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Joint Pain and Falls Among Women with Breast Cancer on Aromatase Inhibitors

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Abstract

PURPOSE: Arthralgia is common among women with breast cancer on adjuvant aromatase inhibitor (AI) therapy. Pain is associated with falls in the general population; however, little is known about the relationship between arthralgia and falls among AI users. Our objective was to determine whether joint pain severity and interference predict future falls.

METHODS: We conducted a prospective cohort study of postmenopausal women with stage I-III estrogen receptor-positive breast cancer who were prescribed a third-generation AI. Arthralgia symptoms were measured at baseline using a modified version of the Brief Pain Inventory. Fall occurrence was obtained at 24-month follow-up.

RESULTS: Among 667 participants (median age 63 years, interquartile range 57–69 years), 232 (35%, 95% CI 31% to 39%) reported falls 12–24 months after baseline. Among women who fell, 65 (28%) reported seeking medical assistance. After controlling for multiple fall risk factors, we found significant non-linear associations between baseline joint pain severity and risk of falls

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($p=0.001$). Women with joint pain severity scores ≥ 4 had a more than two-fold increase in fall-risk compared to those without pain (41% vs. 20%). We observed a similar relationship for pain interference and fall-risk ($p<0.001$). Fewer than half of participants reported having been asked about falls in the past 12 months by their primary care physician (44%) or oncologist (36%).

CONCLUSION: Joint pain increases the risk of falls among women with breast cancer on adjuvant AI therapy. Health care providers should evaluate and manage arthralgia symptoms and implement fall-prevention strategies for those who are at increased risk.

Keywords

breast cancer; aromatase inhibitors; fall risk; arthralgia; joint pain; falls

INTRODUCTION

Over three million women in the United States live with a history of breast cancer.¹ Approximately 75% of these women have estrogen receptor-positive (ER+) breast cancer, which is commonly treated with aromatase inhibitors (AIs). One of the most common and debilitating side effects of AIs is joint pain or arthralgia, which affects approximately 40–50% of women with breast cancer on AI therapy.^{2–5} Joint pain among cancer-free community-dwelling older adults has been reported to be associated with reduced physical function⁶ and increased fall risk.⁷

Falls are a leading cause of hospitalization and mortality among cancer-free community-dwelling older people.⁸ Past studies in this population have reported that musculoskeletal pain—and specifically joint pain—is associated with increased fall risk.^{9–11} However, in women with breast cancer, the association between AI-induced joint pain and falls is not well understood. Studies investigating cancer-related pain as a risk factor for falls are very limited and have often focused on individuals with advanced cancer rather than on women with early stage cancer.^{12,13} Prospective cohort studies suggest that women have a significantly higher risk for falls after a diagnosis of breast cancer.^{14,15} The synergistic effects of natural aging and AI-induced joint pain could exacerbate the risk of falls.

No study to date has prospectively investigated the association between joint pain and falls in women with breast cancer on AI therapy. The primary aim of this study was to evaluate whether joint pain severity and joint pain interference at baseline predict fall occurrence between 12 and 24 months after baseline among our cohort of women with early-stage breast cancer on AI therapy. Understanding the interplay between joint pain and falls could help clinicians evaluate fall risk in this population and implement fall-prevention strategies.¹⁶

METHODS

We drew participants from Wellness After Breast Cancer-II (WABC-II), a prospective cohort study of breast cancer survivors receiving adjuvant AI therapy. In WABC-II, we sought to investigate the relationship between specific genetic variants and patient-reported arthralgia outcomes. We recruited participants at an academic tertiary care teaching hospital and at a

community hospital between November 2011 and June 2014 and conducted follow-up assessments between January 2014 and November 2015. Eligible participants were postmenopausal women with a history of stage I-III hormone receptor-positive breast cancer who had been using a third-generation AI (anastrozole, letrozole, exemestane) for at least six months or who had discontinued AI use before the prescribed therapy end date. Trained research assistants approached subjects in the waiting area of the breast cancer clinics. Consented patients completed the study survey. The Institutional Review Board of the University of Pennsylvania approved the study protocol. We included participants in our analysis who had completed the modified version of the Brief Pain Inventory (BPI) survey at baseline and the fall questionnaire at their 24-month follow-up.

Exposure: Arthralgia

Arthralgia was assessed by patient self-report at baseline on 0 to 10 numerical rating scales using a modified version of the 11-item Brief Pain Inventory (BPI). The BPI is a commonly used, reliable, and validated instrument for measuring pain severity and pain interference.¹⁷ Because women with breast cancer may experience multiple types of pain, we modified the items by adding “in and around joints” to ensure that the pain assessed was specific to arthralgia.^{18,19}

The Cronbach’s alpha was 0.94 for pain severity (4-item) and 0.95 for pain interference (7-item).

Main Outcome: Fall Occurrence

Fall occurrence was assessed by self-report at the 24-month follow-up. Consistent with the Prevention of Falls Network Europe (ProFaNE) consensus²² and with past studies,^{20,21} we asked participants, “In the past 12 months, have you had any fall, including a slip or trip, in which you lost your balance and landed on the floor, ground, or lower level?” Participants who answered, “Yes” were prompted to indicate the number of falls they had experienced in the past 12 months. In addition, we asked participants if in the past 12 months, their oncologist or primary care physician had asked them if they had experienced a fall. Participants were also asked if as a result of a fall in the past 12 months, they had sought medical assistance.

Covariates

We selected covariates based on factors that have previously been reported to be associated with falls in older adults with cancer.^{23,24} We also included covariates related to cancer treatment that have not been previously studied in relation to falls. Demographics and clinical factors including age, race, alcohol use (never drink, <1 drink per day, 1–2 drinks daily, >2 drinks daily), neuropathy, and pain medication use (nerve pain pills, muscle relaxants, opioids) were obtained at baseline through self-report. We obtained other clinical factors including chemotherapy history, radiation history, breast surgery type (lumpectomy or mastectomy), first AI used (anastrozole, letrozole, or exemestane), and time on AI through chart abstraction.

Statistical Analyses

We developed two multivariable logistic regression models for the outcome of falls reported between 12 and 24 months after baseline. The first model was for the association of joint pain severity with falls and the second model was for the association of joint pain interference with falls. We adjusted these models for factors known to be associated with pain or with the risk of falls including age, race, alcohol use, and neuropathy. Additionally, we adjusted the models for covariates as described above. Restricted cubic splines were used to account for the possibility of a non-linear relationship between baseline pain and fall risk. We used locally-weighted scatterplot smoothing (lowess) to graph the association between baseline joint pain severity or interference and patient falls. Since chemotherapy-related neuropathy may also influence the risk of falls,²⁵ we repeated our analyses excluding patients with a history of chemotherapy at baseline as a sensitivity analysis. We compared the rates of primary care physicians (PCPs) and oncologists asking patients about falls using a two-sided Pearson's chi-squared test. Analyses were performed using Stata 13 (StataCorp, College Station, TX).

RESULTS

Participant Characteristics

We approached 1518 patients and enrolled 1321 into the study; 1280 (84.3%) completed baseline questionnaires and 702 completed follow-up questionnaires (c.f. figure I). Among patients who completed follow-up, 35 were excluded from analysis for lacking data on the primary outcome. Of the 667 remaining participants, median age at baseline (Interquartile Range [IQR]) was 63 years (57 to 69 years) and the majority of participants were white (84%). A typical participant had stage I breast cancer (50%), had undergone lumpectomy (54%), had received chemotherapy (55%), had received radiation therapy (68%), and had taken anastrozole as their first AI (80%), c.f. table I. Median time on AI at baseline (IQR) was 2.8 years (1.4 to 4.5 years). Participants (N=667) in our current analyses did not differ from the rest of the cohort (N=613) in terms of age, education, race, or ethnicity.

Falls Among Breast Cancer Survivors

Among participants, 232 (35%, 95% Confidence Interval [CI] 31% to 39%) reported at least one fall. Among those who fell and reported the number of falls, 48% reported one fall, 31% reported two falls, 11% reported three falls, and 10% reported four or more falls. Among participants who reported at least one fall, 65 (28%, 95% CI 22% to 34%) reported that they had sought medical assistance at a hospital emergency room or doctor's office because of a fall.

Arthralgia and Falls

Median baseline joint pain severity (IQR) was 2.0 (0.5 to 4.0) and median baseline joint pain interference (IQR) was 0.9 (0.0 to 2.9). We found significant nonlinearity in the association between baseline joint pain severity and risk of falls ($p=0.004$) and between baseline joint pain interference and risk of falls ($p<0.001$), c.f. table II. Both baseline pain severity

($p=0.001$) and baseline joint pain interference ($p<0.001$) were associated with an increased risk of falls after adjusting for covariates.

The risk of falls increased non-linearly as pain severity and pain interference increased between scores of 0 and 6 (c.f. figures IIa and IIb). Women with joint pain severity or interference scores of 4 or greater compared to women with scores of 0 had a more than two-fold risk of falling, from approximately 20% to more than 40%. Results for both joint pain measures were similar due to the high correlation between both scores ($\rho =0.81$, $p<0.001$). The risk of falls plateaued for joint pain interference scores higher than 6.

Other Factors Associated with Falls

We found some evidence that white race and higher levels of alcohol consumption were associated with an increased risk of falling and that prior use of chemotherapy was associated with a lower risk of falling. However, these associations did not meet conventional levels of statistical significance (c.f. table II). As a sensitivity analysis, we repeated these analyses excluding patients with a history of chemotherapy. Results were consistent with our main analysis, with higher baseline joint pain severity ($p=0.021$) and joint pain interference scores ($p=0.001$) associated with an increased risk of falls.

Physician Inquiries About Falls

Fewer than half of our participants reported that their PCP (44%) or oncologist (36%) had asked them about falls in the past 12 months (see Figure III). Significantly more participants were asked about falls by their PCPs than by their oncologists ($p<0.001$).

DISCUSSION

Arthralgia is a common and debilitating side effect experienced by women with breast cancer on AI therapy. In our study, we found that more than one in three AI users reported falls and about 10% required medical evaluation and treatment. Both higher baseline joint pain severity and interference increased the likelihood of subsequent falls. Compared to women reporting no joint pain (score of 0), women with baseline joint pain severity or interference scores of 4 or greater had more than twice the risk of falling, with risk increasing from approximately 20% to 40%. Since falls can result in injury and loss of functional independence, our study underscores the importance of managing arthralgia and implementing strategies for fall prevention among aging breast cancer survivors.

Our study adds to a limited existing literature by prospectively investigating the association between arthralgia and falls in a cohort of women with early-stage breast cancer. While AI-induced arthralgia has been widely researched in women with breast cancer,^{4,5} very little attention has been paid to the association between arthralgia and falls. Prospective studies on arthralgia and falls have been conducted among community-dwelling older adults, but not among women with breast cancer.¹¹ Musculoskeletal joint pain and more specifically, joint pain interference and joint pain severity, have been associated with falls among cancer-free community-dwelling older adults.^{11,20,26} Recent systematic reviews of falls in older adults with cancer conclude that studies evaluating falls among women with breast cancer are very limited in number.^{23,24} To our knowledge, the few studies that have investigated falls among

women with breast cancer have been retrospective or have had small sample sizes, and no study has investigated arthralgia as a risk factor for falls.^{27,28}

The fall rate of one in three women we observed appears to be in the range reported by prior studies. A retrospective chart review study reported a 25% fall rate in a five-year period among women with breast cancer on AI therapy,²⁷ which was lower than the fall rate of 35% in a one-year period that we observed prospectively. The discrepancy could be the result of limited inquiries about falls from physicians, which leads to less documentation of falls in medical records. Another small study (N=59) of stage 0-III breast cancer patients reported a fall rate of 58% in a one-year retrospective period.²⁸ Our study is the largest and the only prospective investigation to provide some initial estimate of fall rates for breast cancer survivors on AIs. Participants in our study reported that less than 50% of oncologists and primary care physicians asked them about falls (see figure III). A past study concluded that oncologists do not regularly document the presence of falls in older patients with cancer, with only 10% of fallers having medical record documentation.²⁹ The findings of our study and this past study highlight an important gap in clinicians' awareness of falls in this population. Therefore, more educational efforts are needed for both clinicians and patients.

Screening for fall risk often targets geriatric or hospitalized populations. However, our study highlights that falls frequently occur among non-hospitalized breast cancer survivors younger than 65 (median age 63 years in our sample). Age in fact was not a predictor for falls in our model. This finding raises the question of whether universal screening for falls based on targeted risk factors is needed for this population. Both injurious and non-injurious falls negatively affect patients, increasing their fears of subsequent falls and leading to self-imposed activity limitations.³⁰ As a result, a downward spiral of decreasing mobility and increasing risk for falls can occur. The mean cost of a fall in the US was recently estimated to be \$3,476 to \$10,749 per injurious fall and \$26,483 per fall requiring hospitalization.³¹ Among non-geriatric patients, appropriate medical staff should assess the presence of arthralgias or other factors contributing to an increased risk of falls. Referrals to rehabilitation medicine consultations or physical therapy may be helpful in such high-risk patients in order to discern appropriate, personalized interventions.

The underlying mechanism by which arthralgia contributes to falls is unknown, but likely involves both physiological and psychological processes.^{26,32,33} Recent work in a rat model showed that AIs increase mechanical and chemical nociceptive excitability of sensory neurons, suggesting a possible mechanism for increased joint sensitivity.³⁴ Additionally, AI-induced estrogen deprivation may accelerate cartilage turnover and erosion and cause arthralgia.^{4,35,36} Such erosion may also lead to joint instability and thereby to increased fall risk. Joint pain is associated with decreased physical activity, which may further contribute to muscle weakness, leading to an increased fall risk.^{11,37} Arthralgia may also interfere with the reflex muscle activity needed to prevent a fall, thereby debilitating autonomic protective responses that would otherwise prevent or mitigate a fall.¹⁰ Lastly, arthralgia may distract or interfere with the cognitive activity required to interrupt a fall.¹¹ Future research should evaluate the mechanisms by which arthralgia contributes to falls so more targeted interventions can be developed to mitigate the risk of falls.

Our study has several limitations. First, recall bias is a concern. Participants were asked to report falls in the prior 12 months. Past studies report that recall of falls is specific (91–95%) but not very sensitive (80–89%), suggesting that people are likely to accurately recall not falling, but may not recall falling when they have actually fallen.^{38,39} The low sensitivity of fall recall in past studies suggests that women likely underreported falls in our study, implying that the true fall incidence was higher than reported. Second, our study design established a temporal association and does not permit us to claim a causal relationship. We also lacked the resources to follow up with all participants on patient-reported outcomes. Nevertheless, the characteristics of participants in our follow-up cohort did not appear to differ from those of the original cohort. Further, we did not collect data on bifocal use or eyesight, which may be associated with falls. Nor did we collect a comprehensive drug list to evaluate polypharmacy, which may also be associated with falls. Lastly, our study sample was drawn from an academic cancer center with predominantly white participants and results may not be generalizable to other populations.

Nevertheless, this study has numerous strengths including a prospective design, a large sample size, and the use of validated instruments to assess joint pain and falls. We found that one in three AI users reported falls in a 12-month period and that approximately one in three of those falls (10% in total) resulted in additional medical visits. We found that arthralgia predicted falls among women on AI therapy. Our findings suggest that health care providers should regularly evaluate joint pain severity and assess fall risk among women with breast cancer. Women at increased risk should be educated about fall-prevention strategies. More research is needed to evaluate how to best manage arthralgia among women with breast cancer. This will help not only in preventing falls in this population, but also in improving functional independence and healthy aging.

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REFERENCES

1. Society AC. Breast Cancer Facts & Figures 2015–2016. Atlanta 2015.
2. Howell A Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *The Lancet*. 2005;365(9453):60.
3. Coombes R, Kilburn L, Snowdon C, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *The Lancet*. 2007;369(9561):559–570.
4. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *Journal of Clinical Oncology*. 2007;25(25):3877–3883. [PubMed: 17761973]
5. Sestak I, Cuzick J, Sapunar F, et al. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. *The lancet oncology*. 2008;9(9):866–872. [PubMed: 18703382]
6. Jinks C, Jordan K, Croft P. Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community:(KNEST 3). *Rheumatology*. 2007;46(5):877–881. [PubMed: 17308312]

7. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. *Physical therapy*. 1997;77(8):812–819. [PubMed: 9256869]
8. Masud T, Morris RO. Epidemiology, of falls. *Age and ageing*. 2001;30:3–7.
9. Kitayuguchi J, Kamada M, Okada S, Kamioka H, Mutoh Y. Association between musculoskeletal pain and trips or falls in rural Japanese community-dwelling older adults: A cross-sectional study. *Geriatrics & gerontology international*. 2015;15(1):54–64. [PubMed: 24418209]
10. Leveille SG, Bean J, Bandeen-Roche K, Jones R, Hochberg M, Guralnik JM. Musculoskeletal pain and risk for falls in older disabled women living in the community. *Journal of the American Geriatrics Society*. 2002;50(4):671–678. [PubMed: 11982667]
11. Leveille SG, Jones RN, Kiely DK, et al. Chronic musculoskeletal pain and the occurrence of falls in an older population. *Jama*. 2009;302(20):2214–2221. [PubMed: 19934422]
12. Stone CA, Lawlor PG, Savva GM, Bennett K, Kenny RA. Prospective study of falls and risk factors for falls in adults with advanced cancer. *Journal of Clinical Oncology*. 2012;30(17):2128–2133. [PubMed: 22585687]
13. Walle NV, Kenis C, Heeren P, et al. Fall predictors in older cancer patients: a multicenter prospective study. *BMC geriatrics*. 2014;14(1):135. [PubMed: 25511244]
14. Chen Z, Maricic M, Aragaki A, et al. Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: results from the Women's Health Initiative. *Osteoporosis international*. 2009;20(4):527–536. [PubMed: 18766294]
15. Spoelstra SL, Given BA, Schutte DL, Sikorskii A, You M, Given CW. Do older adults with cancer fall more often? A comparative analysis of falls in those with and without cancer. Paper presented at: *Oncology nursing forum* 2013.
16. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age and ageing*. 2006;35(suppl_2):ii37–ii41. [PubMed: 16926202]
17. Cleeland CS, Ryan K. The Brief Pain Inventory. Available online: https://www.mdanderson.org/education-andresearch/departments-programs-and-labs/departments-and-divisions/symptom-research/symptomassessment-tools/BPI_UserGuide.pdf (accessed on 1 March 2016). 1994.
18. Mao JJ, Xie SX, Farrar JT, et al. A randomised trial of electro-acupuncture for arthralgia related to aromatase inhibitor use. *European Journal of Cancer*. 2014;50(2):267–276. [PubMed: 24210070]
19. Mao JJ, Bruner DW, Stricker C, et al. Feasibility trial of electroacupuncture for aromatase inhibitor —related arthralgia in breast cancer survivors. *Integrative cancer therapies*. 2009;8(2):123–129. [PubMed: 19679620]
20. Blyth FM, Cumming R, Mitchell P, Wang JJ. Pain and falls in older people. *European journal of pain (London, England)*. 2007;11(5):564–571.
21. Stanmore EK, Oldham J, Skelton DA, et al. Fall incidence and outcomes of falls in a prospective study of adults with rheumatoid arthritis. *Arthritis care & research*. 2013;65(5):737–744. [PubMed: 23139011]
22. Lamb SE, Jørstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *Journal of the American Geriatrics Society*. 2005;53(9):1618–1622. [PubMed: 16137297]
23. Sattar S, Alibhai SM, Spoelstra SL, Fazlizada R, Puts MT. Falls in older adults with cancer: a systematic review of prevalence, injurious falls, and impact on cancer treatment. *Supportive care in cancer*. 2016;24(10):4459–4469. [PubMed: 27450557]
24. Wildes TM, Dua P, Fowler SA, et al. Systematic review of falls in older adults with cancer. *Journal of geriatric oncology*. 2015;6(1):70–83. [PubMed: 25454770]
25. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast cancer research and treatment*. 2016;159(2):327–333. [PubMed: 27510185]
26. Patel KV, Phelan EA, Leveille SG, et al. High prevalence of falls, fear of falling, and impaired balance in older adults with pain in the United States: findings from the 2011 National Health and Aging Trends Study. *Journal of the American Geriatrics Society*. 2014;62(10):1844–1852. [PubMed: 25283473]
27. Choksi P, Williams M, Kidwel K, Stella J, Soyster M. Adjuvant Aromatase Inhibitors in Early Breast Cancer May Not Increase the Risk of Falls. *Bone Rep Recommendations*. 2016;2:2.

28. Winters-Stone KM, Torgimson B, Horak F, et al. Identifying factors associated with falls in postmenopausal breast cancer survivors: a multi-disciplinary approach. *Archives of physical medicine and rehabilitation*. 2011;92(4):646–652. [PubMed: 21367394]
29. Guerard EJ, Deal AM, Williams GR, Jolly TA, Nyrop KA, Muss HB. Falls in older adults with cancer: Evaluation by oncology providers. *Journal of oncology practice*. 2015;11(6):470–474. [PubMed: 26175532]
30. Murphy SL, Williams CS, Gill TM. Characteristics associated with fear of falling and activity restriction in community-living older persons. *Journal of the American Geriatrics Society*. 2002;50(3):516–520. [PubMed: 11943049]
31. Davis JC, Robertson MC, Ashe MC, Liu-Ambrose T, Khan KM, Marra CA. International comparison of cost of falls in older adults living in the community: a systematic review. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2010;21(8):1295–1306.
32. Munch T, Harrison SL, Barrett-Connor E, et al. Pain and falls and fractures in community-dwelling older men. *Age and ageing*. 2015:afv125.
33. Stubbs B, Binnekade T, Eggermont L, Sepehry AA, Patchay S, Schofield P. Pain and the risk for falls in community-dwelling older adults: systematic review and meta-analysis. *Archives of physical Medicine and Rehabilitation*. 2014;95(1):175–187.e179. [PubMed: 24036161]
34. Robarge JD, Duarte DB, Shariati B, Wang R, Flockhart DA, Vasko MR. Aromatase inhibitors augment nociceptive behaviors in rats and enhance the excitability of sensory neurons. *Experimental neurology*. 2016;281:53–65. [PubMed: 27072527]
35. Borrie AE, Kim RB. Molecular basis of aromatase inhibitor associated arthralgia: known and potential candidate genes and associated biomarkers. *Expert Opinion on Drug Metabolism & Toxicology*. 2016:1–8.
36. 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 research and treatment*. 2010;120(3):525–538. [PubMed: 20157776]
37. Brown JC, Mao JJ, Stricker C, Hwang WT, Tan KS, Schmitz KH. Aromatase inhibitor associated musculoskeletal symptoms are associated with reduced physical activity among breast cancer survivors. *The breast journal*. 2014;20(1):22–28. [PubMed: 24165356]
38. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *Journal of the American Geriatrics Society*. 2005;53(12):2190–2194. [PubMed: 16398908]
39. Sanders KM, Stuart AL, Scott D, Kotowicz MA, Nicholson GC. Validity of 12-month falls recall in community-dwelling older women participating in a clinical trial. *International journal of endocrinology*. 2015;2015.

Figure I.
Patient Enrollment and Cohort Information

1321 postmenopausal women with stage I-III hormone receptor-positive breast cancer who had been using a third-generation AI (anastrozole, letrozole, exemestane) were enrolled between November 2011 and June 2014. 702 follow-up assessments were conducted between January 2014 and November 2015. Of these, 667 were analyzed for reporting the primary outcome.

Figure IIa.

Association Between Joint Pain Severity at Month 0 and Risk of Any Falls Between 12 and 24 Months (solid line) with 95% Confidence Intervals (dashed lines) and Distribution of Joint Pain Severity Scores^a

Median baseline joint pain severity (IQR) was 2.0 (0.5 to 4.0). Figure portrays significant non-linearity in the association between baseline joint pain severity and risk of falls ($p=0.004$). Women with joint pain severity scores of 4 or greater compared to women with scores of 0 had a more than two-fold risk of falling, from approximately 20% to more than 40%.

Figure IIb.

Association Between Joint Pain Interference at Month 0 and Risk of Any Falls Between 12 and 24 Months (solid line) with 95% Confidence Intervals (dashed lines) and Distribution of Joint Pain Interference Scores^b

Median baseline joint pain interference (IQR) was 0.9 (0.0 to 2.9). Figure portrays significant non-linearity in the association between baseline joint pain interference and risk of falls ($p < 0.0001$). Women with joint pain interference scores of 4 or greater compared to women with scores of 0 had a more than two-fold risk of falling, from approximately 20% to more than 40%.

Figure III.

Physician Inquiries About Falls

Figure compares % of participants who were asked about falls by their oncologist (36%) to % of participants who were asked about falls by their PCP (44%).

Table I.

Patient Characteristics at Baseline

	N=667
Age at baseline	63 (57, 69)
BMI at baseline	26.6(23.0,31.6)
Joint pain severity at baseline	2.0 (0.5, 4.0)
Joint pain interference at baseline	0.9 (0.0, 2.9)
Chemotherapy received prior to baseline	370 (55%)
Radiation received prior to baseline	451 (68%)
Type of breast cancer surgery	
Lumpectomy	362 (54%)
Mastectomy	305 (46%)
Cancer stage at baseline (N=659) ^a	
Stage 0/I	331 (50%)
Stage II	229 (35%)
Stage III	99 (15%)
First aromatase inhibitor type	
Anastrozole	531 (80%)
Exemestane	40 (6.0%)
Letrozole	96 (14%)
Time on aromatase inhibitor at baseline (years)	2.8 (1.4,4.5)

Data are presented as frequency (%) or median (interquartile range).

^aDue to missing data

Table II.

Multivariable Analyses: Joint Pain Severity or Interference and Falls

	Joint Pain Severity			Joint Pain Interference		
	OR	95% CI	p-value	OR	95% CI	p-value
Baseline joint pain	NA ^a	NA ^a	0.001	NA ^a	NA ^a	<0.0001
Age at baseline	1.00	0.98–1.02	0.9	1.00	0.98–1.02	0.9
White race vs. non-white race	1.56	0.94–2.58	0.083	1.63	0.98–2.69	0.058
Neuropathy	1.35	0.93–1.96	0.12	1.27	0.87–1.85	0.2
Alcohol use						
Never	Ref.	-	0.038	Ref.	-	0.053
<1 drink daily	1.68	1.10–2.57		1.71	1.12–2.61	
1–2 drinks daily	1.15	0.64–2.07		1.18	0.65–2.11	
>2 drinks daily	2.88	0.88–9.44		2.27	0.70–7.28	
Use of nerve pain pills at baseline	1.69	0.80–3.57	0.2	1.67	0.79–3.54	0.2
Use of muscle relaxants at baseline	2.29	0.80–6.60	0.12	2.20	0.76–6.39	0.15
Use of narcotics at baseline	1.02	0.48–2.18	0.9	1.04	0.49–2.21	0.9
Chemotherapy received prior to baseline	0.72	0.49–1.05	0.087	0.74	0.50–1.08	0.12
Radiation received prior to baseline	1.04	0.67–1.60	0.9	1.06	0.69–1.65	0.8
Mastectomy vs. lumpectomy	0.97	0.64–1.49	0.9	0.96	0.63–1.48	0.9
First AI						
Anastrozole	Ref.	-	0.3	Ref.	-	0.3
Exemestane	0.61	0.27–1.35		0.59	0.27–1.31	
Letrozole	1.20	0.74–1.95		1.24	0.76–2.02	
Time on AI at baseline, (years)	1.00	0.90–1.11	>0.9	1.01	0.91–1.12	0.8

^aThe estimates for baseline joint pain severity and interference are not reported as these were modeled using non-linear terms.