Increased Clinical Pain Locations and Pain Sensitivity in Women After Breast Cancer Surgery

Influence of Aromatase Inhibitor Therapy

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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). 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 nonsurgical 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 body mass index, AI therapy was associated with a greater increase in the number of painful nonsurgical 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.

Conclusions: 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 aromatase inhibitor-associated musculoskeletal syndrome worthy of future investigation.

Key Words: breast neoplasms, aromatase inhibitors, pain, pain threshold, widespread pain

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Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer mortality among women worldwide.[1] Approximately 80% of postmenopausal women with BC have hormone receptor-(estrogen and/or progesterone receptor) positive disease[2] and their overall and disease-free survival rates are significantly improved with 5 to 10 years of aromatase inhibitor (AI) therapy.[3,4] Although effective, AI is unfortunately associated with AI-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% to 85%) but represents the most common reason for women to stop AI therapy, with 12% to 73% of patients discontinuing AI therapy because of AIMSS.[8–11] In addition, AIMSS is associated with decreased quality of life and physical functioning, with 48% to 64% of AI users reporting a decline in their ability to carry out their daily activities because of 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% to 99%),[14–19] estrogen suppression is the most obvious and studied mechanistic target.[20] However, the high interindividual 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 the 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 nonsurgical areas. Second, pain assessments of patients with AI therapy have typically consisted of a single patient report of pain (0 to 10), and not included more extensive, specific, and localizing pain self-report tools, nor more objective measures of pain sensitivity using quantitative sensory testing (QST). 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

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include baseline pain assessment before AI initiation. The current study addresses these gaps, as a longitudinal analysis of women with early-stage BC undergoing BC surgery. We aimed to compare (1) clinical pain in a variety of surgical and nonsurgical 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 BC 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 after surgery. Patients from the Institutional Review Board–approved parent study were recruited from the preoperative anesthesia clinic at Brigham and Women's Hospital in Boston, MA, from September 2014 to March 2017. Eligibility criteria included women ages 18 to 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 (eg, tamoxifen). Participants who received AI therapy (ie, anastrozole, letrozole, exemestane) were compared with 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]) × (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 nonsurgical locations (including head, neck, shoulders, lower back, hips, knees, ankles/feet, stomach, lower abdomen, and others) and the overall pain severity (0 to 10). BPI mean severity (range: 0 to 10) was calculated by averaging the self-reported current, worst, least, and average pain in the preceding week, and BPI interference (range: 0 to 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 BC 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) 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 ~2 to 3 cm above the scapular spine, midway between C7 prominence and humeral head (truncal site).

Data analysis were conducted using IBM SPSS Statistics version 27.0 (IBM Corp.). Descriptive statistics were reported as means and SDs for continuous variables and counts and percentages for categorical variables. χ^2 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. 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 nonsurgical location, linear regression analysis using generalized estimating equations with autoregressive correlation structure was performed. As 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, 2 groups of patients were identified: (1) AI group (n = 49) in which women received AI therapy during their first year after surgery (ie, anastrozole, letrozole, and 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 to 440 days. Preoperative demographic and treatment-related characteristics for AI and no-AI groups are detailed in Table 1. As expected, as AI therapy is the first-line treatment for postmenopausal women with hormone-sensitive BC, 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 postsurgery, surgical site pain was comparable between AI and no-AI groups, as measured using the surgery-specific pain questionnaire (BCPQ PSI), or the 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).

TABLE 1. Demographic and Treatment-related Characteristics at Presurgery

	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 (%)	49	—	106	—	11.25	**0.004**
Lumpectomy	—	34 (69)	—	50 (47)	—	—
Mastectomy	—	8 (16)	—	12 (11)	—	—
Mastectomy with reconstruction	—	7 (14)	—	44 (42)	—	—
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

Significant *P*-values are shown in bold.
AI indicates aromatase inhibitor; BMI, body mass index.

Pain at Nonsurgical 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 nonsurgical pain and number of pain locations before surgery and 12 months later, after the onset of AI therapy (Fig. 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 nonsurgical site increased from 53% (preoperative) to 63% (12 mo postoperative) in the AI

TABLE 2. Description of Pain Assessments and Psychosocial Outcomes at Presurgery and Postsurgery (12-month Post)

	Presurgery						12-month Postsurgery					
	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
No. pain at other location	47	—	103	—	−0.859	0.390	46	—	105	—	−2.451	**0.014**
0, n (%)	—	22 (47)	—	59 (57)	—	—	—	17 (37)	—	64 (61)	—	—
≥1, n (%)	—	25 (53)	—	44 (43)	—	—	—	29 (63)	—	41 (39)	—	—
1, n (%)	—	16 (34)	—	25 (24)	—	—	—	16 (35)	—	21 (20)	—	—
2, n (%)	—	7 (15)	—	11 (11)	—	—	—	7 (15)	—	10 (10)	—	—
3, n (%)	—	2 (4)	—	3 (3)	—	—	—	3 (7)	—	5 (5)	—	—
4, n (%)	—	0 (0)	—	4 (4)	—	—	—	1 (2)	—	1 (1)	—	—
5, n (%)	—	0 (0)	—	1 (1)	—	—	—	0 (0)	—	2 (2)	—	—
6, n (%)	—	0 (0)	—	0 (0)	—	—	—	1 (2)	—	1 (1)	—	—
7, n (%)	—	0 (0)	—	0 (0)	—	—	—	1 (2)	—	1 (1)	—	—
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	103	1 (1)	<0.001	1.000	46	1 (2)	105	0	0.181	0.670
Lower abdomen, n (%)	47	2 (4)	103	2 (2)	0.073	0.788	46	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, mean (SD)	48	21.3 (7.1)	103	20.9 (7.4)	−0.318	0.751	46	21.1 (6.8)	103	20.7 (7.6)	−0.475	0.635
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

Significant *P*-values are shown in bold.
AI indicates aromatase inhibitor; BCPQ, Breast Cancer Pain Questionnaire; BPI, Brief Pain Inventory; PANAS, Positive Affect Negative Affect Scale; PROMIS, Patient-Reported Outcomes Measurement Information System.

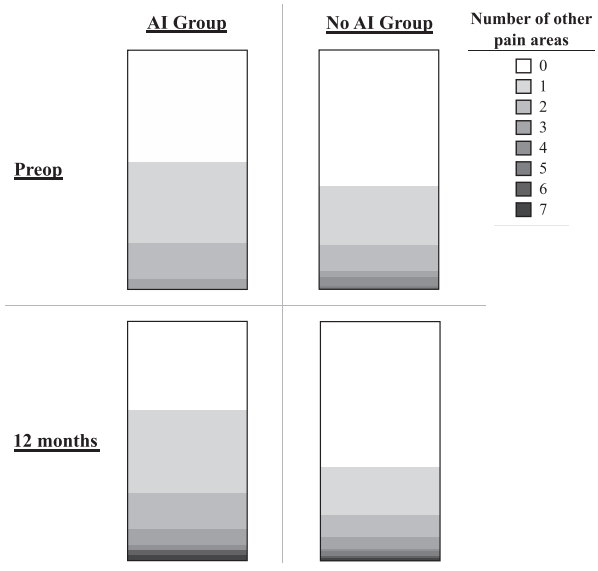


FIGURE 1. Number of nonsurgical areas with pain. Patients reported locations with pain preoperatively and 12 months after surgery, including nonsurgical locations as part of the Breast Cancer Pain Questionnaire. Bar charts show the proportion of AI and no-AI groups reporting different total number of pain locations at baseline and 12 months after surgery.

group, whereas the proportion slightly decreased in the no-AI group (43% preoperative vs. 39% 12 mo 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 toward higher overall pain severity ($P = 0.084$) (Table 2). To assess the relationship of AI to other body site pain over time, while taking into account relevant covariates (ie, age, BMI, and surgery type), we used generalized estimating equation linear regression. We observed a significant treatment by time interaction, such that there was an increase in the number of nonsurgical pain sites between preoperative and 12 months postoperative for the AI group (treatment by time interaction, $\beta = 0.420$, $P = 0.024$), but not in the no-AI group. A similar, but nonsignificant, trend was observed when pain severity at nonsurgical areas was investigated as the outcome (treatment by time interaction, $\beta = 0.819$, $P = 0.088$) (Table 3).

To further characterize this reported increase in the 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 with 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 with 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, whereas the AI group remained with a similar pressure pain threshold (Fig. 3). No statistically significant changes in pressure pain tolerance at 12 months after surgery were observed for either group.

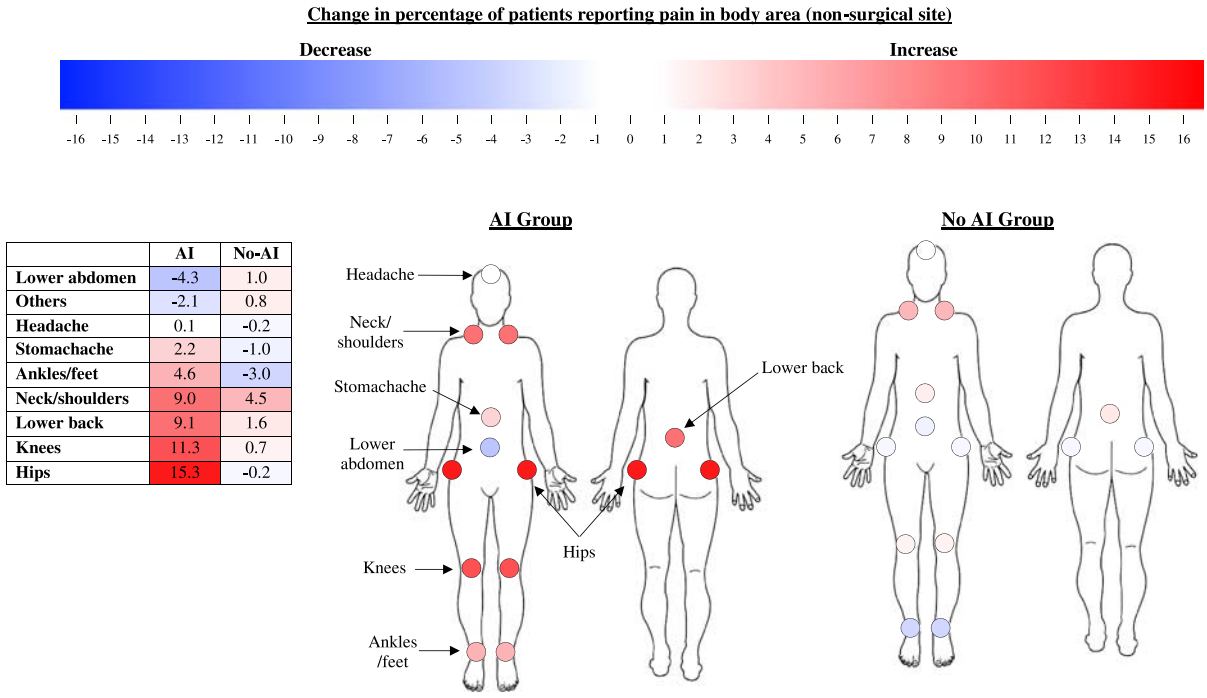
DISCUSSION

Adjuvant hormonal therapy for BC substantially reduces morbidity and mortality from BC. 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] AIs are one of the most potent agents approved for the treatment of early-stage BC. However,

TABLE 3. Parameter Estimates for Pain at Nonsurgical Locations Between Aromatase Inhibitor and No–Aromatase Inhibitor Groups by Using Generalized Estimating Equation Modeling

	n*	β	SE	95% CI lower	95% CI upper	Wald χ^2	*P*
Musculoskeletal pain sum†	301	—	—	—	—	—	—
Intercept	—	−0.396	0.357	−1.096	0.304	1.230	0.267
Time	—	0.036	0.081	−0.124	0.195	0.192	0.662
Treatment	—	−0.039	0.149	−0.331	0.253	0.069	0.793
Treatment × Time	—	0.420	0.186	0.055	0.784	5.093	**0.024**
BMI	—	0.037	0.014	0.010	0.064	7.128	0.008
Pain severity at other location	277	—	—	—	—	—	—
Intercept	—	−1.119	0.849	−2.783	0.545	1.737	0.188
Time	—	−0.150	0.242	−0.625	0.325	0.384	0.535
Treatment	—	−0.348	0.452	−1.234	0.539	0.591	0.442
Treatment × Time	—	0.819	0.480	−0.123	1.760	2.904	0.088
BMI	—	0.112	0.033	0.048	0.176	11.814	0.001

Significant *P*-values are shown in bold. References: time (presurgery), group (no-AI).
*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.
BMI indicates body mass index.



	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

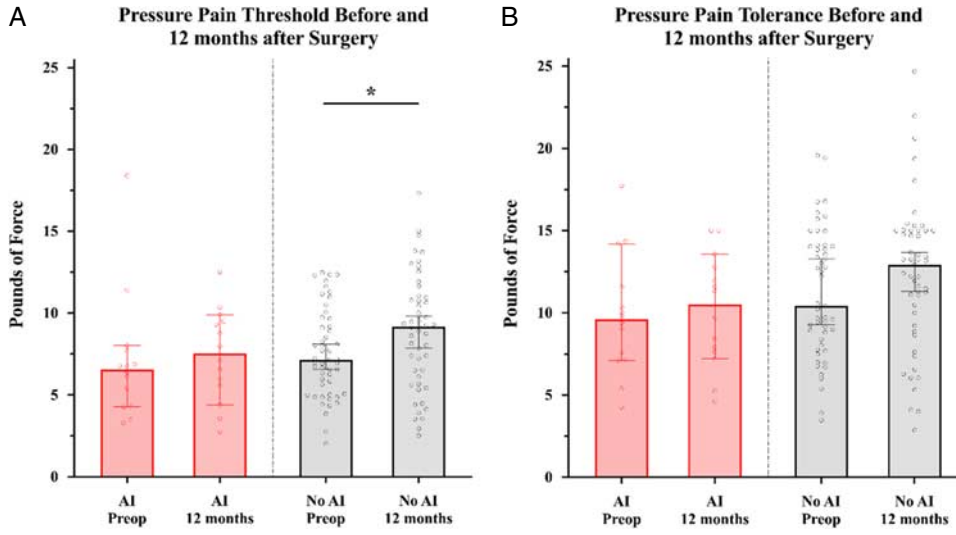
FIGURE 2. Body maps of increase and decrease in reported pain locations in patients taking versus not taking aromatase inhibitors during the first year after surgery. Patients reported locations with pain preoperatively and 12 months after surgery, including nonsurgical locations (head, neck, shoulders, 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 (postsurgery minus presurgery) in percentage at each location are calculated and display in the Figure 2. Red indicates increase and blue indicates decrease in reported pain among the group.

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 the characterization of pain quality and progression in AIMSS by using comprehensively assessed pain outcomes (clinical pain at surgical site and whole body, and objective pressure pain sensitivity) between BC patients who did or did not receive AI therapy, both before and after starting this therapy. Although AI treatment was not associated with greater surgical site pain, our findings suggest that AI may significantly increase pain in nonsurgical areas, particularly joints (ie, 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 with the no-AI group who became less sensitive compared with their preoperative timepoint.

It is notable, but not completely unexpected, that AI therapy did not impact surgical area pain (breast, axilla, upper arm, and 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 postmastectomy pain (PPMP) at the surgical site (20% to 65%).[28,29,36–39] Although 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 statistically significant trend toward increased pain severity at those nonsurgical 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 statistically nonsignificant trend toward 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 symptoms 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



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	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

FIGURE 3. Pressure pain threshold and tolerance: baseline and 12 months after surgery. A, Pressure pain thresholds at baseline and 12 months after surgery for AI and no-AI groups (mean, 95% CI, with individual participants' values shown with individual dots). B, Pressure pain tolerance for AI and no-AI groups (mean, 95% CI, with individual participants' values shown with individual dots). C, Paired samples Wilcoxon Signed-Ranks were used to test for change from baseline, which indicated a significant increase in pain threshold in no-AI group. AI indicates aromatase inhibitor; QST, quantitative sensory testing.

McMaster Universities Osteoarthritis Index,[55] and Disabilities of the Arm, Shoulder, and Hand[56] in both clinical investigations and clinical care of patients undergoing AI therapy for BC.

Our quantitative assessment of pain sensitivity revealed that AI-treated patients also maintained a relatively higher pain sensitivity at nonjoint sites (eg, trapezius muscle), which together with increased incidence of joint pain, may indicate increased general pain sensitivity. Although more extensive QST has been reported in chemotherapy-induced peripheral neuropathy,[57] only 1 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 with 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 with their preoperative baseline value, potentially indicating that the maintenance of pain sensitivity in the AI group is not normal. Future studies using more comprehensive objective measures of pain (eg, a full battery of QST), 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.[59–62] It is interesting to note that we observed AI-associated increases in pain at some of these typical sites of chronic pain (eg, back and 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 (eg, temporal summation and conditioned pain modulation) that seem to be highly relevant to chronic pain symptoms.

The finding of increased number of clinical nonsurgical 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 is 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 BC 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 presurgical vs. postsurgical 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 BC survivors. Some preclinical studies implicate neuroinflammation as a potential mechanism, as estrogen inhibits proinflammatory cytokine and chemokine release by glial cells (eg, 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] Research is needed to investigate the degree and importance of neuroinflammation in AIMSS.

We observed that a higher 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 (eg, back pain, knee pain), in particular for pain at the lower extremity.[69–72] This finding has multiple implications for clinical practice and research. First, it suggests that BMI may serve as a risk factor of increased salience to women undergoing treatment with AI for BC, 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 to mitigate increases in musculoskeletal pain during AI therapy.[72] In addition, biological mechanisms shared by obesity and chronic musculoskeletal pain (eg, chronic proinflammatory state)[73–75] should be examined in BC patients with AIMSS. In addition, psychosocial factors, which have also been closely associated with both obesity and pain (eg, depression and 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 versus nonsurgical 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 BC, 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 BC diagnosis and other cancer treatments (eg, surgery, radiation, and chemotherapy). Nevertheless, there are important limitations to consider. First, we could not conduct post hoc group comparisons among different types of AIs because of the limited sample size for each individual AI agent. Second, as a secondary analysis of a data set powered to detect risk factors of PPMP, our analysis may be underpowered to detect differences between groups receiving versus 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 QST, 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 QST, potentially implicating a more centralized pain sensitization with AI therapy. Studies are needed to better understand the role of central sensitization in the development and maintenance of musculoskeletal pain during adjuvant AI therapy for BC. 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 BC 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.

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