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Insulin-like growth factor 1 and musculoskeletal pain among breast cancer patients on aromatase inhibitor therapy and women without a history of cancer

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Abstract

Purpose—Musculoskeletal pain is a common side effect of aromatase inhibitors (AIs), the adjuvant hormonal treatment of choice for postmenopausal estrogen receptor-positive breast cancer. Although the pain is usually attributed to the estrogen depletion associated with AIs, not all women on AIs experience these symptoms. Thus, the goal of this study was to examine whether changes in the insulin-like growth factor (IGF) axis were associated with pain among women initiating AI therapy or a comparison group of women without a history of cancer.

Methods—Data were analyzed from a cohort study of 52 breast cancer patients for whom AI therapy was planned and 88 women without a history of cancer. Questionnaire data on pain symptoms were collected and blood was drawn at baseline (prior to AI therapy for patients) and 6-months after baseline. The blood samples were assayed for IGF-1 and IGF binding protein-3 (IGFBP-3).

Results—While results showed no statistically significant changes in any of the measures across time for either the breast cancer or the comparison group, increases in both IGF-1 concentrations and the IGF-1:IGFBP-3 ratio over the first 6-months of AI treatment were significantly associated with the onset or increase in musculoskeletal pain among the breast cancer patients. Associations between IGF-1, IGFBP-3, and the IGF-1:IGFBP-3 ratio and pain were not observed in the comparison group.

Conclusions—Although preliminary, findings from this study implicate the IGF axis in the development of AI-associated musculoskeletal pain and represent a first step in developing effective interventions to alleviate this side effect.

Keywords

Aromatase inhibitors; breast cancer; hormonal therapy; insulin-like growth factor 1; musculoskeletal pain

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

INTRODUCTION

Aromatase inhibitors (AI) are currently the adjuvant hormone therapy of choice for women with postmenopausal estrogen-receptor positive breast cancer. AIs reduce the risk of breast cancer recurrence by approximately 40 % (Early Breast Cancer Trialists' Collaborative Group 2005), and, because of their treatment efficacy, are also being investigated for possible preventive use among women at high-risk of breast cancer (Litton et al. 2012; Goss et al. 2011). AIs have a more favorable safety profile than tamoxifen, including a lower incidence of endometrial cancer (Howell et al. 2005; Goss 2007; Coombes et al. 2004; Coombes et al. 2007; Thurlimann et al. 2005; Coates et al. 2007). However, AIs are associated with the occurrence of musculoskeletal symptoms that can be extremely debilitating (Helzlsouer et al. 2012), affecting quality of life and, potentially, medication adherence (Presant et al. 2007; Henry et al. 2008). Although it was thought that the severe estrogen depletion resulting from AI therapy was the primary cause of these symptoms, not all women on AIs experience musculoskeletal pain; thus, a number of other potential causes have been investigated, including insufficient vitamin D concentrations (Helzlsouer et al. 2012) and underlying autoimmune disorders (Laroche et al. 2007; Shanmugam et al. 2012). The results of these studies have been inconclusive; hence, the etiology behind the AI-association musculoskeletal symptoms remains unknown.

A more recent hypothesis is that circulating insulin-like growth factor-1 (IGF-1) plays a role in the onset of the musculoskeletal symptoms associated with AI therapy (Lintermans and Neven 2011; Lintermans et al. 2011). IGF-1 is a potent mitogen that, in circulation, is primarily bound to the IGF binding protein-3 (IGFBP-3) (Jones and Clemmons 1995). Several lines of evidence support the role of IGF-1 in the musculoskeletal symptoms experienced by breast cancer patients taking AIs. First, a recent study reported that, among healthy older women, increasing IGF-1 concentrations by growth hormone administration was associated with a significant increase in the incidence of arthralgias (Blackman et al. 2002). In addition, it is well-known that IGF-1 is regulated by estrogens, with data showing that oral estrogen suppresses circulating IGF-1 levels in postmenopausal women (Janssen et al. 2000; Bellantoni et al. 1996). Importantly, several studies have shown that IGF-1 concentrations increase with AI therapy (Bajetta et al. 1997; Ferrari et al. 2002; Lien et al. 1992), likely as a result of the total estrogen suppression caused by this drug. Finally, increases in IGF-1 and the incidence of musculoskeletal symptoms, each of which have been observed independently with AI administration, have not been observed among breast cancer patients treated with the hormone therapy tamoxifen, a drug that does not affect circulating estrogen concentrations (Decensi et al. 2003).

Thus, the goal of this study was to examine whether IGF-1 (and IGFBP-3) concentrations were associated with the onset of or increase in musculoskeletal pain among women initiating AI therapy. Data were analyzed from a prospective cohort study of breast cancer patients that also enrolled a comparison group of postmenopausal women without a history of cancer. Understanding whether IGF-1 underlies the AI-related musculoskeletal symptoms experienced by breast cancer patients is important, as therapies targeting IGF-1 exist and can potentially be employed as preventive or treatment options to manage these potentially debilitating symptoms.

MATERIALS AND METHODS

Study sample

Data were analyzed from a 6-month prospective cohort study of breast cancer patients on AIs and a comparison group of postmenopausal women without a history of cancer. Detailed methods of this study are described elsewhere (Helzlsouer et al. 2012). Briefly, women with

newly diagnosed non-metastatic postmenopausal estrogen receptor-positive breast cancer whose adjuvant treatment plan included an AI and a comparison group of postmenopausal women with no history of cancer except possibly cervical cancer in-situ or non-melanoma skin cancer were recruited from Mercy Medical Center in Baltimore, Maryland. Women who reported a history of rheumatoid arthritis or fibromyalgia were not eligible for enrollment into either group. A total of 100 breast cancer patients and 200 women without a history of cancer were enrolled; however, one breast cancer patient did not initiate AI therapy as planned. The study was approved by the Institutional Review Board at Mercy Medical Center in Baltimore, Maryland. Written informed consent was obtained from all participants.

Women enrolled into the study were asked to complete a questionnaire at a baseline visit, which occurred prior to AI treatment for the breast cancer patients, and at 3- and 6-months after baseline. The questionnaire collected information on demographics, musculoskeletal symptoms, medical history, and health habits. In addition, participants were asked to donate a blood sample at all three time points. Fifty-seven (n = 57) breast cancer patients adherent to their medication regimen (determined based on medical chart review) who had their blood drawn and analyzed for other biomarkers (vitamin D, calcium, phosphorus (Helzlsouer et al. 2012)) and provided data on pain at all three time points were included in the present study. One hundred thirty-nine (n = 139) women in the comparison group who donated blood and had data on pain and other biomarkers at baseline and 6-months were considered for possible inclusion in the present study. Of these 139 women, all 50 women in the comparison group reporting no pain at baseline and a random sample of 40 women in the comparison group reporting any pain at baseline had samples assayed for IGF-1 and IGFBP-3 and were included in the analysis.

Variable definitions

Data on age, race, height, weight, supplement use, and prior cancer treatments were collected using the self-administered questionnaire. Body mass index (BMI) was calculated using self-reported height and weight; for analyses, BMI was categorized as normal (<25.0 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (≥30.0kg/m^2).

Musculoskeletal pain was assessed at each time point by asking participants: “In the past 4 weeks, have you experienced any of the following types of pain: Joint, Muscle, Bone?” Women who responded ‘yes’ for 1 or more of the types of pain were directed to a module with more detailed pain questions pertaining to that specific type of pain. Included in that module was a 10-centimeter visual analog scale (VAS) on which the participant was asked to mark her average pain severity for each type of pain reported. Participants who responded that they did not experience a specific type of pain or who scored less than 1 on the VAS for a specific type of pain were categorized as having ‘no pain’ for that type of pain. Onset or worsening of pain (measured using participant ratings on the VAS) over the study period was examined as an outcome.

IGF assays

Serum levels of IGF-1 and IGFBP-3 were assayed in the laboratory of Dr. Michael Pollak at the Lady Davis Research Institute of the Jewish General Hospital and McGill University using chemiluminescence technology and reagents from Immunodiagnostic Systems (Boldon, Tyne & Wear, UK). Aliquots from quality control serum samples were inserted randomly. The mean intra-assay coefficients of variation for IGF-1 and IGFBP-3 for the quality control samples were 1.5% and 1.8%, respectively.

Statistical analysis

Five breast cancer patients and two women without a history of breast cancer had biomarker values outside of 3 standard deviations from the mean and were considered outliers; these participants were excluded. Thus, 52 breast cancer patients initiating AI therapy and 88 women in the comparison group comprised the analytic study sample.

All biomarker values were normally distributed and, thus, did not violate assumptions made for inferential testing. Baseline characteristics of the breast cancer patients and the women without a history of breast cancer were compared using χ^2 tests and Fisher's Exact tests. Tests of mean differences between women in the breast cancer group and women in the comparison group were analyzed using independent sample t-tests, and differences between baseline and the 6-month follow-up values were analyzed with paired t-tests separately for each group. In order to assess differences in the mean change across time between breast cancer patients and women in the comparison group, a change variable was computed for each biomarker and analyzed with independent sample t-tests. Finally, the associations between the change in biomarkers and the onset of or increase in musculoskeletal pain over time among the breast cancer patients and women in the comparison group were analyzed with independent sample t-tests and paired t-tests. Adjustment for potential confounders (age, race, BMI, smoking status) in multivariate models did not change the estimates of association; therefore, only the unadjusted associations are reported. A $p<0.05$ was considered statistically significant.

RESULTS

Of the participants included in the analytic study sample, the breast cancer patients were significantly more likely to be overweight or obese, to be of worse self-rated health, and to report being ever smokers than women in the comparison group (Table 1). There were no statistically significant differences between the groups in terms of age, race, and the baseline musculoskeletal pain. Approximately 42% of the breast cancer patients had prior chemotherapy treatment; 71.2% underwent radiation therapy.

Table 2 shows the changes in IGF-1, IGFBP-3, and the IGF-1: IGFBP-3 ratio over the 6-month study period among the breast cancer patients and the women in the comparison group. There were no statistically significant changes in any of the measures across time for either the breast cancer patients or the women in the comparison group. Further, neither the mean concentrations of IGF-1, IGFBP-3, and the IGF-1: IGFBP-3 ratio at baseline and 6-months nor the mean percent changes in each of the biomarkers was significantly different between the two groups.

The associations between the mean baseline and 6-month concentrations of IGF-1, IGFBP-3, and IGF-1: IGFBP-3 as well as the percent change in these biomarkers over the study period and the onset or worsening of pain are shown in Table 3. Among the breast cancer patients, IGF-1 concentrations increased over the study period for those reporting new onset or worsening of pain (percent change: 7.3; $p = 0.1$) but significantly decreased among those with no new pain or no worsening of pain (percent change: −9.2; $p = 0.009$; difference in percent change between two groups: $p = 0.048$). This statistically significant difference in the percent change for IGF-1 between those experiencing new onset of or worsening of pain and those with no new pain or no worsening of pain with was not observed among women in the comparison group ($p = 0.2$).

While there were no statistically significant differences in the change in IGFBP-3 concentrations across time by pain status among either group, the mean percent change in the IGF-1: IGFBP-3 ratio was significantly different among the breast cancer patients

reporting new onset or worsening of pain compared to those with no new pain or no worsening of pain ($p = 0.001$ for difference between the groups). Specifically, those experiencing new onset or worsening of pain had an increase in the IGF-1: IGFBP-3 ratio (3.8%; $p = 0.2$) while those with no new pain or no worsening of pain had a statistically significant decrease (−16.7%; $p = 0.005$). This statistically significant difference in the mean percent change of the IGF-1: IGFBP-3 ratio between those experiencing new onset of or worsening of pain and those with no new pain or no worsening of pain was not observed among women in the comparison group ($p = 0.7$).

DISCUSSION

The results of this study suggest that increases in IGF-1 concentrations over the first 6-months of AI treatment are associated with the onset or increase in musculoskeletal pain among breast cancer patients prescribed this medication. Although the magnitude of the percent increase among this group was small (7.3%), the percent change among the breast cancer patients not reporting any or an increase in musculoskeletal pain was in the opposite direction (−9.2%), and the difference in percent change between the groups was statistically significant ($p = 0.046$). Further, an association between musculoskeletal pain and IGF-1 was not observed in a comparison group of women without a history of cancer who were not taking an AI and who were followed over a similar time period. To our knowledge, this is the first study to report on such an association, providing preliminary evidence that musculoskeletal symptoms experienced by breast cancer patients taking AIs may be the result, at least in part, to changes in the IGF-1 axis.

The mechanism by which AIs reduce the risk of breast cancer recurrence and mortality is through the inhibition of the aromatase enzyme, leading to estrogen depletion, which starves the tumor of its estrogen source. Evidence supports an inverse association between endogenous estrogen and IGF-1 concentrations: first, as women age and their estrogen levels decrease, IGF-1 concentrations increase (Corpas et al. 1993); second, studies have shown that women taking oral estrogens have lower IGF-1 levels than women of the same age who are not (Holmes et al. 2002; Helle et al. 1996; Raudaskoski et al. 1998). In contrast to the results of the present study, previously published research, primarily conducted in small samples without a comparison group, has reported increases in IGF-1 concentration with the initiation of AI therapy [range of percentage increase reported over first year: 11% (Cigler et al. 2010) to 42% (Bajetta et al. 1997)] (Bajetta et al. 1997; Ferrari et al. 2002; Lien et al. 1992; Cigler et al. 2010; Frost et al. 1996). Interestingly, however, Ferrari et al. noted that, in a study of 34 postmenopausal breast cancer patients treated with anastrozole, the increase in IGF-1 measured over three months was only observed among responders, or women whose tumors responded to treatment, and not those who were not unresponsive. If musculoskeletal pain predicts AI treatment response among breast cancer patients, as suggested in a recent study by Hadji et al., the increase in IGF-1 levels may only be observed among women who experience musculoskeletal pain, as reported in the present study.

Because little is known about the etiology of AI-associated musculoskeletal symptoms, there is, to date, no specific treatment known to alleviate the pain, which may be severe. If changes in the IGF-1 axis are associated with the onset or increase in pain after AI initiation, there is the potential for treatment of this symptom with therapies that modulate the IGF-1 axis. Currently, monoclonal antibodies directed at the IGF-1 receptor are under investigation as part of a strategy to overcome resistance to adjuvant hormonal therapies among women with estrogen receptor-positive breast cancer (Hou et al. 2011; Weroha et al. 2008). It is thought that both the estrogen and IGF-1 pathways, and the cross-talk between these pathways, are involved in the development of resistance to both tamoxifen and AIs, and

certain IGF-1 receptor inhibitors have shown promise in preventing resistance to these therapies (Hou et al. 2011; Weroha et al. 2008). However, the results of this study should be replicated in a larger study, and, if similar results are found, an investigation of possible IGF-axis therapies to alleviate musculoskeletal symptoms could be a next step.

A limitation of this study is the small number of breast cancer patients in the analytic dataset. Because of the small sample size, caution should be taken when interpreting the results, which showed small statistically significant changes that may be clinically relevant. Because of the small sample size of patients in the current study, the associations between IGF-1, IGFBP-3 and musculoskeletal symptoms among women on AIs should be investigated in a larger sample. Despite this limitation, the study had several strengths, including the detailed data on musculoskeletal pain and the collection of data from a comparison group of women of the same age without a history of cancer. Data from this comparison group suggest IGF-1 may be related with AI-associated musculoskeletal pain but not musculoskeletal symptoms experienced by postmenopausal women in the general population.

AI-associated musculoskeletal symptoms can be severe, and often times can be a reason for a woman to discontinue or to be non-adherence to treatment. Adherence is key to reducing a woman's risk for recurrence from breast cancer; thus, maintaining reducing or alleviating symptoms associated with AI therapy is extremely important. Although preliminary, results from this study implicate the IGF axis in the development of AI-associated musculoskeletal pain, a first step in developing effective interventions.

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Table 1

Selected baseline characteristics of women with breast cancer (n = 52) and those in the comparison group (n = 88)

	Women with breast cancer (n = 52)		Comparison group (n = 88)		
Characteristics	**n**	**%**	**n**	**%**	**p-value***
Age (years)					0.9
<60	25	48.1	43	48.9	
≥60	27	51.9	45	51.1	
Body mass index, kg/m^2					0.037
<25.0	16	30.8	45	51.1	
25.0 to 29.9	20	38.5	19	21.6	
≥30.0	16	30.8	24	27.6	
Race					0.3
White	44	84.6	80	90.9	
Non-white	8	15.4	8	9.1	
Smoking status					0.046
Never	21	40.4	50	56.8	
Ever	30	57.7	35	39.8	
Self-rated health					<0.001
Excellent/Very Good	27	51.9	72	81.8	
Good	17	32.7	15	17.0	
Fair/ Poor	7	13.5	1	1.1	
Prior chemotherapy treatment					
Yes	22	42.3	NA	NA	NA
No	30	57.7			
Prior radiation treatment					
Yes	37	71.2	NA	NA	NA
No	15	28.8			
Any pain					0.4
Yes	27	51.9	39	44.3	
No	25	48.1	49	55.7	
Joint pain					0.9

	Women with breast cancer (n = 52)		Comparison group (n = 88)		
Characteristics	**n**	**%**	**n**	**%**	**p-value***
Yes	22	42.3	36	40.9	
No	30	57.7	52	59.1	
Muscle pain					0.4
Yes	15	28.8	20	22.7	
No	37	71.2	68	77.3	
Bone pain					0.4
Yes	7	13.5	7	8.0	
No	45	86.5	81	92.0	

Percentages for some characteristics may not add up to 100% due to missing data

*computed using χ^2 and Fisher's exact tests

Table 2

Baseline and 6-month IGF-I, IGFBP3, and IGF-I/IGFBP3 ratio concentrations among breast cancer patients initiating aromatase inhibitor therapy and women in the comparison group

	Baseline		6-months			
	n	**mean (SD)**	**n**	**mean (SD)**	**% change (range)**	**p-value** [b]
IGF-1 (ng/mL)						
Women with breast cancer	52	129.7 (39.3)	52	133.8 (42.5)	3.2 (−31.0 to 178.6)	0.4
Comparison group	88	122.7 (35.6)	88	123.5 (30.3)	0.7 (−25.9 to 114.3)	0.7
p-value		0.3[a]		0.2[a]	0.5[c]	
IGFBP-3 (ng/mL)						
Women with breast cancer	52	4244.9 (985.1)	52	4436.2 (1127.9)	4.5 (−25.2 to 107.2)	0.09
Comparison group	88	4273.9 (851.3)	88	4224.4 (730.3)	−1.2 (−34.9 to 67.8)	0.4
p-value		0.9[a]		0.1[a]	0.034[c]	
IGF-1: IGFBP-3 ratio						
Women with breast cancer	52	0.031 (0.01)	52	0.031 (0.01)	1.0 (−31.0 to 85.9)	0.7
Comparison group	88	0.029 (0.01)	88	0.030 (0.01)	2.2 (−29.2 to 41.3)	0.2
p-value		0.1[a]		0.4[a]	0.3[c]	

[a] Independent samples t-test for mean differences between women with breast cancer and the comparison group

[b] Paired t-test for mean differences between baseline and 6-month follow-up

[c] Independent samples t-test for mean change differences between women with breast cancer and the comparison group.

Table 3

Musculoskeletal pain and baseline, 6-month, and change in IGF-I, IGFBP3, and IGF1:IGFBP3 ratio concentrations among women with breast cancer patients initiating aromatase inhibitor therapy and women in the comparison group

	Women with breast cancer					
	Baseline		6-months			
	n	mean (SD)	n	mean (SD)	% change (range)	p-value [b]
IGF-1 (ng/mL)						
New or increase in pain	41	123.6 (34.1)	41	132.6 (41.9)	7.3 (−31.0 to 178.9)	0.1
No new or increase in pain	11	152.3 (49.9)	11	138.3 (46.4)	−9.2 (−24.9 to 8.4)	0.009
p-value		0.097[a]		0.7[a]	0.048[c]	
IGFBP-3 (ng/mL)						
New or increase in pain	41	4206.4 (976.2)	41	4333.4 (1093.5)	3.0 (−25.2 to 107.2)	0.3
No new or increase in pain	11	4388.3 (1052.9)	11	4819.6 (1224.6)	9.8 (−14.5 to 48.0)	0.09
p-value		0.6[a]		0.3[a]	0.3[c]	
IGF-1: IGFBP-3 ratio						
New or increase in pain	41	0.030 (0.01)	41	0.031 (0.01)	3.8 (−31.0 to 85.9)	0.2
No new or increase in pain	11	0.035 (0.01)	11	0.029 (0.01)	−16.7 (−30.8 to 14.0)	0.005
p-value		0.092[a]		0.4[a]	0.001[c]	

	Women in the comparison group					
	Baseline		6-months			
	n	mean (SD)	n	mean (SD)	% change (range)	p-value[b]
IGF-1 (ng/mL)						
New or increase in pain	49	122.9 (35.8)	49	124.3 (31.7)	1.1 (−25.9 to 114.3)	0.6
No new or increase in pain	39	122.5 (35.8)	39	122.4 (28.7)	0.01 (−25.4 to 59.2)	1.0
p-value		1.0[a]		0.8[a]	0.2[c]	
IGFBP-3 (ng/mL)						
New or increase in pain	49	4179.8 (806.0)	49	4203.5 (716.8)	0.6 (−16.1 to 67.8)	0.7
No new or increase in pain	39	4392.0 (901.7)	39	4250.8 (755.4)	−3.2 (−34.9 to 57.0)	0.2
p-value		0.3[a]		0.8[a]	0.7[c]	

	Women in the comparison group					
	Baseline		6-months			
	n	mean (SD)	n	mean (SD)	% change (range)	p-value[b]
IGF-1: IGFBP-3 ratio						
New or increase in pain	49	0.029 (0.01)	49	0.030 (0.01)	1.6 (−29.2 to 32.0)	0.5
No new or increase in pain	39	0.028 (0.01)	39	0.029 (0.01)	2.8 (−19.6 to 41.3)	0.3
p-value		0.5[a]		0.6[a]	0.7[c]	

[a]Independent samples t-test for mean differences between women who report new or increase in pain compared to no new or increase in pain

[b]Paired t-test for mean differences between baseline and 6-month follow-up

[c]Independent samples t-test for mean change differences between women who report new or increase in pain compared to no new or increase in pain