The Clinical Journal of Pain Publish Ahead of Print
DOI:10.1097/AJP.0000000000001073

Increased Clinical Pain Locations and Pain Sensitivity in Women after Breast Cancer Surgery: Influence of Aromatase Inhibitor Therapy.

Authors:
Yehui Zhu[1], PhD, MSN
Marco L. Loggia[1], PhD
Robert R. Edwards[2], PhD
Kelsey M. Flowers[2], MA
Dennis W. Muñoz-Vergara[3], DVM, MPH
Ann H. Partridge[4], MD, MPH
Kristin L. Schreiber[2], MD, PhD

Affiliations:
[1] Department of Radiology, Massachusetts General Hospital, A. A. Martinos Center for Biomedical Imaging, Harvard Medical School, Boston, Massachusetts, USA
[2] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3] Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[4] Department of Medical Oncology, Dana-Farber Cancer Institute and Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Corresponding author:
Yehui Zhu, PhD, MSN
Massachusetts General Hospital, A. A. Martinos Center for Biomedical Imaging
149 13th St. Charlestown, MA 02129
yzhu21@mgh.harvard.edu
Phone: 310-795-0892

Acknowledgement:

This study was funded by grants from NIH/NIGMS (K23GM110540 and R35GM128691, PI: Dr. Kristin Schreiber). Yehui Zhu is supported by the NIH/NCI (K00CA234782). The authors declare no conflicts of interests.

Abstract

Objectives

Aromatase inhibitors (AIs), which potently inhibit estrogen biosynthesis, are a standard treatment for hormone sensitive early-stage breast cancer. AIs have been associated with substantial joint pain and muscle stiffness

(aromatase inhibitor-associated musculoskeletal syndrome, AIMSS). However, the link between AIs and number of clinical pain locations and pain sensitivity are less well understood. The aim of this study was to compare longitudinal changes in clinical pain and quantitative pain sensitivity between women who did or did not receive AI therapy.

Methods

Women with early-stage breast cancer were prospectively enrolled and assessed for clinical pain in surgical and non-surgical body areas using the Brief Pain Inventory and Breast Cancer Pain Questionnaire, and for pain sensitivity using quantitative sensory testing preoperatively and at 1 year postoperatively. Pain outcomes between participants who did and did not begin adjuvant AI therapy were compared using Wilcoxon Signed-Ranks and generalized estimating equation linear regression analyses.

Results

Clinical pain and pain sensitivity were comparable between AI(n=49) and no-AI(n=106) groups preoperatively. After adjusting for BMI, AI therapy was associated with a greater increase in number of painful non-surgical body sites (significant time by treatment interaction, p=0.024). Pain location was most frequent in knees (28%), lower back (26%), and ankles/feet (17%). Quantitative sensory testing revealed a significant decrease in pain sensitivity (increased pressure pain threshold) in the no-AI group over time, but not in the AI group.

Conclusion

AI therapy was associated with increased diffuse joint-related pain and greater post-treatment pain sensitivity, potentially implicating central sensitization as a contributing pain mechanism of AIMSS worthy of future investigation.

Keywords:
Breast neoplasms, aromatase inhibitors, pain, pain threshold

Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer mortality among women worldwide.(1) Approximately 80% of post-menopausal women with breast cancer have hormone receptor (estrogen and/or progesterone receptor) positive disease (2) and their overall and disease-free survival rates are significantly improved with 5-10 years of aromatase inhibitor (AI) therapy.(3, 4) While effective, AI is unfortunately associated with aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), which includes symptoms of arthralgia, myalgia, and joint and muscle stiffness.(5-7) The reported incidence of AIMSS is quite variable (4-85%) but represents the most common reason for women to stop AI therapy, with 12-73% of patients discontinuing AI therapy due to AIMSS.(8-11) Additionally, AIMSS is associated with decreased quality of life and physical functioning, with 48-64% of AI users reporting a decline in their ability to carry out their daily activities due to AIMSS.(12, 13)

Effective management of AIMSS is limited by an incomplete understanding of its underlying biological mechanisms, particularly those impacting pain processing. Because AI therapy achieves almost total inhibition of estrogen biosynthesis (97%-99%),(14-19) estrogen suppression is the most obvious and studied mechanistic target.(20) However, the high inter-individual variability of expression of AIMSS symptoms suggests that simple estrogen suppression cannot fully explain it,(21) with recent literature suggesting that other biological mechanisms underlying AIMSS remain understudied.(22,23)

Despite pain being a prominent symptom of AIMSS, there are important gaps in the reporting and characterization of pain in previous studies of patients receiving AI therapy. First, most current studies focus on arthralgia generally (6, 7, 24) rarely including a comprehensive evaluation of pain in a variety of surgical and non-surgical areas. Second, pain assessments of patients with AI therapy have typically consisted of a single patient-report of pain (0-10), and not included more extensive, specific, and localizing pain self-report tools, nor more objective measures of pain sensitivity using quantitative sensory testing. Third, a comparison group undergoing other treatments for BC is rarely included. Finally, the majority of studies have been cross-sectional, and therefore do not include baseline pain assessment before AI initiation. The current study addresses these gaps, as a longitudinal analysis of women with early-stage breast cancer undergoing breast cancer surgery. We

aimed to compare 1) clinical pain in a variety of surgical and non-surgical body areas, and 2) general pressure pain sensitivity between women who did or did not receive AI therapy, measured over time in the first year after breast cancer surgery.

Materials and Methods

Participants enrolled in a completed, prospective, observational longitudinal cohort study that evaluated a wide range of biopsychosocial factors using validated, brief measures preoperatively and subsequently throughout the first year following surgery. Patients from the IRB approved parent study were recruited from the preoperative anesthesia clinic at Brigham and Women's Hospital in Boston, Massachusetts from 9/2014 – 3/2017. Eligibility criteria included women ages 18-85 scheduled to undergo breast surgery, English proficiency, and no cognitive impairments interfering with questionnaire completion. The design and inclusion/exclusion criteria have been detailed in our previous publications of this cohort.(25, 26) Participants who completed follow-up pain assessment at 12 months after surgery and did not receive any other type of endocrine therapy (e.g., tamoxifen, etc.). Participants who received AI therapy (i.e., anastrozole, letrozole, exemestane) were compared to those not receiving AI therapy in this secondary analysis.

After providing informed consent, participants were assessed for clinical pain, pain sensitivity and other psychosocial symptoms preoperatively and 12 months after breast surgery. Surgery-specific and general pain were measured using an extended version of the Breast Cancer Pain Questionnaire (BCPQ) and Brief Pain Inventory (BPI), respectively. A Pain Severity Index (PSI) score was calculated using: PSI=Σ[Pain score at each site (0-10)] x [frequency (1-5)].(27) The BCPQ assessed the impact of surgical pain on physical activities relevant to the body area (Physical Impact of Pain). The BCPQ also inquired about the presence of pain at other non-surgical locations (including head, neck, shoulders, lower back, hips, knees, ankles/feet, stomach, lower abdomen, and others) and the overall pain severity (0-10). BPI Mean Severity (range: 0-10) was calculated by averaging the self-reported current, worst, least, and average pain in the preceding week, and BPI Interference (range: 0-100) was calculated by averaging the items that examined the extent pain interfered with general activities. Both BCPQ and BPI have been well-validated and widely used in breast cancer population.(26, 28-30)

Psychosocial symptom assessments were made using the NIH PROMIS short forms for depressive symptoms, anxiety, and sleep disturbance (31) and the Positive Affect Negative Affect Scale (PANAS).(32) Pressure pain threshold and tolerance were examined using a digital pressure algometer (Wagner RDX, Greenwich, CT, USA) with a flat round transducer, probe area 0.785 cm^2, as in previous studies, (26, 29) bilaterally over the trapezius muscle at the upper back approximately 2-3 cm above the scapular spine, midway between C7 prominence and humeral head (truncal site).

Data analysis was conducted using IBM© SPSS© Statistics version 27.0 (IBM© Corp., Armonk, NY). Descriptive statistics are reported as means and standard deviations for continuous variables and counts and percentages for categorical variables. Chi-square tests were used for comparisons of categorical variables. The Shapiro-Wilk test was used to test continuous variables for normality. T-tests and Mann-Whitney U tests were conducted to compare continuous data with a normal or non-normal distribution, respectively. For participants with complete pain sensitivity data, Wilcoxon Signed-Ranks test was performed to compare changes in pressure pain threshold and tolerance for AI and no-AI groups. In order to examine the effect of administration of AI therapy, time, and their interaction, on pain outcomes, including numbers of musculoskeletal-related locations with pain and pain severity at non-surgical location, linear regression analysis using Generalized Estimating Equations (GEE) with autoregressive correlation structure was performed. Since age, body mass index (BMI), and surgery type were not comparable between AI and no-AI groups, they were included as covariates in the regression model. Covariates with a significant relation to the outcome were included in the final parsimonious model. A p-value < 0.05 was considered statistically significant.

Results

Study Participants and Baseline Characteristics

In total, 283 participants initially agreed to participate in the longitudinal cohort study, with 259 providing any baseline psychosocial and pain assessment. Of these participants, 155 patients had complete psychosocial, pain and psychophysical (QST) data for this analysis, with 49 excluded from analysis because endocrine therapy status was not known, and 55 were missing other psychosocial/pain assessment/QST data.

For the 155 patients included in the final analysis, two groups of patients were identified: 1) AI group (n=49) in which women received AI therapy during their first year after surgery (i.e., anastrozole, letrozole, exemestane) and 2) no-AI group (n=106): women did not receive any type of endocrine therapy (including tamoxifen and AI) during this time period. Participants were predominantly Caucasian (87.7%), had mean age of 57 (SD=12) years, with 54% undergoing lumpectomy (breast conserving surgery) and the remainder total mastectomy, and 56% receiving radiation therapy, and 30% chemotherapy. The average duration of AI therapy for those receiving it was 296 days at the time of assessment, with a range of 93-440 days. Preoperative demographic and treatment-related characteristics for AI and no-AI groups are detailed in Table 1. As expected, since AI therapy is the first-line treatment for postmenopausal women with hormone-sensitive breast cancer, women in the AI group were older, had higher BMI, and were more likely to receive breast conserving surgery (lumpectomy) rather than total mastectomy with or without reconstruction. No other demographic and treatment-related differences were observed between AI and no-AI groups. Similarly, no differences in baseline pain or psychosocial characteristics were observed between AI and no-AI groups (Table 2).

Pain at surgical area and general pain at 12 months after surgery

At 12 months post-surgery, surgical site pain was comparable between AI and no-AI groups, as measured using the surgery-specific pain questionnaire (BCPQ pain severity index), or the brief pain inventory (BPI severity), which were centered around surgical area pain. Similarly, no difference in surgical area pain-related functional impact (BCPQ physical impact of pain) and general pain interference (BPI interference) was observed between groups. (Table 2).

Pain at non-surgical areas at 12 months after surgery

In contrast to surgical area pain, we observed differences in pain reported at other body sites between the AI and no-AI groups, including change in both the incidence of any non-surgical pain and number of pain locations before surgery and 12 months later, after the onset of AI therapy (Figure 1, see supplemental figure for individualized pre-post change graphs, Supplemental Digital Content 1, http://links.lww.com/CJP/A893).

Specifically, the proportion of participants reporting pain at ≥1 non-surgical site increased from 53% (preoperative) to 63% (12 months postoperative) in the AI group, whereas the proportion slightly decreased in the no-AI group (43% preoperative vs. 39% 12 months postoperative). At 12 months postoperative, those who received AI therapy reported a significantly greater number of nonsurgical body sites with pain (p=0.014), with a trend towards higher overall pain severity (p=0.084) (Table 2). In order to assess the relationship of AI to other body site pain over time, while taking into account relevant covariates (i.e., age, BMI, and surgery type), we employed GEE linear regression. We observed a significant treatment by time interaction, such that there was an increase in the number of non-surgical pain sites between preoperative and 12 months postoperative for the AI group (treatment by time interaction, β=0.420, p=0.024), but not in the no-AI group. A similar, but nonsignificant, trend was observed when pain severity at non-surgical areas was investigated as the outcome (treatment by time interaction, β=0.819, p=0.088) (Table 3).

In order to further characterize this reported increase in number of clinical pain sites, we investigated changes in reported pain in specific individual pain locations. At 12 months after surgery, the most frequently reported pain locations in patients receiving AI therapy were knees (28%), lower back (26%), neck/shoulders (20%), hips (17%), and ankles/feet (17%). Figure 2 depicts changes in reported pain after AI-treatment at nonsurgical body areas, with red indicating an increase in pain occurrence at a particular body area and blue indicating a decrease in pain occurrence, compared to baseline. Among patients who received AI treatment, the most common sites where an increase in those reporting pain were hips (+15%), knees (+11%), lower back (+9%), neck/shoulders (+9%), and ankles/feet (+5%). Compared to the no-AI group, those receiving AI reported pain at knees (p=0.042), ankles/feet (p=0.023), and lower back (p=0.056, trend) more frequently (Table 2).

Pressure pain threshold and tolerance

Pressure pain threshold and tolerance, measured using a handheld algometer over the trapezius, were performed at baseline and 1-year follow-up in a subset of patients. Fourteen (out of 49) participants in the AI group and 51 (out of 106) participants completed both baseline and 1-year follow-up assessment of pain

sensitivity and were included in analysis of pain sensitivity. Paired samples Wilcoxon Signed-Ranks test indicated that the no-AI group became less sensitive to pain (significant increase in pain threshold, p=0.022) at 12 months after surgery, while the AI group remained with a similar pressure pain threshold (Figure 3). No significant changes in pressure pain tolerance at 12 months after surgery were observed for either group.

Discussion

Adjuvant hormonal therapy for breast cancer substantially reduces morbidity and mortality from breast cancer. However, in recent years adherence to hormonal therapy has been recognized as a substantial barrier to optimizing the effectiveness of these life-saving medications.(33, 34) Aromatase inhibitors are one of the most potent agents approved for the treatment of early-stage breast cancer. However, burdensome side effects, especially musculoskeletal pain, can lead to AI discontinuation in a large proportion of women.(35) Understanding the mechanisms of this toxicity is critical to the development of strategies to manage AIMSS and allow patients to benefit from the suppressant effects of these drugs on BC.

This analysis expands characterization of pain quality and progression in AIMSS by employing comprehensively assessed pain outcomes (clinical pain at surgical site and whole body, and objective pressure pain sensitivity) between breast cancer patients who did or did not receive AI therapy, both before and after starting this therapy. While AI treatment was not associated with greater surgical site pain, our findings suggest that AI may significantly increase pain in non-surgical areas, particularly joints (i.e., knees, ankles, lower back), consistent with previous descriptions of AIMSS involving joint pain and muscle stiffness.(10) In addition, we observed a relatively lower pressure pain threshold at muscle sites (trapezius) at 1 year after surgery among the AI group compared to the no-AI group, who became less sensitive compared to their preoperative timepoint.

It is notable, but not completely unexpected, that AI therapy did not impact surgical area pain (breast, axilla, upper arm, chest). Neither surgical pain scores as assessed using a breast surgery-specific questionnaire nor the general BPI assessment tool indicated a difference between AI and no-AI groups. Previous investigations suggest that a subgroup of women is at risk for of Persistent Post-Mastectomy Pain (PPMP) at the surgical site (20-65%).(28, 29, 36-39). While a variety of demographic, psychophysiological, and psychosocial

risk factors for PPMP have been identified, endocrine therapy has rarely been found to increase the risk of PPMP (26, 29, 36, 37, 40-42), consistent with our findings that AI was not associated with greater surgical site pain.

In contrast, nonsurgical site pain did increase. The AI group reported an increased number of locations with pain and a trend toward increased pain severity at those non-surgical areas. This finding is consistent with multiple previous reports of musculoskeletal pain (arthralgia and myalgia) during AI therapy in both clinical trials(43-48) and clinical research.(9, 10, 12, 24, 49-52) The specific locations of reported increased pain included the knees and ankles/feet, with a nonsignificant trend towards increased lower back and hip pain. In contrast, headache and stomachache were similar in occurrence between groups, implicating joint sites as particularly vulnerable. AIMSS symptoms have previously been reported at many of these locations (wrists/hands, ankles/feet, elbows, and knees).(10) In addition, the increasing incidence of arthritis and other musculoskeletal pain after menopause in women(53, 54) may make the second hit of AI therapy particularly unwelcome. Indeed, joint-related comorbidity has also been found to be a risk factor for the development of joint pain during AI therapy. (52) Thus, it seems clear that AI therapy and chronic musculoskeletal complaints may mutually exacerbate the pain observed with either. This suggests the importance of prospective screening for pain at musculoskeletal locations, and aggressive and early management of musculoskeletal complaints in postmenopausal women who would benefit from AI therapy. There may also be utility in incorporating detailed musculoskeletal-specific pain evaluation tools such as the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC],(55) and Disabilities of the Arm, Shoulder, and Hand [DASH] (56) in both clinical investigations and clinical care of patients undergoing AI therapy for breast cancer.

Our quantitative assessment of pain sensitivity revealed that AI-treated patients also maintained a relatively higher pain sensitivity at non-joint sites (e.g., trapezius muscle), which together with increased incidence of joint pain, may indicate increased general pain sensitivity. While more extensive quantitative sensory testing (QST) has been reported in chemotherapy-induced peripheral neuropathy (CIPN),(57) only one previous study assessed the effect of AI on pain sensitivity using QST in the first 6 months after AI therapy, and found no change in pain sensitivity (pressure pain threshold) after AI therapy.(58) This is in fact consistent with

our findings, as we also did not observe a statistically significant increase in sensitivity in the AI group compared to their baseline. However, our study had the advantage of a no-AI comparison group, which allowed us to observe that the no-AI group became less sensitive (increased pressure pain threshold) compared to their preoperative baseline value, potentially indicating that the maintenance of pain sensitivity in the AI group is not normal. Future studies employing more comprehensive objective measures of pain (e.g., a full battery of quantitative sensory testing), including the relative degree of neuropathic features, or changes in descending modulation, will further enhance our understanding of changes in pain processing that occur during AIMSS. Prior investigations of patients with chronic low back pain and chronic knee/leg pain have revealed amplified central-sensitization-associated processes such as temporal summation of pain and decrements in endogenous pain-inhibitory processes such as conditioned pain modulation (CPM).(59-62) It is interesting to note that we observed AI-associated increases in pain at some of these typical sites of chronic pain (e.g., back, knees) which have been linked to more central sensitivity in those studies. Future work in this area may benefit from evaluating potential AI effects on specific pain-modulatory processes (e.g., temporal summation, CPM) that appear to be highly relevant to chronic pain complaints.

The finding of increased number of clinical non-surgical pain sites in AI-treated patients may suggest a potential role for central sensitization in the development and maintenance of musculoskeletal pain during AI therapy. Similarly, the fact that AI was associated with a maintenance of pain sensitivity, while the no-AI group had an increase of pressure pain threshold), may suggest greater central sensitization. Potential explanations for the decline in sensitivity seen in the no-AI group include that the baseline measurement in the preoperative period, coming soon after breast cancer diagnosis, may represent a timepoint of particularly heightened anxiety, potentially accounting for a relatively higher pain sensitivity, which is not the case at the 12-month follow-up, although previous studies of test-retest of QST (not necessarily done in the pre- vs post- surgical context) do not necessarily show this pattern (63), although few previous studies are available to answer this question. Further investigation of central sensitization could uncover potential biological mechanisms underlying AIMSS for breast cancer survivors. Some preclinical studies implicate neuroinflammation as a potential mechanism, as estrogen inhibits proinflammatory cytokine and chemokine release by glial cells (e.g., microglia,

astrocytes).(64-66) It is plausible that AI therapy, by inducing substantial depletion in estrogen levels, may deprive these patients of the protective inhibitory effect of estrogen on glia-mediated neuroinflammatory responses, which have also been shown in neuroimaging in multiple chronic pain disorders in humans.(67, 68) Future research is needed to investigate the degree and importance of neuroinflammation in AIMSS.

We observed that a higher body mass index (BMI) was associated with greater pain severity and number of pain locations (Table 3). This finding is consistent with a large volume of evidence indicating the concurrence of elevated BMI (obesity) and multiple musculoskeletal pain syndromes (e.g., back pain, knee pain, etc.), in particular for pain at the lower extremity.(69-72) This finding has multiple implications for clinical practice and research. Firstly, it suggests that BMI may serve as a risk factor of increased salience to women undergoing treatment with AI for breast cancer, and practically should be included as a covariate in future studies of AIMSS. Moreover, patients with higher BMI may also benefit from more intensive weight loss programs, in order to mitigate increases in musculoskeletal pain during AI therapy.(72) In addition, biological mechanisms shared by obesity and chronic musculoskeletal pain (e.g., chronic proinflammatory state) (73-75) should be examined in breast cancer patients with AIMSS. In addition, psychosocial factors, which have also been closely associated with both obesity and pain (e.g., depression, sleep disturbance) should be assessed and considered in future studies of AIMSS.

A major strength of our study is the prospective design with comprehensive longitudinal assessment of the pain experienced in both surgical vs. non-surgical body areas, which allowed an examination of the impact of AI therapy on pain in different body areas. Furthermore, parallel assessment of the comparison cohort, who were also treated with surgical management of breast cancer, allowed us to examine the impact of AI therapy in a more controlled way, but also pragmatically within the context of influences of potentially confounding effect of breast cancer diagnosis and other cancer treatments (e.g., surgery, radiation, chemotherapy). Nevertheless, there are important limitations to consider. First, we could not conduct post hoc group comparisons among different types of AIs due to the limited sample size for each individual AI agent. Second, as a secondary analysis of a dataset powered to detect risk factors of PPMP, our analysis may be underpowered to detect differences between groups receiving vs. not receiving AI therapy. Indeed, we observed only borderline

significant differences in some body areas, suggesting that a larger sample is needed to further investigate and confirm these findings. Third, timepoints of assessment were anchored around the index surgical procedure and only extended to approximately 6 months after the initiation of AI therapy. A more definitive assessment of longer-term AIMSS-related pain is not addressed by these data. A more comprehensive assessment of longitudinal pain sensitivity, anchored around the onset of AI, including a more comprehensive battery of quantitative sensory testing, will allow for more definitive pain phenotyping of patients undergoing AI therapy.

In summary, we found that AI therapy was associated with increased number of clinical pain sites, as well as a relative (to the non-AI group) increased mechanical sensitivity on quantitative sensory testing, potentially implicating a more centralized pain sensitization with AI therapy. Additional studies are needed to better understand the role of central sensitization in the development and maintenance of musculoskeletal pain during adjuvant AI therapy for breast cancer. Larger studies including diverse samples of women will elucidate important predictors associated with a higher risk of severe AI-related pain, potentially informing more personalized treatment among breast cancer patients. These studies may lead to novel interventions designed to prevent or better manage pain during AI therapy and help increase the clinical effectiveness of these life-saving medications.

Disclosures and Acknowledgments

This study was funded by grants from NIH/NIGMS (K23GM110540 and R35GM128691, PI: Dr. Kristin Schreiber). Yehui Zhu is supported by the NIH/NCI (K00CA234782). The authors declare no conflicts of interests.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: Cancer J Clin 2015;65:87-108.
2. Osborne CK. Steroid hormone receptors in breast cancer management. Breast Cancer Res Treat 1998;51:227-238.
3. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016;375:209-219.
4. Romera JL, Hernández TdJP, Fernández IP, et al. Update on adjuvant hormonal treatment of early breast cancer. Adv Ther 2011;28:1-18.
5. Lombard JM, Zdenkowski N, Wells K, et al. Aromatase inhibitor induced musculoskeletal syndrome: a significant problem with limited treatment options. Support Care Cancer 2016;24:2139-2146.
6. Zhu Y, Cohen SM, Rosenzweig MQ, et al. Symptom map of endocrine therapy for breast cancer: a scoping review. Cancer Nurs 2019;42:E19.
7. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. The Breast 2007;16:223-234.
8. Chim K, Xie SX, Stricker CT, et al. Joint pain severity predicts premature discontinuation of aromatase inhibitors in breast cancer survivors. BMC Cancer 2013;13:1-7.
9. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 2007;25:3877-3883.
10. Mao JJ, Stricker C, Bruner D, et al. Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. Cancer 2009;115:3631-3639.
11. Presant CA, Bosserman L, Young T, et al. Aromatase inhibitor–associated arthralgia and/or bone pain: frequency and characterization in non–clinical trial patients. Clin Breast Cancer 2007;7:775-778.
12. Egawa C, Hirokaga K, Takao S, et al. Risk factors for joint symptoms in postmenopausal Japanese breast cancer patients treated with anastrozole: a prospective multicenter cohort study of patient-reported outcomes. Int J Clin Oncol 2016;21:262-269.
13. Waltman NL, Ott CD, Twiss JJ, et al. Vitamin D insufficiency and musculoskeletal symptoms in breast cancer survivors on aromatase inhibitor therapy. Cancer Nurs 2009;32:143.

14. Fabian C. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. Int J Clin Pract 2007;61:2051-2063.
15. Brueggemeier RW, Hackett JC, Diaz-Cruz ES. Aromatase inhibitors in the treatment of breast cancer. Endocr Rev 2005;26:331-345.
16. Brueggemeier RW. Overview of the pharmacology of the aromatase inactivator exemestane. Breast Cancer Res Treat 2002;74:177-185.
17. LP AP. ARIMIDEX® (Anastrozole Tablets) Full Prescribing Information. In: Wilmington, DE: 2005.
18. Corporation NP. FEMARA® (Letrozole Tablets) Full Prescribing Information. In: East Hanover, NJ: 2005.
19. Pharmacia & Upjohn Co. DoPI. Aromasin® (Exemestane Tablets) Full Prescribing Information. In: New York, NY: 2005.
20. Wang J, Lu K, Song Y, et al. Indications of clinical and genetic predictors for aromatase inhibitors related musculoskeletal adverse events in Chinese Han women with breast cancer. PloS One 2013;8:e68798.
21. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 2012;30:936.
22. Zhu Y, Koleck TA, Bender CM, et al. Genetic Underpinnings of Musculoskeletal Pain During Treatment With Aromatase Inhibitors for Breast Cancer: A Biological Pathway Analysis. Bio Res Nurs 2020;22:263-276.
23. Borrie AE, Rose RV, Choi Y-H, et al. Letrozole concentration is associated with CYP2A6 variation but not with arthralgia in patients with breast cancer. Breast Cancer Res Treat 2018;172:371-379.
24. Menas P, Merkel D, Hui W, et al. Incidence and management of arthralgias in breast cancer patients treated with aromatase inhibitors in an outpatient oncology clinic. J Oncol Pharm Pract 2012;18:387-393.
25. Spivey TL, Gutowski ED, Zinboonyahgoon N, et al. Chronic pain after breast surgery: a prospective, observational study. Ann Surg Oncol 2018;25:2917-2924.

26. Schreiber KL, Zinboonyahgoon N, Xu X, et al. Preoperative Psychosocial and Psychophysical Phenotypes as Predictors of Acute Pain Outcomes After Breast Surgery. J Pain 2019;20:540-556.
27. Schreiber KL, Zinboonyahgoon N, Flowers KM, et al. Prediction of Persistent Pain Severity and Impact 12 Months After Breast Surgery Using Comprehensive Preoperative Assessment of Biopsychosocial Pain Modulators. Ann Surg Oncol 2021:1-24.
28. Belfer I, Schreiber KL, Shaffer JR, et al. Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain 2013;14:1185-95.
29. Schreiber KL, Martel MO, Shnol H, et al. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain 2013;154:660-8.
30. Cleeland C, Ryan K. Pain assessment: global use of the Brief Pain Inventory. Annals, academy of medicine, Singapore 1994.
31. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol 2010;63:1179-1194.
32. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063.
33. Partridge, A. H., Wang, P. S., Winer, E. P. et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003;21(4), 602-606.
34. Partridge, A. H., LaFountain, A., Mayer, E., et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 2008; 26(4), 556-562.
35. Hershman, D. L., Kushi, L. H., Shao, T., Buono, D., et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010; 28(27), 4120.
36. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618-25.

37. Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain 2011;12:725-46.

38. Gartner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009;302:1985-92.

39. Meretoja TJ, Leidenius MHK, Tasmuth T, et al. Pain at 12 months after surgery for breast cancer. JAMA 2014;311:90-92.

40. Miaskowski C, Paul SM, Cooper B, et al. Identification of patient subgroups and risk factors for persistent arm/shoulder pain following breast cancer surgery. Eur J Oncol Nurs 2014;18:242-53.

41. Schreiber KL, Kehlet H, Belfer I, et al. Predicting, preventing and managing persistent pain after breast cancer surgery: the importance of psychosocial factors. Pain Manag 2014;4:445-459.

42. Langford DJ, Schmidt B, Levine JD, et al. Preoperative breast pain predicts persistent breast pain and disability after breast cancer surgery. J Pain Symptom Manage. 2015;49(6):981-994.

43. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17:vii10-vii14.

44. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 2007;25:486-492.

45. Coombes RC, 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. Lancet 2007;369:559-570.

46. Howell A, Cuzick J, Baum M, 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;365:60-62.

47. Jakesz R, Jonat W, Gnant M, 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;366:455-462.
48. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99:1845-1853.
49. Shi Q, Giordano SH, Lu H, et al. Anastrozole-associated joint pain and other symptoms in patients with breast cancer. J Pain 2013;14:290-296.
50. Laroche F, Coste J, Medkour T, et al. Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase inhibitor treatments in women with breast cancer: a prospective multicenter cohort study. J Pain 2014;15:293-303.
51. Dizdar O, Özçakar L, Malas FÜ, et al. Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor–related arthralgia. J Clin Oncol 2009;27:4955-4960.
52. Castel LD, Hartmann KE, Mayer IA, et al. Time course of arthralgia among women initiating aromatase inhibitor therapy and a postmenopausal comparison group in a prospective cohort. Cancer 2013;119:2375-2382.
53. Watt FE. Musculoskeletal pain and menopause. Post Reprod Health 2018;24:34-43.
54. Dugan SA, Powell LH, Kravitz HM, et al. Musculoskeletal pain and menopausal status. Clin J Pain 2006;22:325-331.
55. Bellamy, N., Buchanan, W. W., Goldsmith, et al. 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.
56. Beaton, D. E., Katz, J. N., Fossel, A. H., et al. Measuring the whole or the parts?: validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther 2001; 14(2), 128-142.

57. Martland ME, Rashidi AS, Bennett MI, et al. The use of quantitative sensory testing in cancer pain assessment: A systematic review. Eur J Pain 2020;24:669-684.

58. Henry NL, Conlon A, Kidwell KM, et al. Effect of Estrogen Depletion on Pain Sensitivity in Aromatase Inhibitor–Treated Women With Early-Stage Breast Cancer. J Pain 2014;15:468-475.

59. McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. Pain 2020;161:464-475.

60. Carlesso LC, Neogi T. Identifying pain susceptibility phenotypes in knee osteoarthritis. Clin Exp Rheumatol 2019;37:96.

61. Vaegter HB, Palsson TS, Graven-Nielsen T. Facilitated pronociceptive pain mechanisms in radiating back pain compared with localized back pain. J Pain 2017;18:973-983.

62. Edwards RR, Dolman AJ, Martel MO, et al. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. BMC Musculoskelet Disord 2016;17:1-9.

63. Martel, M. O., Wasan, A. D., & Edwards, R. R. (2013). Sex differences in the stability of conditioned pain modulation (CPM) among patients with chronic pain. Pain Medicine, 14(11), 1757-1768.

64. Ji R-R, Nackley A, Huh Y, et al. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 2018;129:343-366.

65. Vegeto E, Benedusi V, Maggi A. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Front Neuroendocrinol 2008;29:507-519.

66. Arevalo M-A, Santos-Galindo M, Bellini M-J, et al. Actions of estrogens on glial cells: implications for neuroprotection. Biochim Biophys Acta Gen Subj 2010;1800:1106-1112.

67. Loggia ML, Chonde DB, Akeju O, et al. Evidence for brain glial activation in chronic pain patients. Brain 2015;138:604-615.

68. Albrecht DS, Forsberg A, Sandström A, et al. Brain glial activation in fibromyalgia–A multi-site positron emission tomography investigation. Brain Behav Immun 2019;75:72-83.

69. Seaman, D. R. (2013). Body mass index and musculoskeletal pain: is there a connection?. Chiropr Man Ther, 21(1), 1-9.

70. Viester, L., Verhagen, E. A., Hengel, K. M. O., et al. The relation between body mass index and musculoskeletal symptoms in the working population. BMC Musculoskelet Disorders 2013; 14(1), 1-9.

71. Mendonça, C. R., & Noll, M. High prevalence of musculoskeletal pain in individuals with severe obesity: sites, intensity, and associated factors. Korean J Pain 2020; 33(3), 245.

72. Okifuji, A., & Hare, B. D. (2015). The association between chronic pain and obesity. J Pain Res, 8, 399.

73. Bays, H. E., Gonzalez-Campoy, J. M., Henry, et al. Is adiposopathy (sick fat) an endocrine disease?. Int J Clin Pract 2008; 62(10), 1474-1483.

74. de Heredia, F. P., Gómez-Martínez, S., & Marcos, A. Obesity, Inflammation and the Immune system. Proc Nutr Soc 2012; 71(2), 332-338.

75. Shoelson, S. E., Herrero, L., & Naaz, A. Obesity, inflammation, and insulin resistance. Gastroenterology 2007; 132(6), 2169-2180.

Figure 1: Number of Non-surgical Areas with Pain. Patients reported locations with pain preoperatively and 12 months after surgery, including non-surgical locations (head, neck, shoulders, lower back, hips, knees, ankles/feet, stomach, lower abdomen, and others) as part of the Breast Cancer Pain Questionnaire. Bar charts show the proportion of AI and no-AI groups reporting different total number of pain locations at baseline and 12 months after surgery.

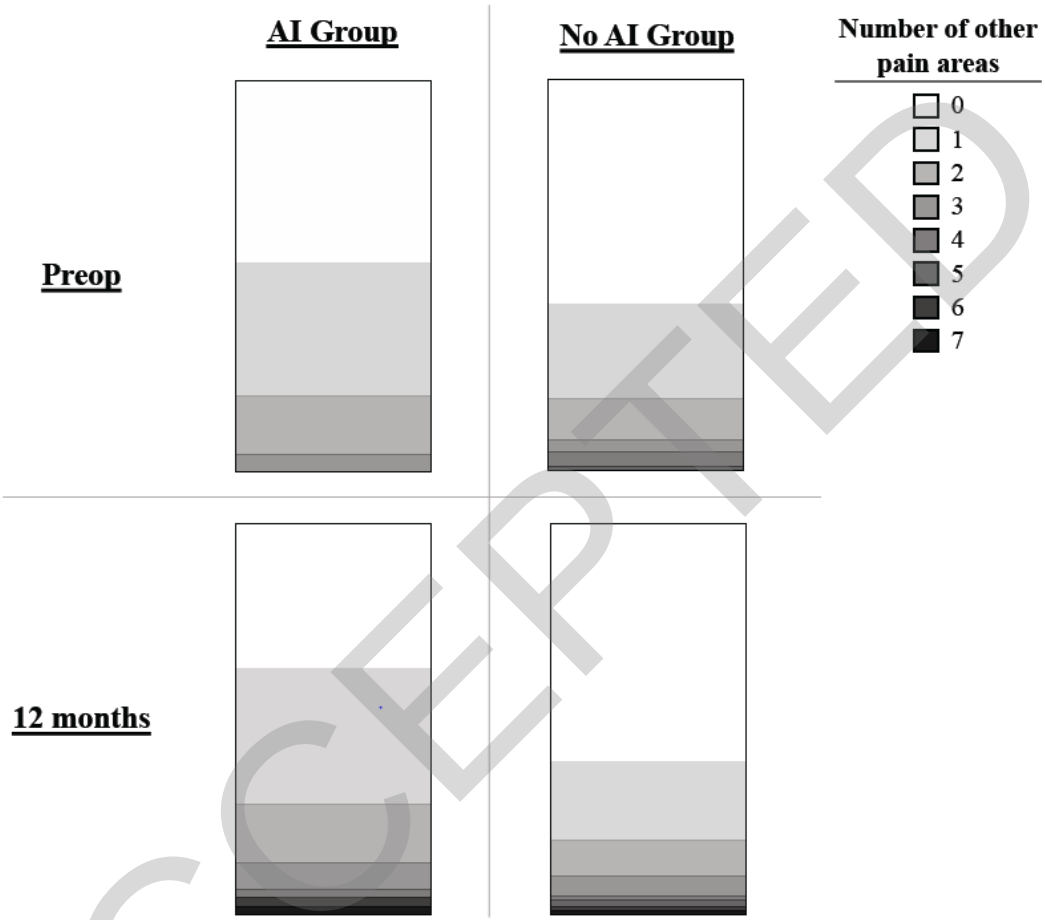
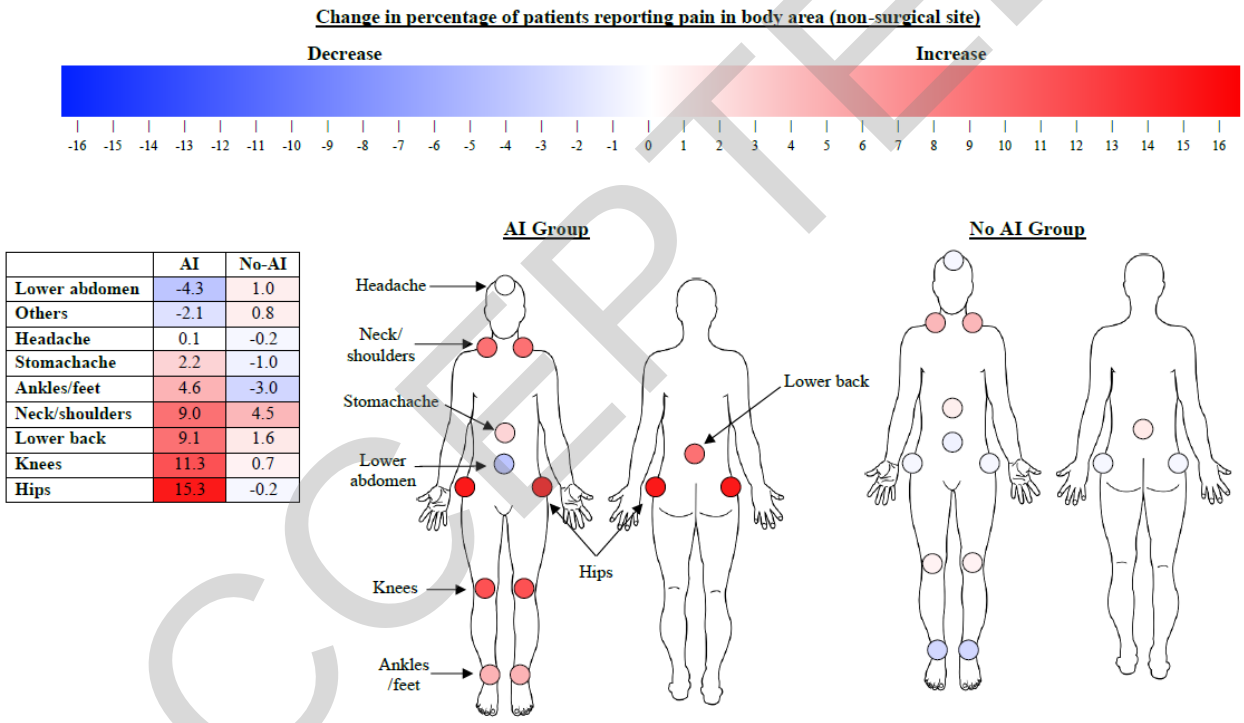
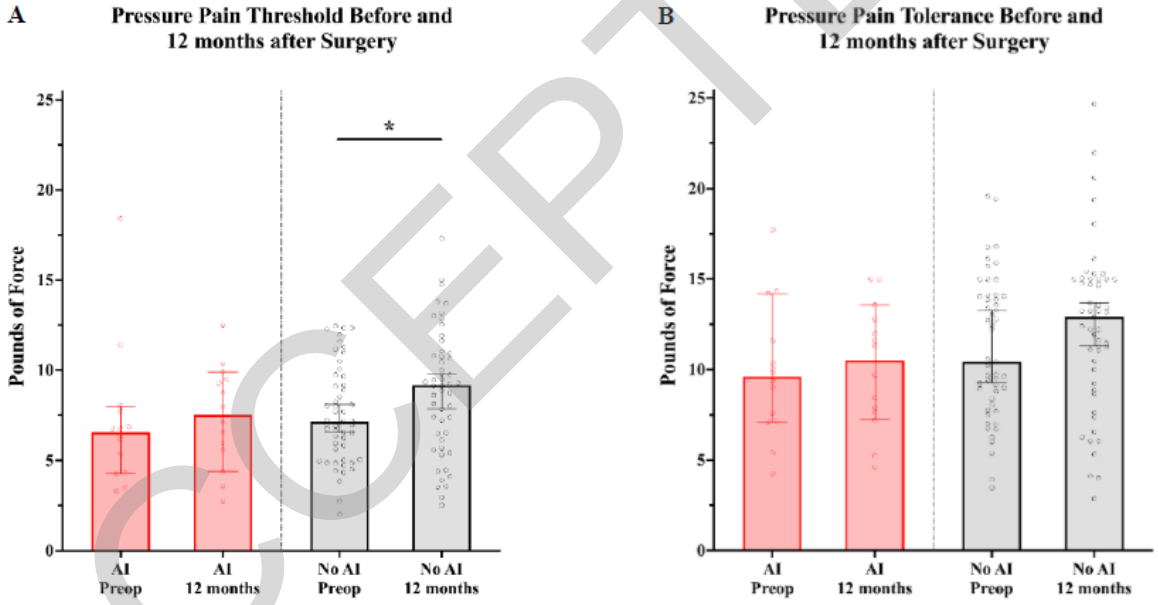


Figure 2: Body Maps of Increase and Decrease in Reported Pain Locations in Patients Taking vs Not Taking Aromatase Inhibitors During the First Year after Surgery. Patients reported locations with pain preoperatively and 12 months after surgery, including non-surgical locations (head, neck, shoulders, lower back, hips, knees, ankles/feet, stomach, lower abdomen, and others) as part of the Breast Cancer Pain Questionnaire. The occurrence of pain at each location is listed in Table 2 and the changes (post-surgery minus pre-surgery) in percentage at each location are calculated and displayed in Figure 2. Red indicates increase and blue indicates decrease in reported pain among the group.



	AI	No-AI
Lower abdomen	-4.3	1.0
Others	-2.1	0.8
Headache	0.1	-0.2
Stomachache	2.2	-1.0
Ankles/feet	4.6	-3.0
Neck/shoulders	9.0	4.5
Lower back	9.1	1.6
Knees	11.3	0.7
Hips	15.3	-0.2

Figure 3: Pressure Pain Threshold and Tolerance: Baseline and 12 months after Surgery. Pressure pain threshold and tolerance were examined using a handheld algometer (Wagner RDX, Greenwich, CT, USA) to steadily increase pressure applied at the trapezius muscle belly both before surgery and 12 months after surgery. A)Pressure pain thresholds at baseline and 12 months after surgery for AI and no-AI groups (mean, 95% confidence interval, with individual participants' values shown with individual dots). B) Pressure pain tolerance for AI and no-AI groups (mean, 95% confidence interval, with individual participants' values shown with individual dots). C)Paired samples Wilcoxon Signed-Ranks was used to test for change from baseline, which indicated a significant increase in pain threshold in no-AI group.



C

	AI				No AI			
QST	n	Change	Z	*p*	n	Change	Z	*p*
PP threshold (trapezius)	14	.355 (3.81)	-.910	.363	51	1.308 (3.41)	-2.295	**.022**
PP tolerance (trapezius)	14	.910 (2.75)	-.063	.950	51	.919 (2.74)	-1.275	.202

Table 1. Demographic and treatment-related characteristics at pre-surgery

	AI		no-AI		Z/χ^2	p
Demographic and treatments	n		n			
Age, mean (SD)	49	62.6 (10.4)	106	54.9 (12.0)	-4.043	<0.001
Caucasian, n (%)	49	44 (90)	105	92 (87)	0.153	0.695
Married/partnered, n (%)	49	34 (69)	105	85 (81)	2.544	0.111
BMI, mean (SD)	49	29.0 (6.6)	106	26.4 (5.9)	-2.646	0.008
Surgery type, n (%) - Lumpectomy - Mastectomy - Mastectomy with reconstruction	49	 34 (69) 8 (16) 7 (14)	106	 50 (47) 12 (11) 44 (42)	11.25	0.004
Chemotherapy, n (%)	49	12 (25)	106	34 (32)	0.924	0.336
Radiation therapy, n (%)	49	30 (61)	106	56 (53)	0.956	0.328
AI therapy duration days, mean (SD)	40	296 (82)	NA	NA	NA	NA

AI=aromatase inhibitor; BMI=body mass index; SD=standard deviation.
Bolded values are statistically significant.

Table 2. Description of pain assessments and psychosocial outcomes at pre- and post-surgery (12-month post)

	Pre-surgery						12-month post-surgery					
	AI		no-AI		$t/Z/\chi^2$	p	AI		no-AI		$t/Z/\chi^2$	p
PAIN	n		n				n		n			
BPI_severity, mean (SD)	49	1.0 (1.2)	104	1.1 (1.7)	-0.919	0.358	46	1.5 (1.5)	106	1.4 (1.8)	-1.184	0.237
BPI_interference, mean (SD)	47	1.1 (1.8)	102	1.0 (1.8)	-0.755	0.450	45	1.3 (1.9)	103	1.1 (1.8)	-1.345	0.179
BCPQ-pain severity index, mean (SD)	49	0.7 (1.2)	106	1.1 (1.8)	-1.405	0.160	47	2.0 (2.4)	106	1.9 (2.4)	-0.505	0.614
BCPQ-physical impact of pain, mean (SD)	45	0.9 (2.6)	93	1.0 (2.4)	-0.121	0.903	40	2.6 (4.2)	98	2.7 (4.8)	-0.531	0.596
Severity of other pain, mean (SD)	41	1.9 (2.5)	97	1.8 (2.7)	-0.532	0.594	39	2.4 (2.4)	100	1.7 (2.6)	-1.727	0.084
# of pain at other location 0, n (%) ≥1, n (%) 1, n (%) 2, n (%) 3, n (%) 4, n (%) 5, n (%) 6, n (%) 7, n (%)	47	 22 (47) 25 (53) 16 (34) 7 (15) 2 (4) 0 (0) 0 (0) 0 (0) 0 (0)	103	 59 (57) 44 (43) 25 (24) 11 (11) 3 (3) 4 (4) 1 (1) 0 (0) 0 (0)	-0.859	0.390	46	 17 (37) 29 (63) 16 (35) 7 (15) 3 (7) 1 (2) 0 (0) 1 (2) 1 (2)	105	 64 (61) 41 (39) 21 (20) 10 (10) 5 (5) 1 (1) 2 (2) 1 (1) 1 (1)	-2.451	0.014
headache, n (%)	47	3 (6)	103	8 (8)	<0.001	1.000	46	3 (7)	105	8 (8)	0.057	0.811
neck shoulders, n (%)	47	5 (11)	103	14 (14)	0.255	0.614	46	9 (20)	105	19 (18)	0.046	0.831
lower back, n (%)	47	8 (17)	103	12 (12)	0.806	0.369	46	12 (26)	105	14 (13)	3.650	0.056
hips, n (%)	47	1 (2)	103	10 (10)	1.723	0.189	46	8 (17)	105	10 (10)	1.886	0.170
knees, n (%)	47	8 (17)	103	14 (14)	0.303	0.582	46	13 (28)	105	15 (14)	4.136	0.042
ankles / feet, n (%)	47	6 (13)	103	9 (9)	0.220	0.639	46	8 (17)	105	6 (6)	5.185	0.023
stomachache, n (%)	47	0 (0)	103	1 (1)	<0.001	1.000	46	1 (2)	105	0 (0)	0.181	0.670
lower abdomen, n (%)	47	2 (4)	103	2 (2)	0.073	0.788	46	0 (0)	105	3 (3)	0.275	0.600
others, n (%)	47	3 (6)	103	7 (7)	<0.001	1.000	46	2 (4)	105	8 (8)	0.554	0.457
PSYCHOSOCIAL SYMPTOMS												
PROMIS_Anxiety, mean (SD)	49	16.8 (4.7)	103	17.5 (5.9)	-0.340	0.734	44	13.8 (5.3)	103	13.4 (4.9)	-0.482	0.630
PROMIS_Depression, mean (SD)	49	12.7 (3.8)	106	13.1 (5.5)	-0.314	0.754	46	12.3 (5.0)	106	12.6 (5.1)	-0.413	0.679
PROMIS_Sleep,	48	21.3	103	20.9	-0.318	0.751	46	21.1	103	20.7	-	0.635

mean (SD)		(7.1)		(7.4)				(6.8)		(7.6)	0.475	
PANAS_Positive, mean (SD)	49	35.2 (7.6)	100	33.6 (7.8)	-1.127	0.260	45	34.1 (7.7)	102	33.8 (8.3)	-0.181	0.856
PANAS_Negative, mean (SD)	49	17.0 (5.2)	100	18.0 (6.8)	-0.543	0.687	45	15.7 (6.0)	93	15.8 (5.8)	-0.148	0.882

AI=aromatase inhibitor; BPI=brief pain inventory; BCPQ=breast cancer pain questionnaire; PROMIS=patient-reported outcomes measurement information system; PANAS=positive affect negative affect scale; SD=standard deviation.
Bolded values are statistically significant.

Table 3. Parameter estimates for pain at non-surgical locations between AI and no-AI groups by using GEE Modeling

	n*	β	SE	95% CI Lower	95% CI Upper	Wald Chi-square	p
Musculoskeletal Pain Sum**	301						
Intercept		-.396	.357	-1.096	.304	1.230	.267
Time		.036	.081	-.124	.195	.192	.662
Treatment		-.039	.149	-.331	.253	.069	.793
Treatment X Time		.420	.186	.055	.784	5.093	.024
BMI		.037	.014	.010	.064	7.128	.008
pain severity at other location	277						
Intercept		-1.119	.849	-2.783	.545	1.737	.188
Time		-.150	.242	-.625	.325	.384	.535
Treatment		-.348	.452	-1.234	.539	.591	.442
Treatment X Time		.819	.480	-.123	1.760	2.904	.088
BMI		.112	.033	.048	.176	11.814	.001

* n represents numbers of observations included in the GEE model

** Musculoskeletal Pain Sum represents the number of endorsed painful areas including neck/shoulders, lower back, hips, knees, and ankles/feet.

References: time (pre-surgery), group (No-AI)