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Anastrozole-Associated Joint Pain and Other Symptoms in Patients With Breast Cancer

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Abstract

More than a third of breast cancer patients undergoing aromatase inhibitor (AI) treatment report joint pain. We conducted a longitudinal study to characterize the course of AI-induced joint pain and other symptoms and to identify potential predictors for developing these symptoms. Patients were recruited before AI initiation. The Brief Pain Inventory, M. D. Anderson Symptom Inventory, and a joint-pain questionnaire were administered at baseline and then biweekly for 1 year. Analysis included logistic regression, Cox models, and mixed-effects models. Of 47 patients assessed, 16 (34%) reported joint pain at least once. Median time to first report of joint pain was 7 weeks (range 1–38). Baseline pain was the only predictor for both incidence of joint pain and time to first event. In the first 6 weeks, emergence of joint pain was associated with increase in general pain, fatigue, disturbed sleep, hot flashes, vaginal dryness, and decreased sexual activity. After week 6, having joint pain was associated with increase in general pain and with persistently high fatigue. Having AI-associated joint pain correlated with increase in or persistence of other symptoms likely related to AI therapy. Further research is needed to validate predictors of AI-associated symptoms.

Keywords

anastrozole; arthralgia; aromatase inhibitor; breast cancer; joint pain; symptoms

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Disclosures

The authors have declared no conflicts of interest.

Trial Registration

Not applicable.

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Introduction

Compared with tamoxifen, aromatase inhibitors (AIs) are associated with higher incidence of arthralgia (joint pain or stiffness).^{2,7,20} Among patients treated with the third-generation AI anastrozole, the incidence of arthralgia has been reported as greater than 30%.¹³ This incidence rate may underestimate what patients truly experience during treatment, because it is based on clinician report of adverse events rather than on patient report¹ (an even higher prevalence of AI-associated arthralgia has been reported by patients using validated self-report instruments⁸). Often, patients experience severe symptoms that lead to therapy interruption: approximately 13% of early breast cancer survivors receiving the AI letrozole after surgery discontinued AI therapy, primarily because of arthralgia and the resulting impairment of daily life⁹; in another study, 20% of patients discontinued AI therapy because of arthralgia and/or bone pain.¹⁸

Other than joint pain, hot flashes, night sweats, fatigue, nausea and vomiting, and mood disturbance have been reported by patients in large AI clinical trials.^{13,20} In the “Arimidex, Tamoxifen, Alone or in Combination” (ATAC) trial, patient-reported endocrine-related symptoms worsened after 3 months of anastrozole therapy and remained relatively stable throughout the 5-year treatment period³; compared with tamoxifen, anastrozole was related to more diarrhea, vaginal dryness, and dyspareunia. The most prevalent letrozole-related toxicities were hot flashes, fatigue, nausea and vomiting, and mood alteration.⁹ None of these studies described how symptoms developed during AI treatment, when joint pain emerged, or how joint pain associated with those symptoms, and no risk factors for symptom development were identified.

Despite progress toward identifying patients at high risk for AI-related joint symptoms, results have been inconsistent. Cross-sectional studies have identified shorter length of time since menopause,¹⁵ development of osteoporosis while on AI treatment,¹⁷ obesity, and previous chemotherapy as risk factors.¹⁹ One prospective study found that 45% of patients developed arthralgia, but the study failed to associate any pretreatment factors with its development.¹² A more-recent study of patients receiving exemestane or letrozole indicated that younger age, higher baseline pain level, and previous taxane-containing chemotherapy were risk factors for discontinuation of AI therapy as a result of any symptom.¹¹

We employed frequent symptom assessment to estimate the incidence and time-to-onset of joint pain during AI treatment, describe the development of other treatment-related symptoms, describe the relationship between joint pain and symptoms, and identify pretreatment factors that might predict incidence and onset of AI-induced joint pain and changes in other symptoms.

Materials and Methods

Sample

We conducted a prospective cohort study of patients receiving anastrozole therapy at The University of Texas MD Anderson Cancer Center in Houston, Texas. Patients were recruited from the breast oncology clinic between 2008 and 2011. Eligible patients had a diagnosis of early-stage, estrogen-receptor positive breast cancer (stage I, II, or IIIA), were naïve to anastrozole treatment, and were at least 18 years old.

This study was approved by the MD Anderson Institutional Review Board, and all patients gave written informed consent to participate prior to the baseline evaluation.

Outcome Measurements

General Pain Severity—General pain was measured with the Brief Pain Inventory (BPI), which asks patients to rate their pain for the last 24 hours on a 0–10 scale at its worst, least, average, and now. Each scale is bounded by the words “no pain” at the 0 end and “pain as bad as you can imagine” at the other. The BPI’s validity and reliability have been examined in detail.⁵

Multiple Symptoms—Other symptoms were measured using the M. D. Anderson Symptom Inventory (MDASI),⁴ a validated assessment tool that measures the intensities of 13 core cancer-related symptoms and 6 items of symptom interference with functioning. The MDASI used in this study includes 3 additional menopause-like symptoms that breast cancer patients have reported experiencing during tamoxifen treatment (hot flashes, vaginal dryness, and decreased sexual interest).¹⁶ Patients rated the intensity of the symptom items on 0–10 numeric scales ranging from “not present” to “as bad as you can imagine,” and the intensity of the interference items on 0–10 numeric scales ranging from “did not interfere” to “interfered completely.”

AI-Induced Joint Pain—Patients self-reported the severity and location of joint pain using a joint pain assessment (JPA) form developed for this study. Using this form, respondents indicated whether they had experienced pain in any of 5 joint areas (hand, wrist, elbow, knee, ankle) in the past week. If yes, respondents indicated the painful joint(s) on a diagram adapted from the Disease Activity Scores (DAS 44).¹⁰ Questions about the severity of the joint pain included the 4 pain severity items from the BPI (worst pain, least pain, average pain, and pain now).

During the study, if the BPI worst-pain level increased by 1 point for 2 consecutive assessments and was 3 or greater, a JPA questionnaire with instructions was mailed to the patient’s home. High correlation has been reported between the BPI worst-pain score and the pain score from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a disease-specific questionnaire used to measure joint pain; further, the BPI’s sensitivity to change in pain levels in patients with osteoarthritis was similar to that of the WOMAC,¹⁴ suggesting that increase in BPI ratings could be used to indicate the onset of joint pain. After the JPA was mailed, research staff called patients to remind them to complete the form and return it to the project office in a preaddressed, stamped envelope. If a patient reported pain in any joint at least once during treatment, she was considered as having AI-induced joint pain.

Assessment Schedule—At the baseline evaluation, patients were asked to complete the BPI, the MDASI, and the JPA. Demographic information, body mass index (BMI), and clinical characteristics were also collected.

Between routine clinic visits, the BPI and MDASI were administered every 2 weeks for 52 weeks through an interactive voice response (IVR) system. The IVR allows patients to use their touch-tone telephone to rate symptoms while away from the clinic. Using the telephone keypad, a patient can, for example, rate pain at its worst in the past 24 hours from 0–10. At the baseline investigation, the IVR was configured to call patients every 2 weeks at a time convenient for them.

When patients returned to the clinic for follow-up assessment (every 4–6 months), they completed the BPI, the MDASI, and the JPA. Information about medication use and change in demographic or clinical status was collected.

Statistical Analysis

The incidence of AI-induced joint pain was estimated as time to the first joint pain event and calculated on the basis of the date of the patient's JPA report.

Logistic regression modeling was used to define risk factors for developing joint pain during anastrozole treatment, including demographic characteristics, BMI, clinical factors, and baseline BPI worst-pain level.

Cox regression modeling was used to estimate how the factors predicted the onset of AI-induced joint pain. To estimate the probability of developing joint pain, 1 minus cumulative survival was calculated every 2 weeks from week 2 to week 12 of AI therapy. All demographic and clinical factors were adjusted in this model.

We also explored the development of other potential treatment-related symptoms in patients with or without joint pain. The top 6 symptoms were selected by their severities over time. Mixed-effects models were used to describe how joint pain and other factors associated with change in general pain and symptoms over time, adjusted for all demographic and clinical factors. We used piecewise linear mixed models to describe symptom-change trends before and after week 6.

Descriptive statistics include mean, median, range, standard deviation (SD), standard error (SE), and 95% confidence interval (95% CI). Analyses were performed with SAS 9.2 (Cary, NC). All tests were 2-sided with .05 as the significance level.

Results

Fifty-two patients were recruited for this study; 5 withdrew after the baseline investigation. The remaining 47 patients were included in the analysis. Of these, 100% had assessments in the first 12 weeks and 72% (34/47) completed their 1-year assessments. The early drop-out status was included in all multivariate analyses. Baseline demographic and clinical characteristics and pain severity and interference are summarized in Table 1.

Incidence of AI-Induced Joint Pain

During the first year of AI therapy, 16/47 patients (34%) reported having joint pain. Of the 16 patients, 2 reported joint pain at baseline that worsened during the treatment, and the remaining 14 patients reported newly developed joint pain. The severity of joint pain at its onset was 5.23 (SD 2.54), and the severity of pain interference was 3.29 (SD 2.16). The most-prevalent joints involved were knees and hands. The mean number of affected joints was 4.12 (range 1–18). At month 6 after AI initiation, 50% of those with joint pain and 40% of those without joint pain used analgesia. The difference was not significant ($P = .57$). Non-steroidal anti-inflammatory drugs were the most-used analgesia in both groups.

For those patients with AI-induced joint pain, only BPI worst pain at pretreatment baseline ($P = .036$) showed a significant association with the development of joint pain during treatment. Because of the small sample size, several variables (insurance status, previous radiotherapy, disease stage, previous surgery, and pre-existing osteoarthritis) were not included in the logistic regression modeling.

Logistic regression modeling, after controlling for the covariates in Table 1, demonstrated that report of baseline BPI worst pain at 1 or above (1–10 vs. 0) was the only significant predictor of the development of AI-induced joint pain (odds ratio [OR] = 10.66; 95% CI, 1.50–75.89; $P = .018$) (Table 2). After adjustment for covariates, the probabilities of

reporting joint pain were 0.56 (95% CI, 0.46–0.65) for baseline worst pain above 0 and 0.26 (95% CI, 0.19–0.33) for baseline worst pain equal to 0.

Time to Onset of Joint Pain

The median time of joint pain onset was 7 weeks (range, 1–38 weeks). The average time to onset of joint pain was 9.4 weeks (95% CI, 5.1–13.7). Only baseline BPI worst pain >0 significantly predicted the time to onset of joint pain (Fig 1). Compared with patients who reported 0 worst pain at baseline, those who rated pain as 1 or greater had 5 times the risk of developing joint pain (hazard ratio [HR] = 5.55; 95% CI, 1.64–18.81; $P = .006$). The cumulative risk of joint pain by the end of week 12 was 0.55, indicating that more than half of patients who reported baseline pain developed joint pain during the first 12 weeks of therapy (Fig 1). No other factor showed significant association with time to development of AI-induced joint pain (Table 3).

Symptom Development

Overall, the top 6 symptoms reported by all patients were general pain, fatigue, hot flashes, vaginal dryness, decreased sexual interest, and disturbed sleep. Using mixed-effects modeling with time as a categorical variable, we found that after 6 weeks on therapy, patients' general pain (BPI pain worst) levels were significantly higher than at baseline (data not shown).

During the first 6 weeks of AI therapy, general pain, hot flashes, and decreased sexual interest increased in all patients, while fatigue, disturbed sleep, and vaginal dryness increased only in patients who developed joint pain. After 6 weeks of treatment, patients with joint pain continued to report worsening general pain ($P = .022$); patients without joint pain reported a slight decrease in general pain (estimate = -0.02 ; $P = .075$). Fatigue and disturbed sleep decreased in patients without joint pain but persisted at the 6-week level in patients with joint pain. After 6 weeks, hot flashes, vaginal dryness, and sexual interest did not change or differ significantly between patients with or without joint pain (Table 4, Fig 2).

Compared with patients who did not report general pain at baseline, those with baseline general pain reported significantly higher levels of general pain, fatigue, and disturbed sleep over time. No significant associations were found between baseline pain and hot flashes, vaginal dryness, or sexual interest. Being overweight (BMI ≥ 25 kg/m²) was a risk factor for greater general pain and fatigue. No significant associations were found between BMI and disturbed sleep, hot flashes, vaginal dryness, or sexual interest (Table 4).

Discussion

Results from our longitudinal study indicate that approximately 1 in 3 patients with breast cancer receiving AI therapy reported incidence or worsening of joint pain. During the first 6 weeks of AI, emergence of expected symptoms (general pain, fatigue, disturbed sleep, hot flashes, vaginal dryness, and decreased sexual interest) was seen in all patients but was more pronounced and persistent in patients who reported joint pain. Reporting any pain prior to the initiation of AI therapy was the only predictor for onset of AI-induced joint pain, and half of patients with any baseline pain developed joint pain within the first 3 months of treatment, compared with 27% of those without it. Pre-AI pain also predicted more fatigue and disturbed sleep. Obesity was a predictor for general pain and fatigue, but not for other symptoms.

The median time to onset of the first event of AI-related joint pain was 7 weeks, comparable to the 1.6-months reported elsewhere.¹² Compared with studies having less-frequent

symptom measurements, our every-2-week pain assessment provided more-accurate pinpointing of the emergence of joint pain. Our incidence rate of AI-induced joint pain was 10% lower than rates of musculoskeletal symptoms others have reported.^{8,15} Nonetheless, because we focused specifically on measuring joint pain, our results confirm previous reports that pain in the joints of the hands, wrists, and knees is a major problem reported by patients receiving AI therapy and may affect functions related to those joints.¹⁵

Although several studies reported the occurrence of multiple symptoms in breast cancer patients undergoing AI therapy,^{13,20} none examined how AI-induced joint pain associates with other major symptoms. Our results indicate the emergence of a high burden of treatment-related hot flashes, vaginal dryness, and decreased sexual interest for all patients with AI. These symptoms have been reported not only in AI-treated patients, but also in most breast cancer survivors undergoing endocrine therapy.⁶ We found that the 3 menopause-like symptoms increased significantly in the first 6 weeks of AI therapy and remained high during the entire first year of treatment. Although hot flashes and decreased sexual interest increased after the first 6 weeks of AI treatment, the increase did not differ significantly between patients with and patients without joint pain. It may be that sudden estrogen suppression contributes to joint symptoms and to these menopause-like symptoms in AI-treated patients.² The independence of joint pain from the menopause-like symptoms suggests a mechanism of AI-induced joint pain that is more complex than estrogen alone might produce.

Overall, fatigue is the most prevalent symptom reported by cancer survivors. In our sample, persistent fatigue was positively related to the presence of joint pain: although fatigue was relatively severe at baseline and increased during the first 6 weeks of therapy for all patients, it decreased thereafter for patients without but not for patients with joint pain. A similar development pattern was found for disturbed sleep, which has been identified as highly associated with pain.⁴ Although the mechanism underlying these symptoms is unclear, the relatively high levels of joint pain, fatigue, and disturbed sleep suggests that monitoring and managing these symptoms should be considered, especially for patients who develop joint pain.

Unlike previous case-control studies,^{15,19} we did not identify any demographic or clinical risk factors for AI-induced joint pain. Reporting any pain at baseline was found to be the only predictor for both incidence of AI-induced joint pain and onset of the first event. However, inconsistency in risk factors in previous reports suggests that focusing only on demographic and clinical factors may not be adequate for identifying predictors of joint pain during AI treatment. In our study, after adjusting all other factors, patient-reported worst pain at baseline showed strong association with the incidence of joint pain during AI treatment. This result is consistent with the findings of Henry et al. that baseline pain may predict symptom-related AI discontinuation.¹¹ In addition, the underlying biological mechanism of AI-induced joint pain is not known, and it is thus difficult to develop biomarkers as predictors. Baseline pain, as an outcome of multiple biological pathways, could be a surrogate marker for identifying patients at higher risk of AI-induced joint pain. Because the baseline pain level can be obtained via a simple questionnaire, even a single-item questionnaire, it can easily be applied in clinical settings with minimal burden to patients and physicians. Validation of this potential predictor in a larger study population is warranted.

Our small sample size limits the study's implication in clinical use. Although we found statistically significant association between baseline pain and incidence of joint pain, the 95% confidence interval was 1.50–75.89, too large to be interpreted in clinical application. Also, the small sample size prevented us from including more factors in the models, which

may have led to underestimation of the contributions of other demographic and clinical factors. Thus, our results need to be interpreted with caution and should be validated in a larger sample. The exclusion of other joint-related symptoms, such as joint stiffness, muscle pain, and tendinitis, may have caused underestimation of AI-induced joint symptoms. A new instrument specifically designed for AI-induced musculoskeletal symptoms needs to be developed to enable the complete study of symptom burden in these patients. Finally, we did not ask patients if they related their pain to AI therapy, which may weaken our findings about the association between AI and symptoms. However, patients who had surgery or any other trauma in the 1 month before their joint pain emerged were not considered as having AI-induced joint pain, and the prevalence of AI-induced joint pain in our population was not overestimated relative to results in previous reports.

In conclusion, our prospective cohort study with longitudinal assessments of pain and other symptoms identified an increase in several treatment-related symptoms after initiation of AI therapy. Report of pain at baseline was a predictor for joint pain caused by AI therapy. Joint pain was also associated with the increase or persistence of other symptoms likely related to AI therapy, whereas patients without joint pain demonstrated a decrease in these symptoms over the study period. Although no intervention has been proven to prevent joint pain, we found in this study that joint pain was associated with other symptoms that can and should be managed. Further research is needed to validate pretreatment pain level as a potential predictor of AI-related joint pain and to examine other risk factors for AI-related symptoms.

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Perspective

We demonstrate for the first time that aromatase inhibitor (AI)-induced joint pain associates with development of other symptoms and that pretreatment pain level is a potential, measurable predictor of symptom development during treatment. Because baseline pain is easily assessed with a brief questionnaire, it can be applied clinically with minimal patient burden.

Number of patients at risk							
Baseline pain	Time interval (week)						
	0	2	4	6	8	10	12
1-10	21	20	19	18	14	13	13
0	26	26	26	23	20	19	19

Figure 1.
Cumulative risk of aromatase-inhibitor-induced joint pain (n = 47). HR, hazard ratio.

Figure 2.
Predicted change in top symptoms during first year of aromatase inhibitor treatment (mixed-effects modeling)

Table 1

Baseline Patient Characteristics

	Joint pain during first year of AI therapy				P
	Yes (n= 16)		No (n=31)		
Age					
mean (SD)	59.3 (6.6)		60.0 (7.5)		.725
median (min-max)	59.1 (48.1–73.3)		58.9 (48.2–71.4)		
BMI					
mean (SD)	28.4 (6.2)		29.6 (7.5)		.587
median (min-max)	27.3 (20.1–43.9)		26.7 (20.8–47.3)		
Brief Pain Inventory worst pain					
mean (SD)	2.1 (2.2)		1.0 (1.5)		.036
median (min-max)	2 (0–7)		0(0–5)		
Brief Pain Inventory pain interference					
	0.82 (1.41)		0.82 (1.26)		.989
	0(0–6)		0(0–6)		
	n	%	n	%	P
Age					
<60	9	56.3	22	71.0	.317
60	7	43.8	9	29.0	
Marital status					
Married	10	62.5	24	77.4	.318
Unmarried	6	37.5	7	22.6	
Race					
White	13	81.3	23	74.2	.725
Other	3	18.8	8	25.8	
Education					
College	11	68.8	20	64.5	.766
Less than college	5	31.3	11	35.5	

	Joint pain during first year of AI therapy					P
	Yes (n= 16)		No (n=31)			
Insurance	Commercial insurance	14	87.5	28	90.3	.772
	Medicare/Medicaid/managed care	2	12.5	3	9.7	
Employment	Employed	11	68.8	16	51.6	.260
	Unemployed	5	31.3	15	48.4	
BMI	<25	6	37.5	8	25.8	.406
	25	10	62.5	23	74.2	
Comorbid conditions	0	11	68.8	24	77.4	.518
	1	5	31.3	7	22.6	
Disease stage	I	8	50.0	12	38.7	.705
	II	7	43.8	15	48.4	
	IIIA	1	6.3	3	9.7	
Previous therapy	Radiotherapy					.162
	Yes	12	75.0	28	90.3	
	No	4	25.0	3	9.7	
	Chemotherapy					.739
	Yes	7	43.8	12	38.7	
	No	9	56.2	19	61.3	
Surgery						.468
	Yes	16	100.0	30	96.8	
	No	0	0	1	3.2	
Previous diagnosis of osteoarthritis	Yes	4	12.9	1	6.3	.483

	Joint pain during first year of AI therapy				P
	Yes (n= 16)		No (n=31)		
	27	87.1	15	93.8	
	No				

Table 2

Predictors of Incidence of Aromatase-Inhibitor-Induced Joint Pain (n = 47)

Effect	OR	95%CI		P
Baseline pain: >0 vs. 0	10.66	1.50	75.89	.018
Age: 60 vs. <60	15.16	0.98	235.63	.052
Marital status: unmarried vs. married	1.63	0.21	12.49	.640
Race: minority vs. non-Hispanic white	0.28	0.03	2.38	.243
Education: less than college vs. college or higher	0.34	0.06	1.93	.222
Employment: unemployed vs. employed	0.13	0.02	1.03	.053
BMI: 25- vs. <25	0.49	0.09	2.49	.388
Previous chemotherapy: yes vs. no	2.15	0.26	07.7	.478

Table 3

Factors Related to Time To Event, Aromatase-Inhibitor-Induced Joint Pain (n = 47)

Effect	HR	95%CI		P
Baseline pain: >0 vs. 0	5.55	1.64	18.814	0.006
Age: 60 vs. <60	7.07	0.99	50.21	0.051
Marital status: unmarried vs. married	1.49	0.32	6.82	0.611
Race: minority vs. non-Hispanic white	0.31	0.07	1.40	0.127
Education: less than college vs. college or higher	0.55	0.16	1.93	0.353
Employment: unemployed vs. employed	0.24	0.05	1.11	0.067
BMI: 25 vs. <25	0.66	0.20	2.11	0.479
Previous chemotherapy: yes vs. no	2.08	0.37	11.66	0.405

Table 4

Predictors for Symptom Change During the First Year of Aromatase Inhibitor Therapy (n = 47)

Effect	Estimate	SE	P
General Pain			
Week 0–6: Joint pain (yes vs. no)			.190
Joint pain	0.22	0.07	.003
No Joint pain	0.12	0.06	.054
Week 6–52: Joint pain (yes vs. no)			<.0001
Joint pain	0.03	0.01	.022
No Joint pain	−0.02	0.01	.075
Baseline pain: >0 vs. 0	1.15	0.30	.001
BMI: ≥25 vs. <25	0.76	0.31	.019
Fatigue			
Week 0–6: Joint pain (yes vs. no)			.072
Joint pain	0.16	0.07	.032
No joint pain	0.01	0.06	.897
Week 6–52: Joint pain (yes vs. no)			.044
Joint pain	0.003	0.01	.814
No joint pain	0.02	0.01	.048
Baseline pain: >0 vs. 0	1.07	0.35	.004
BMI: ≥25 vs. <25	0.87	0.36	.022
Disturbed sleep			
Week 0–6: Joint pain (yes vs. no)			.037
Joint pain	0.24	0.08	.003
No joint pain	0.052	0.06	.415
Week 6–52: Joint pain (yes vs. no)			.076
Joint pain	−0.001	0.01	.923
No joint pain	−0.02	0.01	.045
Baseline pain: >0 vs. 0	1.37	0.35	.0004
Hot flashes			
Week 0–6: Joint pain (yes vs. no)			.299
Joint pain	0.26	0.08	.006
No Joint pain	0.17	0.06	.006
Week 6–52: Joint pain (yes vs. no)			.382
Joint pain	−0.002	0.01	.874
No Joint pain	−0.01	0.01	.246
Vaginal dryness			
Week 0–6: Joint pain (yes vs. no)			.040
Joint pain	0.28	0.08	.0003
No Joint pain	0.09	0.06	.111

Effect	Estimate	SE	P
Week 6–52: Joint pain (yes vs. no)			.442
Joint pain	0.02	0.02	.184
No Joint pain	0.01	0.02	.562
Decreased sexual interest			
Week 0–6: Joint pain (yes vs. no)			.594
Joint pain	0.23	0.09	.008
No Joint pain	0.28	0.06	<.0001
Week 6–52: Joint pain (yes vs. no)			.657
Joint pain	0.001	0.02	.939
No Joint pain	−0.01	0.02	.658

Variables controlled: age, race, education, marital status, employment status, BMI, and pre-chemotherapy.