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Endocrine-Related Quality of Life in a Randomized Trial of Exercise on Aromatase Inhibitor-Induced Arthralgias in Breast Cancer Survivors

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Abstract

Purpose: The purpose of this study was to evaluate the role of a 12-month exercise intervention on endocrine-related quality of life (QOL) and overall QOL among breast cancer survivors with aromatase inhibitor (AI)-induced arthralgia in the Hormones and Physical Exercise (HOPE) Study.

Methods: We conducted a randomized controlled trial of 121 breast cancer survivors who were currently taking AIs and experiencing at least mild arthralgia. QOL was assessed using the Functional Assessment of Cancer Therapy (FACT) questionnaires and the 36-Item Short Form Survey (SF-36) at baseline, 6-, and 12-months. Participants were randomized to either a one-year gym-based, supervised exercise intervention group (150 minutes of aerobic exercise and two strength-training sessions each week) or usual care. Effects of the intervention on QOL were assessed using mixed-model repeated measures analysis.

Results: At 12 months, the exercise group had greater improvement in the overall QOL measures, as well as the breast cancer-specific (2.2 vs. 0.7, $P = 0.02$), endocrine-specific (5.6 vs. 1.6, $P < 0.001$), and fatigue-specific (5.8 vs 0.5, $P < 0.001$) subscales compared with the usual care group. Our results show a stronger effect at 12 months compared to 6 months of the intervention.

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The authors have no conflicts of interest to disclose.

Conclusion: In this study, combined aerobic and resistance exercise, such as treadmill walking and strength training, improved endocrine-related and overall QOL among breast cancer survivors experiencing adverse side effects from AIs. Since adverse side effects associated with AI use are quite common and this is the main reason for treatment discontinuation, this non-pharmacologic intervention could benefit many breast cancer survivors and increase successful adherence to AIs in breast cancer treatment.

Presis:

In this study, combined aerobic exercise, such as treadmill walking and strength training, improved endocrine-related and overall QOL among breast cancer survivors experiencing adverse side effects from AIs.

Keywords

breast cancer; aromatase inhibitors; exercise; quality of life; randomized controlled trial

Introduction

Breast cancer is the leading cancer diagnosis in women in the United States. Of those diagnosed, approximately 70% present with estrogen receptor-positive tumors.[1] Aromatase inhibitors (AIs) have been shown to be the most effective adjuvant endocrine therapy for postmenopausal women with estrogen receptor-positive breast cancer, and are therefore considered standard of care.[1] Because of their physiological mechanism, AIs cause lowered levels of estrogen which are associated with AI-induced arthralgias (i.e., joint pain) and menopausal symptoms, such as hot flashes and night sweats which in turn may impair quality of life.[2] Given long-term treatment (up to 10 years) with AIs is effective in reducing both risk of recurrence and breast cancer death, and therefore the strong recommendation by clinicians for their patients to take AIs, understanding how to reduce the severity of AI-related adverse side effects is necessary to increase AI adherence and improve quality of life.

Previous studies have shown that exercise significantly improves quality of life (QOL),[3–7] fatigue,[7–10] depression,[11] and anxiety[7, 11] in women diagnosed with breast cancer.[12–15] A randomized trial in 62 obese breast cancer survivors observed a positive effect of a 6-week walking intervention on AI-associated side effects (i.e. joint pain) but saw no effect on QOL.[16] We conducted a randomized exercise trial in 121 breast cancer survivors randomized to either an exercise intervention or usual-care. We have previously reported that exercise led to a significant 30% improvement in AI-associated arthralgias and improved body composition among previously inactive breast cancer survivors.[17, 18] We have also reported that long term exercise adherence is feasible among breast cancer patients experiencing pain due to AI-associated arthralgia.[18] To our knowledge, the impact of exercise on endocrine-related QOL in women taking an AI for early stage breast cancer and experiencing arthralgia have not yet been reported. We hypothesized that exercise would have a positive effect on endocrine-related QOL among these women. The purpose of this study was to examine the effect of an exercise intervention vs. usual care within the setting of a randomized trial on endocrine-related QOL and overall QOL among 121 postmenopausal breast cancer survivors who had

been taking an AI for at least 6 months and reported at least mild arthralgias in the Hormones and Physical Exercise (HOPE) Study.

Methods

Study Population

The HOPE Study, which has been previously described,[17, 19] was a randomized controlled trial of breast cancer survivors with AI-induced arthralgia. Briefly, postmenopausal women diagnosed with hormone-receptor positive stage I-III breast cancer were eligible for the study. Participants had been taking an AI for at least 6 months and were experiencing side effects of the medication (i.e., at least mild arthralgia, defined as ≥ 3 on the Brief Pain Inventory (BPI) Short Form Questionnaire[20]) for at least 2 months at the time of enrollment. To observe a maximal effect from the exercise intervention, only women reporting less than 90 minutes/week of moderate-to-vigorous intensity aerobic exercise and no strength training in the previous year.

We used the Rapid Case Ascertainment (RCA) Shared Resource Service of the Yale Cancer Center to obtain names of women diagnosed with hormone receptor-positive breast cancer between June 1, 2010 and December 30, 2012 and treated at one of five hospitals in Connecticut. Among those who were screened and eligible, 34% were randomized into this study. Approval for all procedures and written informed consent was obtained from the Yale School of Medicine Human Investigation Committee and Connecticut Department of Public Health Human Investigation Committee.

Data Collection

Clinic visits were completed at baseline, 6-, and 12-months. Participants completed a QOL questionnaire, a 7-day daily activity log, a physical activity questionnaire, and attended a clinic visit for physical measurements at all visits.

Measures

Demographics and medical history.—Self-administered questionnaires were completed by the participants at the baseline visit. Medical history and treatment-related information was obtained from self-report, electronic medical records, and via a physician verification of treatment form.

QOL measures.—QOL was measured by self-report at the baseline, 6-, and 12-month clinic visits using the Functional Assessment of Cancer Therapy (FACT) questionnaires and the 36-Item Short Form Survey (SF-36).[21, 22] The FACT-General (FACT-G) is a 27-item questionnaire assessing physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The FACT-B (for breast cancer patients) includes the FACT-G as well as 10 additional concerns more specific to women with breast cancer. The endocrine subscale (ES) comprises 19 items (e.g., hot flashes, night sweats, weight gain, and joint pain). The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) is a 13-item subscale to assess fatigue-related concerns. Participants indicated how true a statement had been for them over the past 7 days

using a 5-point scale ranging from 0 (none at all) to 4 (very much). All items received equal weighting for the analysis. The SF-36 uses 36 items to measure eight health concepts, including physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Scores were calculated for the eight subscales as well as for the physical component summary score and the mental component summary score. A clinically important difference in physical function and cancer-related fatigue is three points.[23–25]

Randomization

Participants were randomized to either the exercise group or usual care with equal probability, stratified by whether taking a bisphosphonate and whether joint pain started after initiating the AI. Blocked randomization with random block sizes was used to generate lists by the trial statistician and sealed envelopes were prepared according to the list to allocate participants. Those women randomized to the exercise group were scheduled for their first supervised exercise training session at a local health club immediately. Women randomized to the usual care group were contacted by a trained health professional on a monthly basis to discuss relevant health topics to maintain study compliance.

Exercise Intervention

The exercise intervention group received social and behavioral support and contact time with the exercise trainer to encourage them to increase their exercise level to include twice-weekly strength-training sessions and 150 min of aerobic exercise per week (e.g., three 50-min aerobic exercise sessions or five 30-min sessions) over 12 months. Trainers and participants met twice weekly at a local gym designated by the study during designated times. Gym membership was provided for the duration of the study free of charge. Further details on the exercise intervention were described previously.[17]

Usual Care

After randomization, participants in the usual care group were told to continue their usual activities and were not given exercise instruction until the end of the study. Each month, women randomized to usual care were contacted monthly to determine AI adherence and discuss health education topics relevant to breast cancer survivors.

Statistical Analysis

Participants were analyzed according to the intention-to-treat procedure in which all participants were grouped according to their intervention assignment at randomization regardless of adherence. We used the Student’s t-test and the Chi-square test to evaluate group differences at baseline. Due to a funding cut, 25 women were only enrolled for a 6-month study rather than 12 months and were therefore not included in the 12-month analyses. At 6 months, 49 controls (82%) and 58 (95%) exercisers completed the QOL assessment. At 12 months, 38 (80%) controls and 45 (94%) exercisers completed the QOL assessment. The primary QOL outcome of interest was endocrine-related QOL as measured by the FACT-B-ES. We performed a mixed model repeated measures analysis with

maximum likelihood estimation to examine intervention effects by assessing differences in mean change in QOL measures at the 6-month and 12-month follow-up visits between exercise and usual care groups. This approach is as effective as multiple imputation method to handle missing data with assumption that the data is missing at random.[26] Additional sensitivity analyses were performed using multiple imputation under the missing not at random (MNAR) assumption by creating 10 imputed dataset based on observed data in control group only. This method was to show the robustness of results by assuming those who were lost to follow-up in exercise group would have same outcomes as observed in usual care groups.[27] Since baseline characteristics did not differ between the two groups, we only adjusted for age and baseline scores for the corresponding outcome measure. Moreover, the exercise group was stratified by weekly exercise time (≥ 150 mins vs. < 150 mins) at the 12-month visit, as well as attendance to training sessions (80% and above vs. < 80%). Effects of baseline outcome measure, age, time, group and group by time interaction were included in the mixed model analysis. We used SAS software (version 9.4; SAS Institute, Cary, NC) in all analyses. All statistical tests were two-tailed, and a P-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The CONSORT diagram of participants' screening and enrollment status, as well as baseline demographic and clinical characteristics have been reported previously (Figure 1).[17] Briefly, 61 breast cancer survivors were randomized into the exercise arm, while 60 survivors were assigned into the usual care control arm. The average age of study participants in the HOPE study was 61.2 ± 7.0 years old (Table 1). The majority of patients were white (87.6%) and diagnosed with stage I breast cancer (54.5%). The frequencies of race/ethnicity, education, disease stage, radiation therapy, chemotherapy, time on endocrine therapy, and BMI at baseline were similar between the exercise intervention group and the usual care group. Age was slightly higher in the exercise intervention group (62.0 ± 7.0 years) compared to the usual care group (60.5 ± 7.0 years) (P = 0.25).

Intervention Adherence

As previously reported, the participants in this study randomized to the exercise group increased their physical activity by 159 minutes per week while the usual-care group increased their physical activity by 49 minutes per week (P < .001).[17, 19] The exercise group completed an average of 70% of strength training sessions and reported an average of 119 minutes per week of aerobic exercise. The usual-care group attended an average of 53% of monthly telephone calls.

QOL and Fatigue

Table 2 shows the comparison of mean changes in FACT-B, FACT-ES, FACT-G measures and fatigue scores at 6 months and 12 months by randomly assigned group. At baseline, FACT measure scores did not differ between the two groups. At 12 months, the exercise group had greater improvement in breast cancer subscale (BCS) (2.2 vs. 0.7, P = 0.03), endocrine subscale (ESS) (5.5 vs. 1.7, P < 0.01), FACT-B (10.2 vs. 2.0, P = 0.001), FACT-B-

ES (15.6 vs. 3.7, P < 0.001) compared with the usual care group. Additionally, the exercise group had greater improvement in FACT-G (8.0 vs. 1.2, P < 0.01), and Fact-F (5.7 vs. 0.5, P < 0.001) compared with the usual care group. Figure 2 shows the change in total FACT-B-ES score by randomization group at baseline, and after 6 and 12 months of study intervention.

The exercise intervention group had significantly higher baseline SF-36 vitality subscores compared to the usual care group, but no other differences were seen at baseline (Table 3). In terms of SF-36 eight subscale scores, the exercise group had greater improvement of physical functioning (6.3 vs. −1.1, P < 0.0001), role functioning/physical (7.7 vs. 1.5, P < 0.01), bodily pain (8.1 vs. 0.2, P < 0.0001), general health perceptions (3.0 vs. −0.5, P = 0.01), vitality (6.0 vs. 0.9, P < 0.0001), social role functioning (6.2 vs. 1.4, P = 0.001), and mental functioning (4.0 vs. 0.7, P = 0.01) (Table 3). For the summary scores, the physical component score (7.0 vs. −0.8, P < 0.0001) improved to a greater degree in the intervention compared with the usual care group at 12 months (Table 3). When sensitivity analyses were run under the missing not at random assumption, similar results were obtained (Supplemental Tables 1 and 2).

Discussion

In this randomized trial, combined aerobic and resistance exercise, such as moderate-intensity walking and twice-weekly supervised strength training, improved endocrine-related QOL and overall QOL by approximately 10% among breast cancer patients experiencing AI-related arthralgias. We noted similar standardized effect sizes for FACT-B, FACT-ES, and FACT-G improvement in the exercise group (0.46, 0.39, and 0.46, respectively). These results are encouraging for postmenopausal breast cancer survivors who are recommended to take AIs to improve their cancer prognosis.

This is the first study to examine the effect of an exercise intervention on endocrine-related and overall QOL in breast cancer patients taking AIs and experiencing AI-related side effects. Our findings were consistent with other physical activity trials among breast cancer patients not taking AIs that showed improved QOL.[3–8, 10] Similar to the 10% improvement of FACT-B scores among exercisers in our study, Courneya et al found an improvement of 8.2% in FACT-B scores in their trial of exercise among breast cancer survivors.[8] This study did not limit their study to breast cancer survivors taking AIs and experiencing AI-associated side effects but showed similar baseline FACT-B scores and similar improvements in QOL to our study. Additionally, a recent meta-analysis among patients with multiple types of cancer found a favorable effect of exercise on QOL with a standardized mean difference summary estimate of 5.55 (95% CI: 3.19 – 7.90; p<0.001).[28] Adverse side effects associated with taking AIs are the main reason for AI treatment discontinuation or poor adherence, thereby reducing treatment effectiveness and increasing mortality.[29–33] Adverse side effects of AIs, such as joint pain, are associated with decreased physical activity among breast cancer survivors.[34] Previous studies have shown that interventions among breast cancer patients to increase physical activity levels are feasible and effective[35] and may improve QOL.[36] The breast cancer survivors in our study were all experiencing arthralgia or joint pain associated with taking an AI for cancer treatment. Our intervention further was

effective in getting these breast cancer survivors to increase their exercise levels indicating that even survivors experiencing moderate to severe adverse treatment-associated symptoms can increase their exercise levels and improve their QOL. Furthermore, this increase in physical activity can alleviate arthralgia associated with AI use.[17]

A significant effect of exercise on various QOL measures, both on the FACT and SF-36, was observed in our study, particularly measures of physical QOL. Our participants had lower (i.e. worse) baseline scores across all FACT measures compared to other studies of women who were taking AIs.[37, 38] However, the women in these other studies were not required to have joint pain associated with AI use, which may explain lower baseline scores in our study. As we had the FACT subscales, we could examine different aspects of QOL. In this study, we observed significant increases in the physical well-being, functional well-being, breast cancer, endocrine, and fatigue subscales. It is well established that exercise is associated with more beneficial physical and mental health outcomes, including better general and health-related QOL.[39] This study further shows that exercise can lead to better QOL among breast cancer patients with AI-associated arthralgias.

Strengths of this study include the randomized design, population-based recruitment, high adherence to the intervention, and 12-month study duration. This is the first study to examine the effect of exercise specifically on endocrine-related QOL (FACT-B-ES) among breast cancer patients taking AIs and experiencing AI-induced arthralgia. Other studies have used various approaches to improve endocrine symptoms in breast cancer survivors, including mindfulness-based stress reduction,[40] acupuncture,[31] physical therapy, and targeted heat.[29] Pharmacological therapies, such as use of non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-2 (COX-2) inhibitors, glucosamine, and narcotic analgesics, have also been studied to alleviate pain from AI-induced arthralgias, but may be contraindicated or ineffective.[29] A randomized trial of duloxetine in 299 breast cancer patients experiencing AI-associated side effects showed an improvement with 12 weeks of treatment, although low-grade toxicities were more frequent in the treatment group.[41] This study also has practical implications: 1) the aerobic exercise in this study primarily consisted of brisk walking outside or on a treadmill which can be done by most individuals assuming they have a good pair of walking shoes and a safe place to walk and 2) the Livestrong at the YMCA offers free exercise training for cancer survivors that has been found to be safe and effective in increasing physical activity levels.[42]

Limitations of our study include participants were not blinded, potential reporting bias due to patient-reported outcomes, and missing data across time points. The exercise group had significantly greater completion rate, indicating a differential dropout rate between the two groups. However, since exercisers showed improvement in joint pain compared to controls, the potential bias due to greater drop-out in control group is likely towards the null. Additionally, we used mixed model analysis that is robust to remedy such bias from missing data. The sensitivity analysis using multiple imputation under MNAR assumption also reached consistent results. Lastly, as our study specifically aimed to treat AI-associated side effects, rather than prevent AI-associated side effects, thus we were unable to assess the impact of our intervention on AI adherence as all women enrolled were taking AIs despite side effects and were planning on staying on AIs for the duration of the study.

In this study, we observed significant and clinically important improvements in endocrine-related QOL symptoms and fatigue among breast cancer patients randomized to the combined aerobic and resistance exercise intervention. The endocrine-related QOL improvement of approximately 12 points observed with exercise exceeds the clinically-defined improvement in QOL of 3 points. Since adverse side effects associated with AI use are quite common among the breast cancer survivors and this is the main reason for treatment discontinuation, this innovative non-pharmacologic intervention could benefit many breast cancer survivors and increase successful implementation of AIs in breast cancer treatment. The effect of combined aerobic and resistance exercise on these overall and symptom-specific QOL measures is promising for breast cancer survivors whose physicians' have recommended AIs for treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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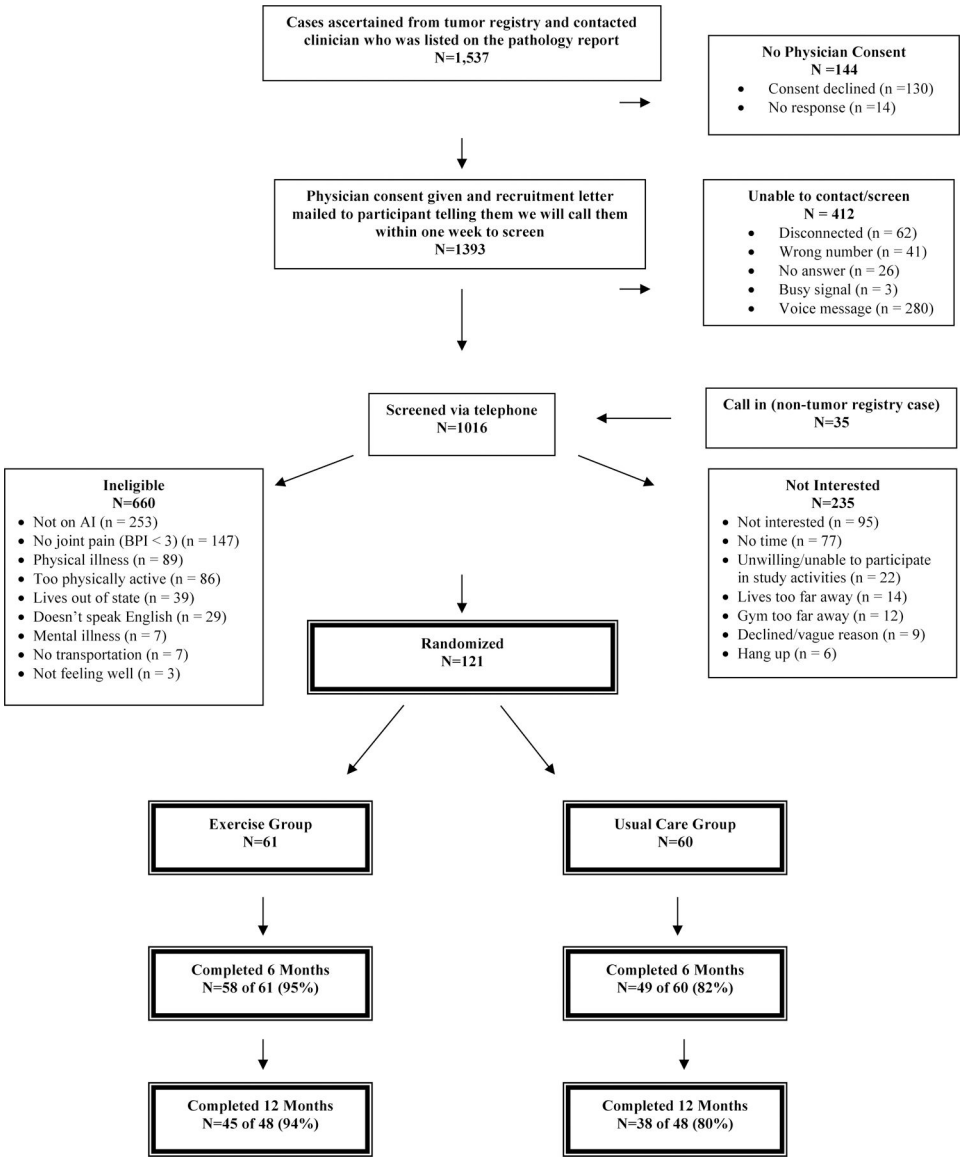

Figure 1.
Flow of participants through the HOPE Study

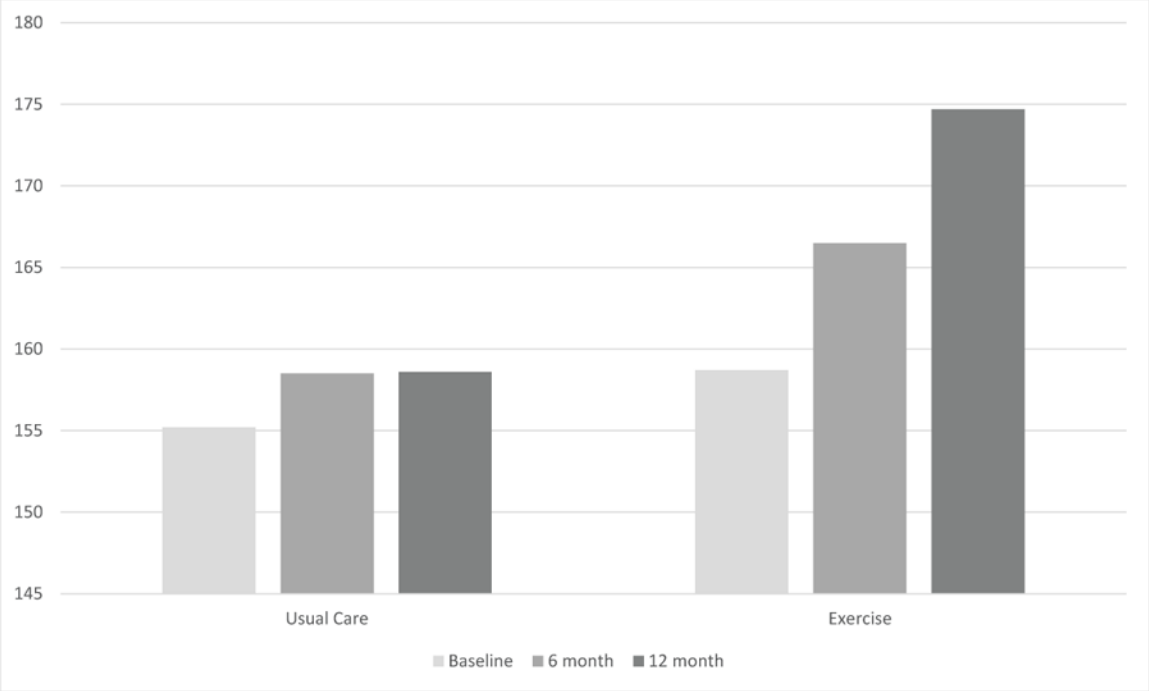

Figure 2.
Change in total FACT-B-ES score by randomization group at baseline, and after 6 and 12 months of study intervention.

Table 1.

Baseline Characteristics among Randomly Assigned Participants in the HOPE Study

	Randomization Group		
	Usual Care (%) (N = 60) Mean (SD)	Exercise (%) (N = 61) Mean (SD)	P Value
Age, Years			
Mean (SD)	60.5 (7.0)	62.0 (7.0)	0.25
Race/Ethnicity			
Non-Hispanic White	84	85	0.85
Hispanic	5	2	
African American	7	10	
Asian/Pacific Islander	2	2	
American Indian	2	0	
Education			
High school graduate	15	10	0.25
Some school after high school	42	33	
College graduate	43	57	
Time since diagnosis, years			
	3.3 (3.9)	2.7 (3.1)	0.30
Time since initiating AI therapy, years			
	1.8 (1.3)	1.9 (2.9)	0.89
Disease Stage			
0	0	1	0.70
I	62	59	
II	32	30	
III	7	10	
Chemotherapy			
Yes	43	54	0.22
No	57	46	
Radiation Therapy			
Yes	75	82	0.65
No	25	18	
BMI, kg/m^2			
	28.7 (5.5)	30.0 (6.8)	0.27
Taking pain medication			
	42	52	
Physician-diagnosed arthritis			
	32	49	

	Randomization Group		
	Usual Care (%) (N = 60) Mean (SD)	Exercise (%) (N = 61) Mean (SD)	P Value
Current glucosamine and chondroitin use			
	18	13	

Table 2.

Effect of Exercise Versus Usual Care on FACT Measures at Baseline and Changes at 6 months and 12 months.

Outcome		Usual Care	Exercise	Exercise Effect	P value
		FACT-G			
Physical well-being	Baseline	21.0 (4.5)	21.8 (4.2)		0.31
	6-month change	0.6(−0.4, 1.5)	1.7(0.8, 2.5)	1.1(−0.0, 2.2)	0.05
	12-month change	−0.1(−1.2, 1.0)	2.4(1.4, 3.5)	2.5(1.0, 4.0)	0.001
Social/Family well-being	Baseline	21.4 (5.0)	21.5 (5.4)		0.89
	6-month change	−0.7(−1.8, 0.3)	0.5(−0.5, 1.5)	1.2(−0.2, 2.7)	0.09
	12-month change	0.4(−0.7, 1.6)	1.4(0.3, 2.5)	1.0(−0.6, 2.5)	0.23
Emotional well-being	Baseline	19.2 (4.4)	19.3 (4.0)		0.90
	6-month change	0.9(0.1, 1.7)	1.1(0.3, 1.8)	0.2(−0.8, 1.1)	0.69
	12-month change	0.7(−0.1, 1.6)	1.7(0.9, 2.4)	0.9(−0.1, 2.0)	0.08
Functional well-being	Baseline	20.4 (4.9)	20.3 (5.2)		0.92
	6-month change	0.9(−0.3, 2.1)	1.1(0.0, 2.2)	0.2(−1.3, 1.8)	0.77
	12-month change	0.1(−1.1, 1.3)	2.6(1.5, 3.7)	2.5(0.9, 4.1)	0.002
FACT-G	Baseline	82.0 (14.8)	82.9 (15.1)		0.73
	6-month change	1.5(−1.4, 4.5)	4.3(1.6, 7.0)	2.7(−1.0, 6.5)	0.153
	12-month change	1.2(−2.0, 4.4)	8.0(5.1, 11.0)	6.8(2.6, 11.0)	0.002
FACT-B					
Breast cancer subscale	Baseline	18.3 (4.8)	19.2 (4.7)		0.26
	6-month change	0.7(−0.2, 1.5)	1.1(0.3, 2.0)	0.5(−0.6, 1.6)	0.39
	12-month change	0.7(−0.2, 1.7)	2.2(1.3, 3.1)	1.4(0.1, 2.7)	0.03
FACT-B	Baseline	100.2 (18.0)	102.2 (18.7)		0.57
	6-month change	2.2(−1.2, 5.6)	5.4(2.3, 8.5)	3.2(−1.1, 7.6)	0.14
	12-month change	2.0(−1.8, 5.7)	10.2(6.7, 13.6)	8.2(3.3, 13.2)	0.001
FACT-ES					
Endocrine subscale	Baseline	54.9 (9.8)	56.5 (10.1)		0.38
	6-month change	1.3(−0.6, 3.3)	2.0(0.2, 3.8)	0.6(−1.9, 3.2)	0.62
	12-month change	1.7(−0.2, 3.6)	5.5(3.7, 7.2)	3.8(1.3, 6.2)	0.003
FACT-B-ES					
FACT-B-ES	Baseline	155.2 (25.5)	158.7 (26.8)		0.46
	6-month change	3.6(−1.1, 8.2)	7.4(3.2, 11.7)	3.9(−1.9, 9.7)	0.19
	12-month change	3.7(−1.3, 8.7)	15.6(11.0, 20.2)	11.9(5.3, 18.5)	0.0005
FACIT-FATIGUE					

Outcome		Usual Care	Exercise	Exercise Effect	P value
		FACT-G			
Fatigue subscale	Baseline	36.2 (10.8)	37.9 (10.6)		0.39
	6-month change	0.5(−1.7, 2.8)	3.8(1.7, 5.9)	3.3(0.4, 6.1)	0.03
	12-month change	0.5(−1.6, 2.6)	5.7(3.8, 7.7)	5.2(2.5, 8.0)	0.0003

Baseline scores are presented as means (standard deviation). 6-month or 12-month change are presented as least square means and 95% confidence interval from mixed model analysis adjusting for baseline score and age.

At 6 months, 47 controls (78.3%) and 58 (95.1%) exercisers completed the QOL assessment. At 12 months, 38 (79.2%) controls and 45 (93.8%) exercisers completed the QOL assessment. Due to a funding cut, 25 women were only enrolled for a 6-month study rather than 12 months and were therefore not included in the 12-month analyses.

Table 3.

Effect on Exercise Versus Usual Care on SF-36 at Baseline and Changes at 6 months and 12 months.

Outcome		Usual Care	Exercise	Exercise Effect	P value
SF-36 SCORES					
Subscales					
Physical functioning	Baseline	42.1 (8.7)	42.8 (8.8)		0.67
	6-month change	0.8 (−1.1, 2.8)	5.8 (4.0, 7.6)	4.9 (2.4, 7.4)	0.0002
	12-month change	−1.1 (−3.2, 1.1)	6.3 (4.3, 8.3)	7.4 (4.5, 10.3)	<.0001
Roles: physical	Baseline	42.1 (11.4)	42.0 (11.7)		0.97
	6-month change	2.6 (−0.4, 5.7)	4.5 (1.8, 7.3)	1.9 (−1.9, 5.7)	0.32
	12-month change	1.5 (−1.6, 4.6)	7.7 (4.8, 10.6)	6.2 (2.3, 10.1)	0.002
Bodily pain	Baseline	42.5 (7.8)	42.2 (9.0)		0.86
	6-month change	2.6 (0.1, 5.0)	4.7 (2.4, 7.0)	2.1 (−1.1, 5.3)	0.19
	12-month change	0.2 (−2.2, 2.7)	8.1 (5.9, 10.4)	7.9 (4.7, 11.1)	<.0001
General health perceptions	Baseline	48.1 (9.0)	49.3 (8.5)		0.46
	6-month change	0.4 (−1.4, 2.3)	2.2 (0.5, 4.0)	1.8 (−0.7, 4.2)	0.15
	12-month change	−0.5 (−2.5, 1.6)	3.0 (1.0, 4.9)	3.4 (0.7, 6.2)	0.01
Vitality	Baseline	44.6 (9.3)	48.2 (8.7)		0.03
	6-month change	0.8 (−1.2, 2.8)	4.4 (2.6, 6.2)	3.6 (1.0, 6.2)	0.006
	12-month change	0.9 (−1.0, 2.8)	6.0 (4.3, 7.8)	5.1 (2.6, 7.6)	<.0001
Social role functioning	Baseline	46.9 (9.3)	47.1 (10.4)		0.92
	6-month change	1.6 (−0.9, 4.1)	2.8 (0.4, 5.2)	1.2 (−1.9, 4.3)	0.45
	12-month change	1.4 (−1.0, 3.8)	6.2 (3.9, 8.5)	4.8 (1.9, 7.7)	0.001
Role: emotion	Baseline	45.3 (12.8)	44.6 (12.3)		0.76
	6-month change	0.2 (−3.1, 3.5)	2.9 (−0.1, 6.0)	2.7 (−1.3, 6.7)	0.18
	12-month change	3.2 (−0.3, 6.6)	5.1 (1.9, 8.3)	2.0 (−2.3, 6.2)	0.36
Mental functioning	Baseline	47.2 (11.0)	48.0 (9.1)		0.69
	6-month change	1.5 (−0.9, 3.8)	2.0 (−0.2, 4.2)	0.5 (−2.5, 3.6)	0.73
	12-month change	0.7 (−1.4, 2.8)	4.0 (2.1, 6.0)	3.3 (0.7, 5.8)	0.01
Component Scores					
Physical component score	Baseline	42.4 (8.8)	42.9 (9.3)		0.74
	6-month change	1.9 (−0.2, 4.1)	5.2 (3.3, 7.2)	3.3 (0.6, 6.1)	0.02
	12-month change	−0.8 (−3.3, 1.7)	7.0 (4.7, 9.3)	7.8 (4.6, 11.0)	<.0001

Outcome		Usual Care	Exercise	Exercise Effect	P value
		SF-36 SCORES			
Mental component score	Baseline	48.1 (11.8)	48.9 (9.9)		0.68
	6-month change	0.5 (−2.2, 3.2)	1.7 (−0.8, 4.2)	1.2 (−2.3, 4.6)	0.50
	12-month change	2.4 (−0.2, 5.0)	4.1 (1.7, 6.6)	1.7 (−1.5, 5.0)	0.30

Baseline scores are presented as means (standard deviation). 6-month or 12-month change are presented as least square means and 95% confidence interval from mixed model analysis adjusting for baseline score and age.