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The CIRAS study: a case control study to define the clinical, immunologic, and radiographic features of aromatase inhibitor-induced musculoskeletal symptoms

Victoria K. Shanmugam,

Division of Rheumatology, Immunology and Allergy, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC, NW 20007, USA

James McCloskey,

Lombardi Comprehensive Cancer Center, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC, NW 20007, USA

Beth Elston,

Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC, NW 20007, USA. Center for Public Health and Clinical Epidemiology, Brown University, Box G-S121-2, Providence, RI 02912, USA

Sandra J. Allison, and

Department of Musculoskeletal Ultrasound, Division of Radiology, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC, NW 20007, USA

Jennifer Eng-Wong

Lombardi Comprehensive Cancer Center, Georgetown University Hospital, 3800 Reservoir Road, Washington, DC, NW 20007, USA

Victoria K. Shanmugam: vks4@gunet.georgetown.edu; Beth Elston: beth_elston@brown.edu

Abstract

Aromatase inhibitors (AIs) are widely prescribed for post-menopausal hormone receptor-positive breast cancer; however, musculoskeletal symptoms limit their tolerability. The purpose of this study was to determine whether joint pain in women receiving AIs is associated with inflammatory arthritis as measured by the disease activity score-28 (DAS-28), and to evaluate association with tenosynovitis on ultrasound. A total of 48 postmenopausal women with stage I–III breast cancer and hand pain were recruited from the Lombardi Comprehensive Cancer Center. Those receiving AIs were cases ($n = 25$), and those not receiving AIs were controls ($n = 23$). During a single study visit, subjects underwent blinded rheumatologic evaluation, DAS-28, health assessment questionnaires, autoantibodies, inflammatory markers, hand X-ray, and hand Duplex ultrasound. There were no significant differences between cases and controls in DAS-28, or inflammatory markers. A positive ANA (titer $> 1:160$) was found in ten patients, four of whom met criteria for autoimmune disease (two with rheumatoid arthritis and two with Sjogren's syndrome, equally distributed among cases and controls). This highlights the importance of considering underlying autoimmune disease in subjects with musculoskeletal complaints. Morning stiffness was more prolonged in women receiving AIs, but this did not reach statistical significance ($P = 0.07$). Ultrasound evidence of flexor tenosynovitis was common in both groups.

Although tenosynovitis was not correlated with AI use ($P = 0.26$), there was a trend toward an association between tenosynovitis and morning stiffness ($P = 0.089$). While aromatase inhibitor-induced musculo-skeletal symptoms (AIMSS) were more common in subjects receiving AIs, they were not unique to AI users. There was no association between presence of AIMSS features and other chemotherapy or medication exposures. Although the majority of subjects had been using AIs for more than 6 months, this study did not find evidence for inflammatory arthritis in women with hand pain receiving AIs. Further studies are needed to develop a case definition of AIMSS, and to confirm whether these symptoms are attributable to AI use.

Keywords

Aromatase inhibitor; Arthralgia; Breast cancer; Ultrasound; Tenosynovitis

Introduction

Postmenopausal hormone receptor-positive breast cancer accounts for 70% of breast cancer cases, and the introduction of aromatase inhibitors (AIs) has been a major therapeutic advance in management. Several studies have demonstrated that adjuvant AIs, either as initial therapy or following 2–5 years of tamoxifen, result in a 13–40% reduction in breast cancer recurrences [1, 3, 4]. Incorporation of these agents is now standard of care in the management of postmenopausal breast cancer [5, 6].

One of the major side effects of AIs is the development of musculoskeletal symptoms. These symptoms were originally referred to as Arthralgia Syndrome [7–9], but more recently the term AI-induced musculoskeletal symptoms (AIMSS) has been used to describe the constellation of joint pain [7, 9–13], symmetric morning stiffness improving with activity [7], a sensation of abrupt aging [14], and soft tissue thickening [9]. Carpal tunnel syndrome has also been demonstrated in a group of women with other symptoms of AIMSS [15]. The hands and wrists are the most common sites of pain, but any joint may be affected [16]. While these features have all been recognized under the auspices of AIMSS, there are no formal diagnostic criteria for this syndrome. Most studies rely on elevation of pain scores in conjunction with AI use to define the syndrome.

Reports on the incidence of AIMSS in patients using AIs vary widely due to differing definitions of the syndrome. In adjuvant trials of third generation AIs (anastrozole, letrozole, and exemestane), the prevalence of bone and joint symptoms was between 5 and 36% [2, 3]. However, more recent studies performed outside of clinical trials suggest that the prevalence is even higher. In a cross sectional survey of women on AIs, 47% of women had joint pain, and 44% had joint stiffness attributable to AIs [17]. Development of musculoskeletal symptoms is thought to contribute to the poor compliance associated with AIs; however, studies also suggest that joint complaints are also associated with better outcomes and less risk of breast cancer recurrence [18].

The mechanisms by which AIMSS develop remain unknown, and several studies have incorporated rheumatologic assessment to investigate whether the symptoms can be attributed to an underlying rheumatologic process. The results are conflicting. Henry et al. performed a prospective study of 97 patients enrolled in a clinical trial comparing two AIs in which patients exceeding threshold scores on health assessment questionnaires (HAQ) and visual analog pain scales (VASs) were evaluated by rheumatology. Of the patients referred for rheumatologic evaluation, 16.2% had a positive antinuclear antibody (ANA) but none had definable autoimmune disease [19]. LaRouche et al. studied a group of 24 women receiving AIs with pain VAS > 5 and found a positive ANA in 37.5% (9 of 24). They report

a higher than expected frequency of Sjogren's syndrome in this group; however, they did not utilize standard diagnostic criteria or biopsy data to make this diagnosis [20]. Both of these studies are limited since only subjects receiving AIs with musculoskeletal complaints were evaluated by the rheumatologist. Moxley incorporated a rheumatologic joint exam, symptom questionnaires, and clinical tests for carpal tunnel syndrome into an audit of 77 consecutive breast cancer clinic outpatients (including 31 receiving AIs, five who had discontinued AI due to arthralgia or osteoporosis and 41 who had never received AI) [21]. This study found a high frequency of hand osteoarthritis (OA) in AI users with joint pain, but this was not significantly elevated compared to non-AI users. The author postulates that altered nociceptive mechanisms triggered by estrogen deprivation in AI users may increase symptomatology from common rheumatologic conditions such as OA and carpal tunnel syndrome. Other authors have similarly hypothesized that AIMSS may represent an exacerbation of "menopausal arthritis" secondary to abrupt estrogen inhibition [7].

Imaging studies in AS have all involved only small numbers of patients. Morales et al. evaluated 33 post-menopausal breast cancer patients (27 receiving AI and six on tamoxifen) using magnetic resonance imaging (MRI) and found an association between AI use, tenosynovial abnormalities, intra-articular fluid, morning stiffness, and reduced grip strength [10, 13, 22]. Studies using ultrasound have similarly found evidence of localized tenosynovitis in AI users [11, 15], and prospective studies suggest that baseline tenosynovial abnormalities may be a risk factor for development of AIMSS [11]. It has been postulated that tenosynovial changes might represent an inflammatory response to estrogen deficiency or that they may be secondary to AI-induced changes in the growth hormone insulin-like growth factor-1 [13, 23].

As with the symptom studies, a major limitation of the imaging studies is that there is no consistent selection of control subjects for this syndrome. While musculoskeletal symptoms are more prominent in AI users, the ATAC study found that patients using tamoxifen also exhibited a high incidence of musculoskeletal complaints [2]. In the MRI study described by Morales et al. and Lintermans et al. although, MRI findings were more frequent in AI users, tenosynovial changes and intra-articular fluid changes from baseline were also seen on MRI in two (33%) and three (50%) of the tamoxifen users, respectively [13, 22]. Other studies suggest that prior use of tamoxifen use may be protective against development of AIMSS [16]. To date, no study has investigated imaging and inflammatory features of post-menopausal breast cancer survivors with joint pain and compared features of subjects receiving AIs to those not receiving AIs. The purpose of the CIRAS study was to evaluate breast cancer survivors with hand pain and compare clinical, immunologic, and radiographic features in those receiving AIs (cases) to those not receiving AIs (controls). To test the primary hypothesis that joint pain in AI users is associated with inflammatory arthritis, our primary outcome measure was the DAS-28, a standardized measure of disease activity in rheumatoid arthritis, which incorporates clinical assessment of synovitis with inflammatory markers [24, 25]. Secondary end-points included the presence of tenosynovitis on Duplex ultrasound, 25-hydroxy-vitamin D levels, other inflammatory indices, and presence of symptoms consistent with the AIMSS.

Methods

The study was approved by the Georgetown University Institutional Review Board (IRB 2008-547, ClinicalTrials.gov #NCT00890058) and all enrolled patients provided written informed consent before completing any testing.

Patient recruitment

A total of 48 stage I–III postmenopausal breast cancer patients with hand pain were recruited from breast cancer follow-up clinics at the Lombardi Comprehensive Cancer Center. Subjects with previously diagnosed autoimmune diseases were excluded. Subjects receiving AIs were considered to be cases ($n = 25$) and those not receiving AIs were controls ($n = 23$). All investigators except the research assistants performing the informed consent (BE and JM) were blinded as to the subjects case or control status. Subjects were requested to abstain from non-steroidal anti-inflammatory drugs (NSAID) for 48 h before the study visit. All investigations and assessments were completed during a single study visit as shown in the study schema (Fig. 1).

Rheumatologic assessment

A single rheumatologist (VKS) completed the history and physical examination, and assessed the tender and swollen joint counts to allow computation of the DAS-28. The use of tender and swollen joint counts and the DAS-28 scale as an outcome measure in this study was based on the extensive use of these outcomes as measures of inflammatory arthritis in clinical trials. It should be noted that there are recognized limitations regarding inter-observer differences in joint counts [26], but studies show that inter and intra-observer correlations can be improved with specialized training of the examiner. In order to maintain integrity of the joint count assessment in this study, a single rheumatologist with experience assessing tender and swollen joint counts in the assessment of patients with RA performed all of the joint examinations.

Assessment of AIMSS features

Since there no published criteria to define AIMSS, we used published reports of the syndrome [16] to identify the most commonly associated features (Table 1). Women were questioned and examined for the presence of the five reported AIMSS features, and all patients had Phalens and Tinnel's testing to assess for carpal tunnel compression. For the purposes of this study, presence of 4 out of five features was used to define AIMSS presence.

Timing of pain onset

Time of pain onset was captured from two sources to try to account for possible recall bias. All patients were questioned as to the time of pain onset during the history and physical exam performed by the rheumatologist. This was then corroborated using data from the oncology clinic chart notes. After unblinding, the duration of pain since AI onset was then calculated for the cases using both data sources.

Assessment of other rheumatologic diseases

Rheumatologic evaluation including history and physical exam was completed on all women to evaluate for American College of Rheumatology criteria for OA [27], fibromyalgia [28], and autoimmune diseases including systemic lupus erythematosus [29], RA [30], scleroderma [31, 32], and Sjogren's syndrome (SjS) [33, 34].

Medication exposures

Medication exposures were captured using patient self report for current and over-the-counter medication. Review of oncology clinic chart notes was used to confirm current medication and capture prior medication exposures, including prior exposures to endocrine agents, chemotherapy, and other adjunctive therapies.

Functional and quality of life questionnaires

All subjects completed a VAS and the Patient Reported Outcome Measurement Information System-Health Assessment Questionnaire (PROMIS-HAQ, Aramis, Stanford, CA). This validated questionnaire is used to assess quality of life and functional status in clinical studies in RA and OA [35].

Laboratory testing

The following blood tests were performed by Quest Diagnostics Nichols Institute: westergren erythrocyte sedimentation rate (ESR) C-reactive protein (CRP, immunoturbidimetric method), antinuclear antibody (ANA, immunofluorescence using HEp2 cell assay), rheumatoid factor (RF, enzyme linked immunosorbent assay), anti-cyclic citrullinated peptide (CCP, immunoassay), and 25-hydroxy-vitamin D levels (liquid chromatography and tandem mass spectrometry).

DAS-28 calculation

The DAS-28, an index of disease activity in inflammatory arthritis which has been well validated in clinical trials of RA, was calculated based on the tender and swollen joint count and the CRP according to established protocol [36]. While there are different DAS-28 calculations that incorporate either ESR, or CRP, CRP was used in the current study since it is thought to be a more direct measure of inflammation than ESR and is more sensitive to short-term changes [37, 38].

Radiographic and ultrasound imaging

All subjects underwent bilateral hand radiographs and bilateral hand ultrasound. Hand radiographs were evaluated by a blinded radiologist for the presence of features suggestive of inflammatory arthritis including joint space narrowing, erosions, and periarticular osteopenia and for the presence of features of OA using the methodology described by Kessler et al. [39].

Hand ultrasound was performed with a Philips Medical Systems iU22 ultrasound system by a single investigator (SJA). Patients were imaged using a 17 MHz transducer; gray scale images were taken, and power Doppler analysis was performed. Use of power Doppler allows rapid and reproducible assessment of presence or absence of increased vascularity which may indicate flexor tenosynovitis. All five digits on both hands were evaluated for the presence or absence of fluid in the tendon sheath, increased vascularity in the sheath or tendon, or tendon sheath thickening (shown in Fig. 2), which are all suggestive of flexor tenosynovitis. In addition, presence or absence of fluid in the metacarpophalangeal (MCP) joints and soft tissue edema was recorded. Results were scored as present (1) or absent (0) for each digit, and a total ultrasound score was computed.

Statistical methods

To evaluate the primary hypothesis that joint pain associated with AI use is an inflammatory arthritis, the primary endpoint in this study was the difference in DAS-28 between cases and controls. Based on studies in RA, the minimum clinically important difference in DAS-28 is 1.2, and RA is considered to be in remission if the DAS-28 is less than 2.6 [40]. Using a two-sided t-test, α level of 0.05 and power of 80% we estimated that we needed to recruit 24 subjects in each group to show a difference of 1.2 (SD 2.00).

Data was analyzed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA). Unpaired t-test and Mann-Whitney *U* Test were used for continuous

variables, and Fisher's exact test was used for dichotomous variables. The P values were always two-tailed, and a $P < 0.05$ was considered significant.

Results

Patient characteristics

There were no significant differences between cases and controls in mean age, time since menopause, or time since breast cancer diagnosis (Table 2). The mean duration of AI use in the cases at the time of enrollment was 1.5 years (median 0.83 years, range 0.04–4.99 years). There was no difference in the number of women previously or currently using tamoxifen, or in the number of women using NSAIDs at enrollment. Body mass index (BMI) was similar in both groups.

DAS-28 and features of inflammatory arthritis

There was no significant difference between the two groups in DAS-28, ESR, or mean morning stiffness (Fig. 3). Total PROMIS-HAQ score and score on the pain component of the PROMIS-HAQ were also similar in cases and controls ($P = 0.91$ and $P = 0.31$, respectively). Reliance on hand pain as an inclusion criterion likely contributed to the high pain score for the control group.

Autoimmune evaluation

A positive ANA at a titer $>1:160$ was found in four controls and six cases ($P = 0.39$). Two patients were identified with previously undiagnosed Sjogren's syndrome and two had previously undiagnosed rheumatoid arthritis. These conditions were evenly distributed among cases and controls.

25-Hydroxy-vitamin D level

Mean 25-hydroxy-vitamin D level was similar in the cases and controls (Table 2, 30.2 ng/mL compared to 33.4 ng/mL, $P = 0.38$).

Prevalence of OA

OA was present clinically in ten of the cases and 11 of the controls ($P = 0.77$). Radiographic evidence of OA was seen in 15 of the cases and 14 of the controls (Table 2, $P = 0.95$); and the number of joints affected based on the radiographic hand OA scale was not significantly different between the two groups. These findings are consistent with the expected prevalence of OA in a group of symptomatic post-menopausal women.

Duration of AI use before pain

Based on patient reporting the mean (SD) duration of AI use before development of pain was 0.87 (1.22) years. Oncology records were also reviewed, and revealed a mean (SD) duration of AI use before development of pain in this population of 1.64 (2.79) years.

AIMSS features

Of the 48 patients enrolled in the CIRAS study, 25 had 4/5 AIMSS features. While AIMSS features were more common in cases than controls (Table 2, $P = 0.04$), it should be noted that eight women in the control arm, several of whom had never been exposed to endocrine therapy, had symptoms consistent with AIMSS. This finding suggests that the constellation of symptoms referred to as AIMSS may not be unique to AI users, and this observation should be considered when planning further studies of this syndrome.

Ultrasound findings

Doppler ultrasound revealed no significant difference between cases and controls in frequency of flexor tenosynovitis, soft tissue edema, or fluid in the MCP joints (Table 3). When ultrasound data was re-analyzed based on the presence of AIMSS features, flexor tenosynovitis was seen in 14 out of 25 subjects with AIMSS features and only 7 of 23 subjects without AIMSS features which was approaching statistical significance ($P = 0.089$, Table 3).

Medication exposures

As described above, of the eight control subjects who had symptoms consistent with AIMSS, three were receiving tamoxifen and five were not receiving any endocrine therapy. This raises the question as to whether the AIMSS is solely related to endocrine therapy or related to some other feature of breast cancer treatment. Exposure to cyclophosphamide and adriamycin was more common in the control arm than the cases, but we suspect this was due to these drugs being more commonly selected for women with estrogen receptor negative tumors. The two groups were otherwise well matched in terms of chemotherapy and other medication exposures (Table 4). Notably, we did not find any significant differences in the exposure to bisphosphonates or biologic therapy in the two groups.

In the control arm, five women had previously received AI therapy, one had completed her course of therapy, one discontinued early due to osteoporosis, and the reason for discontinuation in the three other women was not documented.

Discussion

Based on the results of this study, we did not find evidence to support an inflammatory basis for AIMSS. We identified a higher than expected frequency of positive ANA and previously undiagnosed autoimmune disease, but these issues were evenly distributed among cases and controls, suggesting they are likely not related to medication exposure, and simply reiterating the importance of a thorough rheumatologic work-up for symptomatic patients.

Our study had several important limitations which impact the generalizability of the findings and merit discussion. First, the case definition for AIMSS remains a major challenge. While there are no formal diagnostic criteria for this syndrome, using presence of 4 out of 5 AIMSS features, we found that while AIMSS features were more common in women actively using AIs, they were also seen in some women in the control arm. Although our control group included a small number of women with prior exposure to AI's, none of the women in the control group had used an AI in the 3 months before study enrollment. The half-lives of AIs range from 27 to 50 h [41, 42]. Therefore, even those women with prior exposure to these agents should not have been experiencing therapeutic effects at the time of study enrollment. Furthermore, several of the women in the control arm who exhibited AIMSS features had never received endocrine therapy. This suggests that AIMSS may not be unique to AI users. Data from the large clinical trials comparing AIs and tamoxifen support this observation, showing that while joint complaints are significantly more common in women receiving AIs (35.6% compared to 29.4%, $P < 0.001$), they are also seen in a substantial proportion of women receiving tamoxifen [2, 18]. Previous imaging studies comparing MRI findings in response to endocrine therapy have shown that while increase in MRI tenosynovial changes and intra-articular fluid changes from baseline were more frequent in AI users, some tamoxifen users also exhibited changes over 6 months of endocrine therapy [13, 22]. In view of these observations, we did examine other medication exposures in our cohort, but could not identify any other therapy that correlated with AIMSS features in this small sample.

A second limitation of our study was the small sample size. The original sample size calculation was based on detecting a difference in DAS-28, and not ultrasonographic changes. We did not find a significant difference in DAS-28, and we were not able to demonstrate a significant association between AI use and tenosynovitis, likely due to the small sample size. Other studies evaluating ultrasonographic changes of tenosynovitis in AIMSS suggest that tenosynovial changes may correlate with, or predispose to, syndrome development [11].

Finally, the population studied had more prolonged AI exposure than in other studies of AIMSS, and more than half the patients had previously used tamoxifen. Our study may therefore not have captured patients early in syndrome development, particularly those naïve to endocrine therapy, and this may limit generalizability of our findings. Prior studies of this syndrome suggest that women develop severe joint complaints within 6 months of starting AIs [16]. However, in our cohort, the mean duration of AI use before pain development based on both patient and physician reporting was greater than 6 months. Our data suggests that prior studies may have underestimated the duration of AI use before symptom development in this syndrome. Another possibility is that early symptomatic AIMSS differs from the joint complaints exhibited later in some AI users, and this should be considered both in the interpretation of our findings and in the design of future studies.

The importance of continuing to study AIMSS is 2-fold. First, despite numerous studies showing benefit of endocrine therapy, and while breast cancer survivors are generally well motivated [43], several studies have reported up to 50% of patients started on endocrine therapies discontinue them before completion of the recommended duration [44, 45]. A recent study evaluating rates of switching and discontinuing endocrine therapies found that of patients followed for 5 years, only 49% continuously used endocrine therapy [46]. While this study was not designed to evaluate rationale for treatment cessation, clinical studies of AIs suggest that approximately 5–13% of women discontinue therapy due to the development of musculoskeletal symptoms [4, 47]. Community-based studies suggest the rates of discontinuation attributable to joint complaints may be as high as 20% [48], underscoring the impact of these symptoms on compliance in breast cancer survivors. Since post-hoc analysis of long-term follow-up studies of endocrine therapy show that presence of joint complaints correlates with reduced recurrence [18], the syndrome may actually be a surrogate marker of either drug efficacy or reduced recurrence risk, and as such it merits further investigation to determine pathogenesis.

Future studies need to focus on developing diagnostic criteria for this syndrome so that the relationship with AI use, other therapies, and recurrence risk can be clarified. If this syndrome is indeed shown to be associated with reduced breast cancer recurrence, then improved understanding of the pathophysiology could yield important insights into mechanisms that both drive tenosynovitis and regulate breast cancer recurrence. Finally, better understanding of this syndrome will be vital to improving drug compliance and tolerability.

Conclusion

The current study did not find evidence for inflammatory arthritis in this group of AI users with joint pain. It should be noted that the majority of the population studied had been on AI for more than 6 months at the time of study and more than half had previously received tamoxifen therapy. Notably in this cohort, AIMSS features were not unique to AI users, and this may have limited the power of this study to detect small differences in inflammatory indices. Further studies are needed to better understand the mechanism underlying

musculoskeletal symptoms in breast cancer survivors, and interventions which might improve tolerability of endocrine therapy.

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Abbreviations

AI	Aromatase inhibitor
ANA	Antinuclear antibody
AIMSS	Aromatase inhibitor-induced musculoskeletal symptoms
ATAC study	Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer [1, 2]
BMI	Body mass index
CCP	Anti-cyclic citrullinated peptide antibody
CIRAS study	A case control study to define the clinical, immunologic, and radiographic features of aromatase inhibitor-induced musculoskeletal symptoms
CRP	C-reactive protein
DAS-28	Disease activity score-28
ESR	Erythrocyte sedimentation rate
HAQ	Health assessment questionnaire
NSAID	Non-steroidal anti-inflammatory drug
MCP	Metacarpophalangeal joint
MRI	Magnetic resonance imaging
OA	Osteoarthritis
PROMIS-HAQ	Patient reported outcome measurement information system-health assessment questionnaire
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SjS	Sjogren's syndrome
VAS	Visual analog scale of pain

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Fig. 1.
CIRAS study schema. All evaluations and tests were performed during a single study visit. Subjects were requested to abstain from non-steroidal anti-inflammatory (NSAID) use for 48 h before this visit

Fig. 2. Ultrasound power Doppler images showing tendon sheath thickening in the left fourth flexor tendon consistent with flexor tenosynovitis (*arrow*). Adjacent digit has normal tendon sheath for comparison

Fig. 3.

Mean and SEM of a DAS-28, b ESR and c morning stiffness duration in the cases and controls. While no significant differences were seen in DAS-28 or ESR between cases and controls, the duration of morning stiffness was higher in the cases and this was trending towards significance ($P=0.07$)

Table 1

Features of AIMSS based on published reports

Reported features of AIMSS (references)
Symmetric joint pain [7, 9–13]
Symmetric morning stiffness [7]
Sensation of having aged abruptly [14]
Sensation of thickening of the soft tissues [9]
Carpal tunnel syndrome [15]

For the purposes of this study, we used presence of 4/5 of these features to define presence of AIMSS

Table 2

Demographic characteristics and associated rheumatologic conditions in subjects enrolled in the CIRAS study

		CONTROLS <i>n</i> = 23	CASES <i>n</i> = 25	<i>P</i>
Demographics	Caucasian	21	23	1.00
	African American	0	2	
	Other	2	0	
	Mean (SD) age (years)	62.2 (9.9)	60.8 (9.4)	0.60
	Mean (SD) time since menopause (years)	10.9 (6.8)	8.7 (6.9)	0.33
	Mean (SD) time since breast cancer diagnosis (years)	6.2 (5.4)	5.5 (4.9)	0.64
	Mean (SD) body mass index	27.97 (6.55)	26.91 (5.09)	0.73
Endocrine therapy	Median duration of AI use, years (range)		0.83 (0.04–4.99)	
	Prior or current Tamoxifen exposure (<i>n</i>)	14	14	1.00
	Prior AI use (<i>n</i> , controls only)	5	–	
NSAID exposure	NSAID use at time of enrollment (<i>n</i>)	16	14	0.38
Inflammatory features	Mean (SD) duration of morning stiffness (hours)	1.4 (1.4)	2.4 (2.1)	0.07
	DAS-28	2.3 ± 0.2	2.3 ± 0.1	0.27
	Mean (SD) ESR (mm/hr)	18.5 (13.8)	17.1(15.2)	0.74
	Mean (SD) total PROMIS-HAQ score	10.1 (12.1)	9.7 (9.1)	0.91
	Mean (SD) PROMIS-HAQ pain score	42.8 (26.4)	34.9 (27.3)	0.31
25-OH-Vitamin D	Mean (SD) Vitamin D (ng/ml)	30.2 (12.2)	33.4 (12.4)	0.38
Autoimmune features	Number of pts with ANA titer > 1:160)	4	6	0.39
	Number of pts fulfilling ACR criteria for SjS	1	1	1.00
	Number of pts fulfilling ACR criteria for RA	1	1	1.00
Osteoarthritis features	Number of patients fulfilling ACR criteria for OA	11	10	0.77
	Number of patients with radiographic OA	15	14	0.95
	Mean (SD) radiographic OA joint score	5.3 (6.8)	2.79 (4.6)	0.14
AIMSS features	Number of patients with 4/5 AIMSS features	8	17	0.04

Data was analyzed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA). Unpaired *t*-test and Mann–Whitney *U*-Test were used for continuous variables, and Fisher's exact test was used for dichotomous variables. The *P* values were always two-tailed, and a *P* < 0.05 was considered significant

Table 3

Results from power Doppler ultrasound of the hands

	Controls <i>n</i> = 23	Cases <i>n</i> = 25	<i>P</i>	AIMSS absent <i>n</i> = 23	AIMSS present <i>n</i> = 25	<i>P</i>
Flexor tenosynovitis	8	13	0.26	7	14	0.089
Fluid in MCP joints	4	9	0.20	5	8	0.52
Soft tissue edema	12	16	0.56	11	17	0.25
Tendon sheath thickening	6	5	0.74	3	8	0.17
Mean ultrasound score	6.6	4.9	0.26	9.00	13.8	0.092
Tendon nodules	3	0	0.24	1	2	1.00
DeQuervain's tenosynovitis	4	2	0.67	3	3	1.00
Ganglion cysts	8	8	1.00	8	8	1.00

While there were no significant differences in the ultrasound findings between cases and controls, there was an association between presence of AIMSS features and flexor tenosynovitis which was trending toward significance (*P*0.089)

Table 4
Chemotherapy and other therapy exposures in cases and controls, and subjects with and without AIMSS features

	CONTROLS <i>n</i> = 23		CASES <i>n</i> = 25		RR	<i>P</i>	AIMSS absent <i>n</i> = 23		AIMSS present <i>n</i> = 25		RR	<i>P</i>
Chemotherapy												
Paclitaxel	11		6	0.57	0.13		6		11	1.43	0.24	
Docetaxel	1		1	0.96	1.00		0		2	2.00	0.49	
Doxorubicin	18		12	0.55	0.04		12		18	1.54	0.23	
Cyclophosphamide	19		13	0.54	0.03		13		19	1.58	0.22	
Fluorouracil	0		4	2.10	0.11		0		4	2.09	0.11	
Bevacizumab	4		1	0.36	0.18		3		2	0.75	0.66	
Trastuzumab	4		1	0.36	0.18		2		3	1.73	1.00	
Bisphosphonate	10		11	1.01	1.00		8		13	1.39	0.26	