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Aromatase Inhibitor Associated Musculoskeletal Symptoms are associated with Reduced Physical Activity among Breast Cancer Survivors

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Abstract

Background—Physical activity has numerous health benefits for breast cancer survivors. Recent data suggest that some breast cancer survivors treated with aromatase inhibitors may experience aromatase inhibitor associated musculoskeletal symptoms. It is unknown whether aromatase inhibitor associated musculoskeletal symptoms are associated with reduced physical activity and what other risk factors are associated with such physical activity reductions.

Methods—We conducted a cross-sectional study at a large university-based breast cancer clinic among breast cancer survivors prescribed an aromatase inhibitor. At routine follow-up, we surveyed participants about aromatase inhibitor associated musculoskeletal symptoms, as well as pre-aromatase inhibitor, and current, physical activity levels.

Results—Among 300 participants, 90 (30%) reported a reduction of physical activity since the initiation of aromatase inhibitor therapy. Those with aromatase inhibitor associated musculoskeletal symptoms were more likely to report decreased physical activity (62% versus 38%, $p=0.001$) compared to those without aromatase inhibitor associated musculoskeletal symptoms. In multivariate analyses, aromatase inhibitor associated musculoskeletal symptoms [odds ratio (OR) =2.29 (95% confidence interval (CI): 1.36–3.86)], and body mass index [OR=1.06 (95% CI: 1.02–1.12)] were associated with reductions in physical activity. In subgroup analysis among breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms, self-reported lower extremity joint pain [OR=1.23 (95% CI: 1.00–1.50)] and impaired lower extremity physical function [OR=1.07 (95% CI: 1.01–1.14)] were associated with reductions in physical activity.

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Conclusion—Breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms were more likely to report reductions in physical activity since initiating aromatase inhibitor therapy compared to those without aromatase inhibitor associated musculoskeletal symptoms. Our findings suggest that tailored interventions targeting lower extremity functional limitations are needed to enable breast cancer survivors with aromatase inhibitor associated musculoskeletal symptoms to participate in physical activity.

Keywords

exercise; behavior; symptoms; physical function; psychosocial

Introduction

There are over two million breast cancer (BrCa) survivors in the United States (1). Approximately 75% of BrCa survivors are diagnosed with hormone-receptor-positive BrCa (2). Aromatase inhibitors (AIs) improve disease-free survival by 10–40% (3–5), and have become a part of standard adjuvant therapy for post-menopausal women diagnosed with hormone-receptor-positive BrCa (6). Despite the survival benefits associated with AIs, 5–36% of BrCa survivors experience joint pain resulting from their AI, referred to as aromatase inhibitor associated musculoskeletal symptoms (AIMSS); (7). AIMSS has been associated with poor AI adherence and self-discontinuation of AIs (8–10). Poor adherence or self-discontinuation of AI's because of side effects may attenuate the efficacy of AI's, thereby increasing the likelihood for cancer recurrence (6). The therapeutic benefit achieved with AIs among BrCa survivors demands the development of evidence-based interventions to minimize the manifestation of AIMSS to improve AI adherence (11,12).

Joint pain can interfere with walking or other forms of physical activity (PA); (13), therefore it is plausible that AIMSS may cause BrCa survivors to decrease their PA (8). Identifying the population of BrCa survivors who reduce their PA is important because PA has been shown to increase physical and functional well-being among postmenopausal women with arthritis and joint related pain (14); symptoms similar to AIMSS. Additionally, PA improves disease-free survival (15), and increases bone mineral density among BrCa survivors (16); two frequent concerns among BrCa survivors, particularly when initiating AI therapy (17).

It is currently unknown what proportion of BrCa survivors reduce their PA resulting from AIMSS. Furthermore, it is unknown if this subset of BrCa survivors share common characteristics associated with diminished PA; subsequently precluding them from reaping the therapeutic benefits associated with PA participation.

Therefore, the primary goal of our study was to determine whether AIMSS was associated with reductions in PA. As a secondary aim, we conducted subgroup analyses to focus on the functional limitations associated with reductions in PA among BrCa survivors with AIMSS. The identification and characterization of this subset of women will provide a circumscribed population in which a PA intervention or general PA advocacy may be challenging, and other intervention modalities may be necessary to reduce AIMSS symptoms and serve as a complement to PA.

Methods

Study Design

This was a cross-sectional study of women diagnosed with breast cancer who received care at the Rena Rowan Breast Center in the Abramson Cancer Center of the University of Pennsylvania between April and October 2007.

Patient Selection Criteria

Eligible participants included women who were post-menopausal, diagnosed with Stage I–III, hormone-receptor-positive breast cancer, and were currently prescribed one of three aromatase inhibitors: Anastrozole, Letrozole, or Exemestane. Eligibility included completion of curative therapy (surgery, radiation, chemotherapy) at least one month prior to enrollment in the study. Prior to approaching any potential study participants, the attending oncologist was asked to provide permission to allow his/her patient to be approached to enroll in the study. Confirmation of study eligibility included verification of medical records, and study staff approached potential study participants at regular follow-up appointments. The University of Pennsylvania Institutional Review Board, and the Scientific Review and Monitoring Committee of the Abramson Cancer Center approved this study. Written informed consent was obtained from all participants prior to data collection.

Primary Outcome Measurement

The primary outcome of this study was self-reported change in PA, comparing pre-AI levels of PA to current levels of PA. Participants were asked to answer the following question: “Has your current amount of physical activity changed compared to your amount of physical activity before you started AIs?” The three choices provided were “Yes, I exercise less now”; “Yes, I exercise more now”; “No, I exercise the same amount now.” This variable was dichotomized (“Yes, I exercise *less* now” vs. “Yes, I exercise *more* now and No, I exercise the same amount now”), and used as the primary outcome variable of PA reduction in these analyses. All women reporting AIMSS were required to answer the following question: “What do you believe is the current source of your current joint symptoms” (18,19). The choices to this question included: “AI”, “prior osteoarthritis” or “other medical condition (participants were asked to specify)” (18,19). Women were classified as having self-reported AIMSS if they responded “AI” to this question.

Covariates

Information on covariates were collected using self-report (i.e., race, education) or abstracted from medical records (i.e., stage of cancer, chemotherapy/radiation, tamoxifen use, AI use). Participants completed validated questionnaires to assess physical and functional impairments. These questionnaires included: 1) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire to assess pain, stiffness, and physical function in the hips and knees (20); 2) the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) (21); and 3) the Shortened Disabilities of the Arm, Shoulder and Hand

Questionnaire (Quick DASH); (22). The International Physical Activity questionnaire assessed PA (23).

Statistical Analysis

We performed descriptive statistics and univariate analyses on all study variables using the Wilcoxon Rank Sum or Fishers Exact test. We then developed multivariable logistic regression models to quantify the association of each variable on reductions in PA. Variables that were significant at the $p < 0.15$ level in univariate analyses were included in the multivariable analyses. We then conducted subgroup analyses restricted to BrCa survivors with AIMSS to quantify the impact of each variable on reductions in PA. Statistical tests were two-sided and $p < 0.05$ was the threshold for statistical significance. All logistic regression analyses are presented as odds ratios (OR) and 95% confidence intervals (95% CI). All statistical analyses were conducted with Stata 12.0 (College Station, TX).

Results

Participant characteristics among the study sample

Among 325 potential eligible subjects approached, 300 (92%) participated in the study. Demographic characteristics of the study population are displayed in Table 1. Among the 300 survey participants, the age ranged from 33–86 years. The majority of participants self-reported non-Hispanic, White ethnicity and race. Participants were generally overweight, and had a BMI range of 17.5–48.6. The most common AI prescribed to the 300 participants was Anastrozole (58%), followed by Letrozole (23%), and Exemestane (19%). The median self-reported PA volume was 100 min·wk⁻¹ and ranged from 0–300 min·wk⁻¹.

Factors associated with decreased PA

Among the 300 participants, 90 (30%) reported participating in less PA since starting AI therapy. Participants who reported less PA were younger, had a higher BMI, and were more likely to be on Exemestane (Table 1). The 139 participants with AIMSS were more likely to report decreased PA (62% vs 38%, $p = 0.001$) than participants without AIMSS. Substantiating our primary outcome variable, the median number of self-reported minutes of PA was significantly less among those who reported decreasing their PA since starting AI therapy compared to those who maintained or increased their PA since starting AI therapy [100 min·wk⁻¹ (40–180) vs. 75 min·wk⁻¹ (40–150), $p = 0.03$].

In univariate analyses, age, employment status, BMI, type of AI, years since last menstrual period, and presence of AIMSS were associated with a decrease in self-reported PA levels (Table 2). When entered into a multivariable regression model, two factors—BMI and presence of AIMSS—were associated with participating in less PA since starting AI therapy. Participants who reported AIMSS were more likely to participate in less PA [OR=2.29 (95% CI: 1.36–3.86)]. Participants who had a higher BMI were more likely to participate in less PA [OR=1.06 (95% CI: 1.02–1.12)].

Functional differences associated with decrease PA among BrCa survivors with AIMSS

We conducted subgroup analyses among participants who reported AIMSS (n=139) to identify demographic, clinical, and functional differences between those with AIMSS who did versus did not reduce their self-reported participation in PA since starting AI therapy. Participants with AIMSS who decreased their self-reported participation in PA had poorer physical function of the lower extremities (WOMAC), hands (M-SACRAH), and shoulder (Quick DASH); (Table 3). Among participants with AIMSS, those who reported self-reported participating in less PA since starting AI therapy self-reported significantly less $\text{min}\cdot\text{wk}^{-1}$ of PA compared to those who self-reported maintaining or increasing their PA since starting AI therapy.

In univariate analyses, BMI, type of AI, number of comorbidities, WOMAC, M-SACRAH, and Quick DASH scores were associated with a decrease in self-reported PA levels (Table 4). When entered into a multivariable model, three factors—each of the three WOMAC subscales—were associated with participating in less PA since starting AI therapy. Participants who reported more lower extremity pain and poorer lower extremity function were more likely to report participating in less PA since starting AI therapy, [OR=1.23 (95% CI: 1.00–1.50)], and [OR=1.07 (95% CI: 1.01–1.14)], respectively. Participants who reported lower extremity stiffness were less likely to report a decline in PA participation [OR=0.54 (95% CI: 0.34–0.85)]. Furthermore, in the multivariable analysis we highlight the WOMAC subscales rather than the WOMAC composite measure [OR=1.04 (95% CI: 1.01–1.07)] to underscore specific deficiencies associated with decreased PA levels.

Discussion

In this study, we found that BrCa survivors who report AIMSS are two-fold more likely to reduce their levels of PA compared to those who do not report AIMSS. Among BrCa survivors who report AIMSS, lower extremity pain and functional limitations were associated with self-reported changes in PA levels. Despite the mental and physical health benefits achieved when BrCa survivors engage in an adequate dose of PA (24,25), our research identified an association between decreased PA levels and concurrent side effects from cancer treatment.

The main limitation of this study is the cross-sectional design, which limits causal inference of the identified associations among AIMSS, PA, and physical impairments. Prospective research to identify the causal relationship between AIMSS symptoms and participation in PA is the next step to continue this research. Second, our primary outcome variable of our analyses was self-reported and there may have been recall bias about the reference point for PA levels—it is unknown if women compared their current PA volume to those immediately prior to AI use or prior to BrCa diagnosis. The physical function outcomes were previously validated patient reported outcomes; however, the measurement of functions may be strengthened by clinical examination by trained health care professionals to verify these findings. Third, this study was conducted in an urban academic medical center and thus limits generalizability of the findings. Despite the limitations, strengths of the study included a relatively large sample of patients outside of a clinical trial setting. Our survey response rate was >90% which limits the likelihood of selection bias in our study sample. Further, we

supported the validity of our primary outcome variable with a validated measure of physical activity, the International Physical Activity Questionnaire (23).

The observed association between presences of AIMSS concurrent with reductions in self-reported PA is consistent with observations among those with arthritis. Despite the lack of consistent objective clinical signs of AIMSS, this clinical condition shares similar subjective symptom complaints of arthritis, aching and painful joints. Thus, as we try to understand the impact of AIMSS on a population, we can learn from what is known in the arthritis research. Data from the 2002 National Health Interview Survey examined the association between physical inactivity and functional impairments among 42,704 men and women with arthritis (26). Consistent in direction and magnitude with our findings, functional limitations among those with arthritis were associated with an increased likelihood of being physically inactive. Among those with 1–3, or 4 functional limitations, the likelihood of being physically inactive increased 1.5- and 3.3-fold compared to those without any functional limitations, respectively (26).

Continued research would be particularly important if participation in PA is an effective intervention to minimize AIMSS. Such interventions may be similar in content to those with arthritis (27). For example, the Fitness Arthritis and Seniors Trial (FAST) randomized 365 older adults with knee osteoarthritis to aerobic exercise, resistance exercise, or health-education (13). Participants randomized to aerobic or resistance exercise had improvements in disability, physical performance, and pain compared to the health-education group (13). The FAST trial concluded those with knee osteoarthritis should participate in regular aerobic or strength exercise (13). However, empirical evidence investigating the use of PA among BrCa survivors with AIMSS to date is limited. Trials investigating the efficacy of physical activity and exercise interventions to improve AIMSS among BrCa survivors are ongoing (28,29).

The Center for Disease Control (CDC) acknowledged there are three public health interventions to manage arthritis (30). Interventions include self-management education, physical activity, and weight management. The similarities between AIMSS and arthritis make it plausible that these recommendations be applicable to BrCa survivors with AIMSS. In addition to CDC recommendations, alternative and complementary therapies, and medications to manage AIMSS symptoms are currently being developed and empirically tested that include vitamin-D supplementation (31), acupuncture (32,33), duloxetine (34), and glucosamine and chondroitin supplementation (35,36). As the evidence for these therapies emerge for AIMSS, it is plausible the appropriate integration of these therapies with PA may act synergistically to improve numerous health outcomes beyond that of AIMSS to include improvements in disease free survival, aerobic capacity, muscular strength, body composition, bone mineral density, and an array of mental-health outcomes (24).

Conclusions

Among BrCa survivors receiving AI therapy who experience AIMSS, the risk of reducing PA increases by more than 2-fold. If this finding is confirmed in future research, it may have long-term implications for the overall health and well-being for BrCa survivors who

experience AIMSS. Among those with AIMSS, individuals with lower extremity pain and functional impairments may be more vulnerable to decrease PA. This finding helps to both identify the population and inform intervention design to incorporate more tailored and integrative approaches (e.g. acupuncture, physical therapy) to decrease pain and improve function to engage in PA. BrCa survivors should be encouraged to avoid inactivity within their ability to do so. The American College of Sports Medicine has published exercise guidelines for cancer survivors (24). However, the subgroup of BrCa survivors who experience AIMSS may require tailored exercise prescriptions. At this time, the specific components of the exercise prescription that require tailoring—frequency, intensity, time, or type—remain to be elucidated. Clinicians should aim to diagnose and treat AIMSS in a timely manner so patients are able to maintain adequate levels of PA.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011 Mar-Apr;61(2):69–90. [PubMed: 21296855]
2. Altundag K, Ibrahim NK. Aromatase inhibitors in breast cancer: an overview. *Oncologist*. 2006 Jun; 11(6):553–562. [PubMed: 16794235]
3. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005 Jan 1–7; 365(9453):60–62. [PubMed: 15639680]
4. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003 Nov 6; 349(19):1793–1802. [PubMed: 14551341]
5. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005 Aug 6–12; 366(9484):455–462. [PubMed: 16084253]
6. Bevers TB, Anderson BO, Bonaccio E, Buys S, Daly MB, Dempsey PJ, et al. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. *J Natl Compr Canc Netw*. 2009 Nov; 7(10):1060–1096. [PubMed: 19930975]
7. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. *Breast*. 2007 Jun; 16(3):223–234. [PubMed: 17368903]
8. Donnellan PP, Douglas SL, Cameron DA, Leonard RC. Aromatase inhibitors and arthralgia. *J Clin Oncol*. 2001 May 15; 19(10):2767. [PubMed: 11352973]
9. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol*. 2008 Feb 1; 26(4):556–562. [PubMed: 18180462]
10. Stricker CT, Palmer SC, Demichele A, Mao JJ. Understanding premature discontinuation of aromatase inhibitor (AI) therapy in postmenopausal breast cancer survivors. *Journal of Clinical Oncology*. 2010; 28(15Suppl):458s.

11. Winters L, Habin K, Flanagan J, Cashavelly BJ. "I feel like I am 100 years old!" managing arthralgias from aromatase inhibitors. *Clin J Oncol Nurs*. 2010 Jun; 14(3):379–382. [PubMed: 20529801]
12. Thorne C. Management of arthralgias associated with aromatase inhibitor therapy. *Curr Oncol*. 2007 Dec; 14(Suppl 1):S11–9. [PubMed: 18087604]
13. Mangani I, Cesari M, Kritchevsky SB, Maraldi C, Carter CS, Atkinson HH, et al. Physical exercise and comorbidity. Results from the Fitness and Arthritis in Seniors Trial (FAST). *Aging Clin Exp Res*. 2006 Oct; 18(5):374–380. [PubMed: 17167301]
14. Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, et al. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken)*. 2010 Jul; 62(7):984–992. [PubMed: 20589690]
15. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005 May 25; 293(20):2479–2486. [PubMed: 15914748]
16. Irwin ML, Alvarez-Reeves M, Cadmus L, Mierzejewski E, Mayne ST, Yu H, et al. Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring)*. 2009 Aug; 17(8):1534–1541. [PubMed: 19629060]
17. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat*. 1996; 38(2):183–199. [PubMed: 8861837]
18. Mao JJ, Stricker C, Bruner D, Xie S, Bowman MA, Farrar JT, et al. Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. *Cancer*. 2009 Aug 15; 115(16):3631–3639. [PubMed: 19517460]
19. Mao JJ, Su HI, Feng R, Donelson ML, Aplenc R, Rebbeck TR, et al. Association of functional polymorphisms in CYP19A1 with aromatase inhibitor associated arthralgia in breast cancer survivors. *Breast Cancer Res*. 2011 Jan 20; 13(1):R8. [PubMed: 21251330]
20. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988 Dec; 15(12):1833–1840. [PubMed: 3068365]
21. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the M-SACRAH, a modified, shortened version of SACRAH (Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands). *Rheumatology (Oxford)*. 2004 Nov; 43(11):1409–1413. [PubMed: 15304674]
22. Gummesson C, Ward MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): validity and reliability based on responses within the full-length DASH. *BMC Musculoskelet Disord*. 2006 May 18; 7:44. [PubMed: 16709254]
23. Hagstromer M, Oja P, Sjostrom M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutr*. 2006 Sep; 9(6):755–762. [PubMed: 16925881]
24. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010 Jul; 42(7):1409–1426. [PubMed: 20559064]
25. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*. 2010 Jan 6; 4(2):87–100. [PubMed: 20052559]
26. Shih M, Hootman JM, Kruger J, Helmick CG. Physical activity in men and women with arthritis National Health Interview Survey, 2002. *Am J Prev Med*. 2006 May; 30(5):385–393. [PubMed: 16627126]
27. Younus J, Kligman L. Management of aromatase inhibitor-induced arthralgia. *Curr Oncol*. 2010 Feb; 17(1):87–90. [PubMed: 20179809]
28. Din OS, Dodwell D, Wakefield RJ, Coleman RE. Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more? *Breast Cancer Res Treat*. 2010 Apr; 120(3):525–538. [PubMed: 20157776]

29. [Accessed June 4, 2012] ClinicalTrials.gov. aromatase inhibitors and arthralgia. Available at: <http://clinicaltrials.gov/ct2/results?term=aromatase+inhibitors+and+arthralgia>
30. Theis KA, Helmick CG, Hootman JM. Arthritis burden and impact are greater among U.S. women than men: intervention opportunities. *J Womens Health (Larchmt)*. 2007 May; 16(4):441–453. [PubMed: 17521246]
31. Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, et al. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. *Breast Cancer Res Treat*. 2010 Jan; 119(1):111–118. [PubMed: 19655244]
32. Mao JJ, Bruner DW, Stricker C, Farrar JT, Xie SX, Bowman MA, et al. Feasibility trial of electroacupuncture for aromatase inhibitor--related arthralgia in breast cancer survivors. *Integr Cancer Ther*. 2009 Jun; 8(2):123–129. [PubMed: 19679620]
33. Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *J Clin Oncol*. 2010 Mar 1; 28(7):1154–1160. [PubMed: 20100963]
34. Henry NL, Banerjee M, Wicha M, Van Poznak C, Smerage JB, Schott AF, et al. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. *Cancer*. 2011 Dec 15; 117(24):5469–5475. [PubMed: 21692065]
35. Dent SF, Gaspo R, Kissner M, Pritchard KI. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. *Breast Cancer Res Treat*. 2011 Apr; 126(2):295–310. [PubMed: 21249443]
36. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *J Clin Oncol*. 2007 Sep 1; 25(25):3877–3883. [PubMed: 17761973]

Table 1

Demographic and clinical characteristics of entire sample, and stratified by physical activity change

Variable	Total Sample (n=300)	Decreased PA (n=90)	P-Value
Age — yr.	61.5±9.9	60.1±9.9	0.03
Race/ethnicity			
White	253 (85%)	73 (82%)	0.21
Non-White	47 (15%)	17 (19%)	
Education level			
High school or less	62 (21%)	16 (18%)	0.26
College	111 (37%)	47 (53%)	
Graduate or Professional School	127 (42%)	26 (29%)	
Employment status			
Full time	114 (39%)	41 (46%)	0.14
Part time	40 (13%)	8 (9%)	
Unemployed/retired	142 (48%)	41 (46%)	
BMI — kg/m ²	27.7±5.6	29.4±6.3	0.003
Stage			0.67
I	100 (37%)	28 (35%)	
II	142 (52%)	40 (51%)	
III	32 (12%)	11 (14%)	
Chemotherapy			0.25
No	119 (40%)	31 (33%)	
Yes	181 (60%)	59 (66%)	
Type of AI			0.04
Letrozole (Femara)	69 (23%)	20 (22%)	
Anastrozole (Arimidex)	173 (58%)	45 (50%)	
Exemestane (Aromasin)	58 (19%)	25 (28%)	
Duration of AI therapy, y			0.57
<1	126 (43%)	42 (48%)	
1–3	79 (27%)	21 (24%)	
>3	86 (30%)	25 (28%)	
No. of comorbid conditions, median [IQR]	1 [0–2]	1 [1–2]	0.63
Previous Arthritis — n (%)			0.79
No	197 (65%)	58 (64%)	
Yes	103 (34%)	32 (36%)	
Time Since last menstrual period, y			0.13
>10	51 (18%)	36 (41%)	
5–10	95 (33%)	35 (40%)	
<5	144 (50%)	17 (19%)	

Values are — n (%) or mean ± standard deviation unless otherwise noted and may not sum to 100% due to rounding error.

Table 2

Variables associated with decreased physical activity among all participants (n=300)

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Age — yr.	0.97 (0.96–1.00)	0.11		
Presence of AIMSS	2.48 (1.49–4.12)	<0.001	2.29 (1.36–3.86)	0.002
Employment status				
Full time	1 — Referent			
Part time	0.44 (0.19–1.04)	0.06		
Unemployed/retired	0.72 (0.42–1.22)	0.22		
BMI — kg/m ²	1.07 (1.03–1.12)	0.002	1.06 (1.02–1.12)	0.003
Type of AI				
Letrozole (Femara)	1 — Referent			
Anastrozole (Arimidex)	0.45 (0.24–0.85)	0.01		
Exemestane (Aromasin)	0.52 (0.25–1.09)	0.08		
Time Since last menstrual period, y				
>10	1 — Referent			
5–10	1.76 (1.00–3.10)	0.04		
<5	1.49 (0.74–2.97)	0.26		

Table 3

Physical function characteristics of sample with AIMSS (n=139), and stratified by physical activity change

Variable	Decreased PA (n=56)	Maintained/Increased PA (n=83)	P-Value
Minutes of activity completed per week, median [IQR]	80 [0–150]	150 [60–210]	0.04
WOMAC Composite	36.8±16.5	24.0±17.1	<0.001
Pain	7.8±3.4	5.0±4.0	<0.001
Stiffness	4.0±1.7	3.4±1.8	0.05
Physical Function	25.2±12.6	15.4±12.7	<0.001
M-SACRAH Composite	51.7±14.4	26.0±14.5	0.03
Quality of Daily Function	27.0±10.0	14.3±7.1	0.06
Stiffness	9.3±4.8	6.2±3.3	0.003
Pain	9.4±5.2	5.4±2.5	0.006
Quick DASH Composite	7.6±3.0	4.9±3.4	<0.001

Values are mean ± standard deviation unless otherwise noted.

Table 4
Variables associated with decreased physical activity among participants with AIMSS (n=139)

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI) ^a	P-Value
BMI — kg/m ²	1.09 (1.02–1.15)	0.005		
Type of AI				
Letrozole (Femara)	1 — Referent			
Anastrozole (Arimidex)	0.43 (0.17–1.03)	0.06		
Exemestane (Aromasin)	0.41 (0.15–1.14)	0.09		
No. of comorbidities	1.47 (0.95–2.26)	0.08		
WOMAC Composite Score ^a	1.04 (1.02–1.06)	<0.001		
Pain	1.21 (1.09–1.33)	<0.001	1.23 (1.00–1.50)	0.05
Stiffness	1.22 (0.99–1.50)	0.06	0.54 (0.34–0.85)	0.007
Physical Function	1.06 (1.02–1.09)	<0.001	1.07 (1.01–1.14)	0.02
M-SACRAH Composite Score	1.14 (0.97–1.34)	0.10		
Quality of Daily Function	1.19 (0.94–1.20)	0.14		
Stiffness	1.21 (1.05–1.37)	0.005		
Pain	1.27 (1.07–1.52)	0.006		
Quick DASH Composite	1.28 (1.14–1.43)	<0.001		

^a Subscales were modeled in multivariate analysis to highlight differences among assessment domains.