rather than 12-month trial. Thus, their study compliance was based on 6-month data (Fig 1).

Baseline Characteristics

The average age of study participants was 61 years (Table 1). A majority of participants were white (88%) and had been diagnosed with stage I breast cancer (60%). Average time between diagnosis and enrollment was 3.0 years.

Intervention Adherence

Women randomly assigned to exercise increased their physical activity by an average 159 minutes per week, compared with 49 minutes per week in the usual-care group ($P < .001$; Table 2). Women randomly assigned to exercise also reported their exercise prospectively in daily activity logs and reported an average 119 minutes per week of aerobic exercise, with an average of 70% of strength-training sessions completed, resulting in an average 62% and 42% increase in one-repetition maximum for leg press and bench press at 12 months, respectively. Cardiorespiratory fitness increased by 6.5% in women randomly assigned to exercise, versus a 1.8% decrease in those receiving usual care ($P = .001$). Body weight was reduced by 2.4% in women randomly assigned to exercise, versus no change in the usual-care group ($P = .037$). There were no adverse events associated with the exercise program. Attendance to monthly telephone calls for women randomly assigned to usual care was 53%.

Effect of Exercise on Arthralgia

At baseline, BPI-assessed worst joint pain scores averaged 5.6 (± SD, 2.1) and 5.9 (± SD, 1.9) for exercisers and those receiving usual care, respectively ($P = .42$; Table 3; Fig 2). Over 12 months, worst joint pain scores decreased by 1.6 points (29% decrease) in women randomly assigned to exercise, versus a 0.2-point increase (3% increase) in women randomly assigned to usual care (difference, 1.8; 95% CI, 0.9 to 2.6; $P < .001$). Statistically significant differences in pain severity and pain interference were also observed between exercisers versus the usual-care group (both $P < .001$).

Similar findings were observed when measuring upper- and lower-body symptoms via the DASH and WOMAC questionnaires (Table 4; Fig 1). The WOMAC total score for lower extremities decreased by 9.4 points (37% decrease) in women randomly assigned to exercise at 12 months, compared with a 0.5-point increase (2% increase) in the usual-care group (difference, 9.9; 95% CI, 2.8 to 16.9; $P < .001$). The DASH upper-extremity score decreased by 6.7 points (33% decrease) in women randomly assigned to exercise at 12 months, compared with a 1.3-point increase (12% increase) in those receiving usual care (difference, 8.0; 95% CI, 3.1 to 12.9; $P = .002$). Adjusting for arthritis did not change the effect of exercise on arthralgia.

There was no dose-response effect of exercise on arthralgia assessed via BPI, DASH, or WOMAC. Greater attendance to strength-training sessions, more minutes per week of aerobic exercise, and larger increases in VO_2 max or one-repetition maximum were not associated with greater improvements in arthralgia (data not shown), implying that the average exercise adherence observed in our study of 2 hours per week of aerobic exercise and twice-per-week strength-training sessions, performed over 1 year, is optimal for improving AI-associated arthralgia.

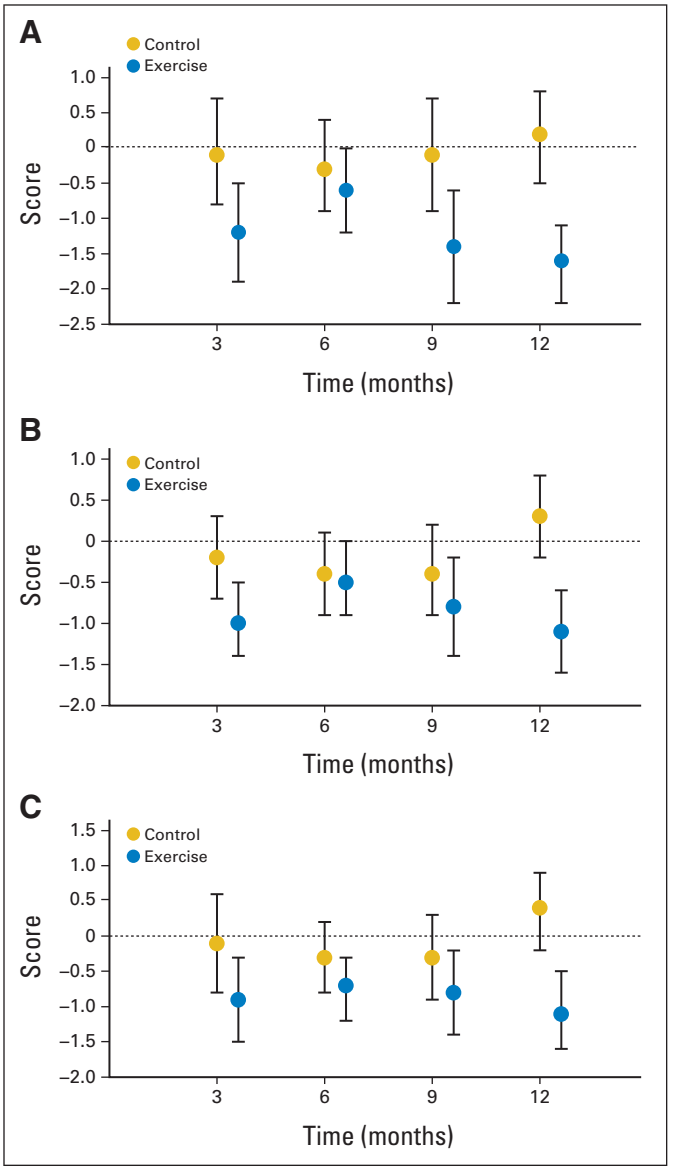

Fig 2. Changes in (A) worst pain, (B) severity, and (C) interference.

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Table 4. Effect of Exercise Versus Usual Care on WOMAC- and DASH-Assessed Symptoms at Baseline and Changes at 3, 6, 9, and 12 Months*

Outcome	Exercise Group		Usual-Care Group		Treatment Effect (control minus exercise)		
	Change From Baseline	95% CI	Change From Baseline	95% CI	Change From Baseline	95% CI	*P*
DASH†							
Baseline	20.0	16.4 to 23.6	19.3	15.9 to 22.7			.77
3 months	−7.6	−10.9 to −4.3	−1.0	−4.6 to 2.6	6.6	1.7 to 11.5	.03
6 months	−6.6	−9.1 to −4.1	−0.5	−3.2 to 2.3	6.1	2.4 to 9.8	.001
9 months	−5.4	−9.5 to −1.4	1.1	−2.9 to 5.1	6.5	0.9 to 12.2	.02
12 months	−6.7	−10.0 to −3.4	1.3	−2.3 to 4.9	8.0	3.1 to 12.9	.002
WOMAC pain scale‡							
Baseline	21.1	15.1 to 27.1	21.1	14.8 to 27.3			.99
3 months	−8.7	−13.0 to −4.3	−6.1	−10.9 to −1.3	2.6	−3.9 to 9.1	.43
6 months	−8.9	−13.4 to −4.4	−2.9	−7.6 to 1.8	6.0	−0.5 to 12.5	.07
9 months	−4.3	−12.5 to 3.8	1.4	−6.8 to 9.6	5.7	−5.8 to 17.3	.32
12 months	−6.0	−11.6 to −0.3	0.7	−5.3 to 6.8	6.7	−1.6 to 15.0	.11
WOMAC physical function scale†							
Baseline	26.8	21.7 to 32.0	24.8	19.6 to 30.0			.58
3 months	−11.6	−15.5 to −7.8	−8.3	−12.7 to −3.9	3.3	−2.5 to 9.2	.26
6 months	−9.3	−13.4 to −5.2	−3.5	−7.9 to 0.9	5.8	−0.2 to 11.8	.06
9 months	−7.9	−15.5 to −0.2	−0.6	−8.3 to 7.1	7.3	−3.6 to 18.1	.19
12 months	−10.4	−15.0 to −5.8	1.1	4.0 to 6.1	11.5	4.7 to 18.3	.001
WOMAC total†							
Baseline	25.7	20.5 to 30.9	24.5	19.1 to 29.9			.76
3 months	−11.1	−15.0 to −7.3	−7.9	−12.2 to −3.5	3.3	−2.5 to 9.1	.27
6 months	−9.2	−13.4 to −5.0	−4.1	−8.5 to 0.3	5.1	−1.0 to 11.1	.10
9 months	−7.9	−15.5 to −0.3	−0.4	−8.1 to 7.3	7.5	−3.4 to 18.3	.18
12 months	−9.4	−14.2 to −4.6	0.5	−4.7 to 5.7	9.9	2.8 to 16.9	< .001
Grip strength, psi							
Baseline	10.6	10.0 to 1.2	10.6	10.0 to 1.1			.88
6 months	0.2	−0.2 to 0.6	−0.6	−1.0 to −0.1	−0.7	−1.4 to −0.1	.03
12 months	0.4	−0.2 to 0.9	0.1	−0.5 to 0.7	−0.3	−1.1 to 0.5	.47

Abbreviations: DASH, Disabilities of the Arm, Shoulder and Hand; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.
*Adjusted for baseline value and pain medication use. Sample sizes for 3 and 6 months were 58 and 49 patients in exercise and usual-care groups, respectively; sample sizes for 9 and 12 months were 45 and 38 patients, respectively.
†DASH-assessed pain on scale of 0 to 25.
‡WOMAC-assessed pain on scale of 0 to 100.

Use of Pain Medications and AI Adherence

At baseline, 47% of women reported pain medication use, assessed via the BPI pain medication use question, whereas slightly fewer used pain medication at 12 months (39%), with no differences between exercisers or those receiving usual care. Specifically, 17% of women stopped taking pain medication at 12 months, 8% started taking pain medication at 12 months, and 75% had no change from baseline. Use of pain medication did not confound the effect of exercise versus usual care on arthralgia. Similar pain medication use was reported on the medicine-supplement questionnaire completed by participants.

Of the 121 women enrolled, four women (control, n = 2; exercise, n = 2) stopped taking AIs during the trial because of joint pain, GI distress, or cognitive function. Adherence to AIs was good, with 80% and 76% of exercisers and those receiving usual care, respectively, adhering to AI therapy daily at 12 months.

DISCUSSION

In this trial of women receiving AIs for breast cancer, we found AI-associated arthralgia symptoms worsened over time in women randomly assigned to usual care, whereas exercise reduced AI-associated arthralgia pain scores by approximately 30% or 1.5 points. On average, pain scores in women randomly assigned to exercise decreased from moderate at baseline to mild at the end of the intervention period (ie, BPI worst pain score of approximately 6 to 4 points). Women randomly assigned to exercise also experienced increases in cardiorespiratory fitness, upper- and lower-body strength, and losses in body weight.

AIs are recommended for postmenopausal women with hormone receptor–positive breast cancer, which represents almost 50% of all newly diagnosed cases of breast cancer.[1,2] Despite the efficacy of AIs, adverse effects often result in poor AI adherence, which can reduce effectiveness and increase mortality.[5-8] Arthralgia is the most common reason for AI discontinuation[5-7]; however, there are few data regarding effective treatments for AI-induced arthralgia. Studies have examined glucosamine, vitamin D, acupuncture, yoga, and tai chi as treatments for arthralgia, with promising results.[21,24-29] However, most studies were small (ie, < 50 participants), uncontrolled, and of short duration. The decrease in AI-associated arthralgia observed in the HOPE study was larger in magnitude than that reported with these other arthralgia treatments. To our knowledge, no other randomized

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trial has examined the impact of exercise on AI-induced arthralgia in breast cancer survivors receiving an AI and experiencing arthralgia.

The etiology of AI-induced arthralgia is not completely understood; however, most hypotheses focus on estrogen deprivation, which is the intended outcome of AI therapy.[30] The mechanisms through which exercise could improve AI-induced arthralgia are not entirely clear. Exercise improves blood flow to tissues and increases maximal oxygen consumption,[31] which in turn could make activities of daily living easier to perform and therefore less painful. Exercise increases range of motion and may improve pain threshold.[32,33] Exercise also improves cancer-related fatigue and overall quality of life and is associated with lowered rates of mortality in breast cancer survivors.[12,19]

Strengths of our study include the randomized design, high adherence to the exercise intervention, and a focus on women experiencing arthralgia resulting from AI use. However, our study also had some limitations. First, the questionnaires used to assess AI-associated arthralgia were not designed to specifically assess this adverse effect. Development of a questionnaire to specifically assess AI-associated arthralgia in breast cancer survivors is needed. Second, our results may only be generalizable to physically inactive breast cancer survivors who continue to take AIs despite adverse effects. Third, our intervention was supervised by exercise trainers; however, community-based exercise programs are increasingly available, such as LIVESTRONG at the YMCA, which offers free exercise programs to cancer survivors at various YMCA locations across the United States. Finally, our primary aim was to examine the impact of exercise on improving AI-associated arthralgia rather than AI adherence. Thus, eligible women had to be receiving an AI and planning to continue to take the medication for 1 year; women also had to be experiencing at least mild AI-associated arthralgia. These eligibility criteria allowed us to examine the effect of exercise on a common adverse effect of AIs (ie, arthralgia) without a potential confounding effect of AI adherence. Given that our results show a beneficial effect of exercise on treating arthralgia, additional work is needed to determine whether exercise can improve AI adherence.

In conclusion, given the efficacy of AIs in preventing breast cancer recurrence and the proportion of women who discontinue these drugs because of adverse events, interventions to improve adverse effects are important. The HOPE study demonstrates that exercise is effective in improving AI-induced arthralgia in previously inactive breast cancer survivors who adhere to their AI medication despite this common adverse effect. Although some benefit of exercise was observed after 3 months of exercise, the strongest benefit occurred after 12 months of exercise. Further research is needed to determine if exercise improves AI adherence and breast cancer survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

aromatase inhibitors: inhibitors used in treating breast cancer in postmenopausal women. Aromatase inhibitors inhibit the conversion of androgens to estrogens by the enzyme aromatase, thus depriving the tumor of estrogenic signals. Because of decreased production of estrogen, estrogen receptors, which are important in the progression of breast cancer, cannot be activated.

estrogen receptor: ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function. ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Exercise Trial of Aromatase Inhibitor–Induced Arthralgia in Breast Cancer Survivors

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