



# 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 ( $p = 0.001$ ). Women with joint pain severity scores  $\geq 4$  had a more than twofold 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 USA 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 function [6] 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.

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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 6 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) consensus [20] and with past studies [21, 22], 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.

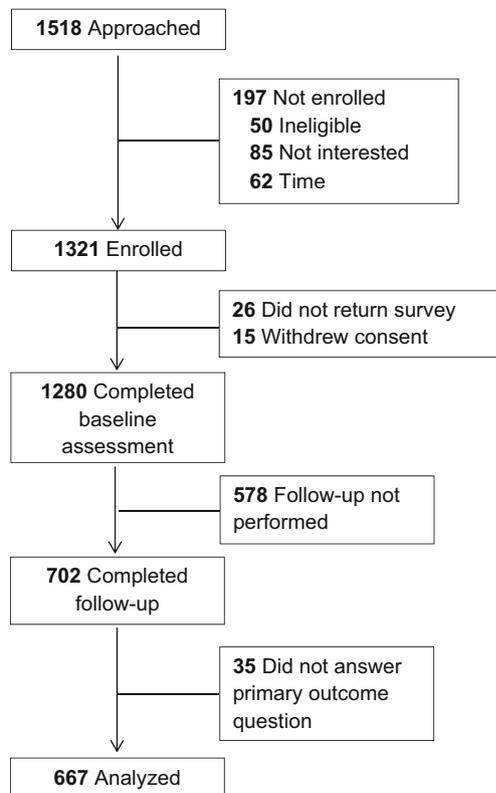
### Statistical analyses

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%) completed baseline questionnaires and 702 completed follow-up questionnaires (c.f. Fig. 1). 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 1). 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.



**Fig. 1** Patient enrollment and cohort information. One thousand three hundred twenty-one 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. Seven hundred two follow-up assessments were conducted between January 2014 and November 2015. Of these, 667 were analyzed for reporting the primary outcome

**Table 1** 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 ( $N=659$ ) <sup>a</sup> |                   |
| 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)

<sup>a</sup> Due to missing data

### 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 non-linearity 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 ( $p<0.001$ ). 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 (c.f. Table 2).

The risk of falls increased non-linearly as pain severity and pain interference increased between scores of 0 and 6 (c.f. Fig. 2a, b). Women with joint pain severity or interference scores of 4 or greater compared to women with scores of 0 had a more than twofold risk of falling, from approximately 20% to more than 40%. Results for both joint pain measures

**Table 2** Multivariable analyses: joint pain severity or interference and falls

|   | Joint pain severity |                 |                | Joint pain interference |                 |                |
|---|---------------------|-----------------|----------------|-------------------------|-----------------|----------------|
|   | OR                  | 95% CI          | <i>p</i> value | OR                      | 95% CI          | <i>p</i> value |
| Baseline joint pain                     | NA <sup>a</sup>     | NA <sup>a</sup> | 0.001          | NA <sup>a</sup>         | NA <sup>a</sup> | < 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            |

<sup>a</sup> The estimates for baseline joint pain severity and interference are not reported as these were modeled using non-linear terms

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 2). 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.

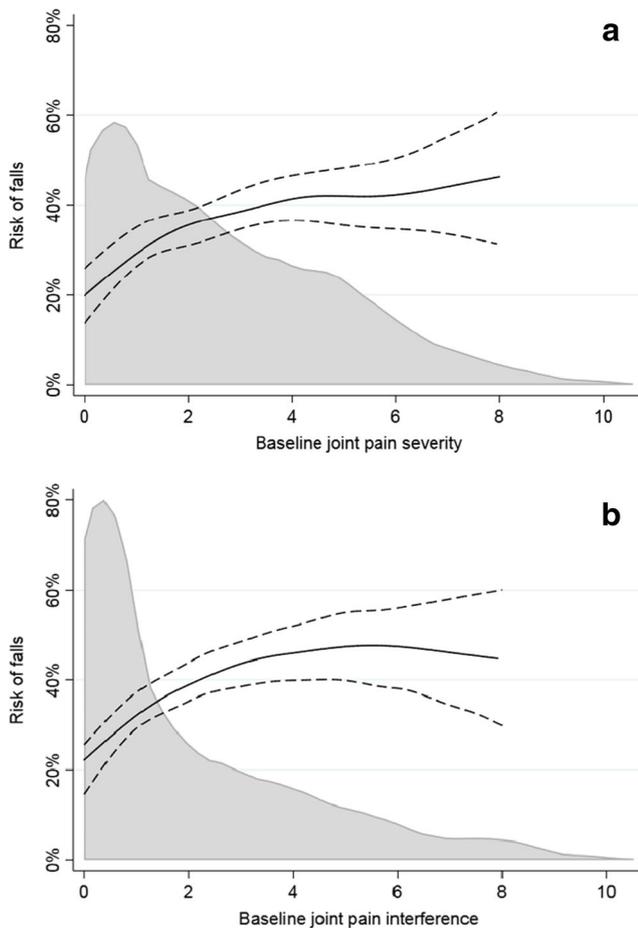
### Physician inquiries about falls

Fewer than half of our participants reported that their PCP (44%) or oncologist (36%) had asked them about falls in the past 12 months (c.f. Fig. 3). Significantly more participants were asked about falls by their PCPs than by their oncologists ( $p < 0.001$ ).

## Discussion

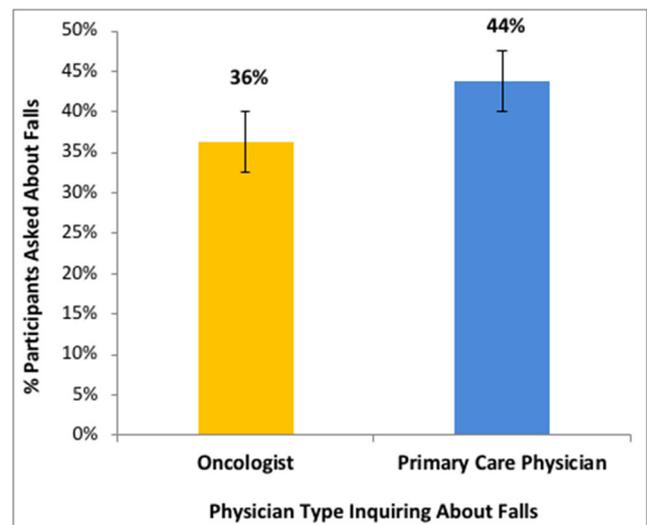
Arthralgia is a common and debilitating side effect experienced by women with breast cancer on AI therapy. In our study, we found that more than one in three AI users reported falls and about 10% required medical evaluation and treatment. Both higher baseline joint pain severity and interference increased 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



**Fig. 2** 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%. 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%

severity have been associated with falls among cancer-free community-dwelling older adults [11, 21, 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].



**Fig. 3** 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%).

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 5-year period among women with breast cancer on AI therapy [27], which was lower than the fall rate of 35% in a 1-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 1-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 (c.f. Fig. 3). 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 USA was recently estimated to be \$3476 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.

**Author contributions** Coby Basal, BA: conceptualization, data curation, investigation, methodology, writing—original draft, and writing—review and editing. Emily Vertosick, MPH: data curation, methodology, formal analysis, visualization, writing—original draft, and writing—review and editing. Theresa A. Gillis, MD: conceptualization, investigation, writing—original draft, and writing—review and editing. Qing Li, MS: conceptualization, data curation, formal analysis, methodology, writing—original draft, and writing—review and editing. Ting Bao, MD, DABMA, MS: conceptualization, investigation, writing—original draft, and writing—review and editing. Andrew Vickers, PhD: conceptualization, data curation, methodology formal analysis, investigation, visualization, writing—original draft, and writing—review and editing. Jun J. Mao, MD, MSCE: conceptualization, data curation, funding acquisition, investigation, methodology, writing—original draft, and writing—review and editing.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Research involving human participants and/or animals** The Institutional Review Board of the University of Pennsylvania approved the study protocol. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Disclaimer** The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

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