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ORIGINAL ARTICLE

Risk factors for joint symptoms in postmenopausal Japanese breast cancer patients treated with anastrozole: a prospective multicenter cohort study of patient-reported outcomes

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Abstract

Background Endocrine treatment-related adverse events have a strong impact on patients' quality of life and sometimes result in treatment discontinuation. Since joint symptoms are the most frequently recognized side effect of aromatase inhibitors, evaluation of associated risk factors may yield significant findings.

Patients and methods A total of 391 postmenopausal Japanese women with estrogen receptor-positive breast cancer and treated with adjuvant anastrozole were enrolled from 28 centers for assessment of patient-reported

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outcomes (PROs) in this prospective cohort study (SAVS-JP, UMIN000002455). Patients completed the self-report questionnaire at baseline and after 3, 6, 9, and 12 months of treatment for evaluation of frequency of treatment-related joint symptoms (arthralgia, decrease in range of joint motion, and joint stiffness).

Results We obtained PROs from 362 patients (92.6 %) at baseline and at one or more subsequent points. New or worsening from baseline of joint symptoms were reported by 260 patients (71.8 %). More than 90 % of the symptoms were mild or moderate and nearly 80 % had occurred by 6 months. Multivariate analysis showed that a short time span after menopause [odds ratio (OR) 0.95, 95 % confidence interval (CI) 0.90–0.99; $P = 0.02$] and adjuvant chemotherapy (OR 2.29, 95 % CI 1.06–4.95; $P = 0.03$) were significant independent risk factors for joint symptoms. No significant relationships between body mass index (BMI) and joint symptoms were identified. Eighteen patients discontinued treatment during the 1st year and eight of them reported joint symptoms.

Conclusion Taking into consideration that PROs may yield higher prevalence rates than physician ratings for symptoms published in pivotal clinical trials, we found that a short time span after menopause and use of adjuvant chemotherapy, but not high BMI, were significantly associated with joint symptoms. These findings might prove useful for counseling before initiating treatment with adjuvant aromatase inhibitors in postmenopausal Japanese women.

Keywords Breast cancer · Aromatase inhibitor · Joint symptoms · Patient-reported outcomes

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Background

Adjuvant endocrine treatment-related adverse events have a strong impact on patients' quality of life and sometimes result in treatment discontinuation. Of these adverse events induced by diminishing estrogen levels, joint symptoms including joint pain and arthralgia are the most frequently recognized side effects associated with aromatase inhibitors [1]. In pivotal trials conducted with large number of patients, increased incidence of arthralgia, arthritis, and joint pain have been established for patients using adjuvant aromatase inhibitors. The frequency of occurrence of arthralgia in patients using letrozole has been reported as 489 out of 2448 (20.0 %) [2]. Similarly, anastrozole-related arthralgia reportedly occurred in 1100 out of 3092 (35.6 %) postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [3]. These findings strongly suggest a high-frequency occurrence of joint symptoms related to aromatase inhibitors. Crew et al. analyzed risk factors for joint symptoms induced by aromatase inhibitors among 200 postmenopausal women and found that overweight [body mass index (BMI) of 25–30 kg/m^2] and prior tamoxifen therapy were inversely associated with joint symptoms [4]. On the other hand, taxane chemotherapy correlated significantly with higher frequency of joint pain and stiffness. Furthermore, an analysis by Sestak et al. of risk factors associated with joint symptoms in patients enrolled in the ATAC trial, in which 2735 women were enrolled in the tamoxifen group and 2698 women in the anastrozole group [5], showed that 829 (30.3 %) patients assigned to the former and 949 (35.2 %) assigned to the latter group experienced joint symptoms (arthralgia, arthrosis, arthritis, or joint disorder). Multivariate analysis of these findings indicated that previous hormone replacement therapy (HRT), previous chemotherapy, positive hormone receptor status, and high BMI (>30 kg/m^2) were significantly associated with joint symptoms. According to these reports, it was speculated that factors related to the estrogen environment, including HRT and BMI as well as chemotherapy, were associated with joint symptoms.

Two studies to evaluate aromatase inhibitor-related joint symptoms in Japanese women have been reported to date. Ohsako et al. investigated 53 patients treated with anastrozole and identified joint symptoms in 14 (26 %) [6], with such symptoms tending to occur more frequently in patients with previous chemotherapy. In addition, a study by Yamamoto et al. reported that 29.4 % of postmenopausal women complained of aromatase inhibitor-related joint symptoms among 507 patients treated with adjuvant (78 %) or metastatic (22 %) therapies [7]. They also found that aromatase-induced joint symptoms correlated significantly with young age, previous chemotherapy, and switching from tamoxifen to aromatase inhibitors.

Since aromatase-related joint symptoms seem to result in discontinuation more frequently, evaluation of associated risk factors may well yield significant results. However, the two aforementioned studies were of a small number of women or retrospective. In addition, since various factors such as BMI and usage of HRT differ between western and Japanese postmenopausal women, we conducted a prospective cohort study based on patient-reported outcomes (PROs) of Japanese breast cancer patients treated with adjuvant anastrozole in order to identify the risk factors for aromatase inhibitor-related joint symptoms.

Patients and methods

Study design and eligible criteria

Postmenopausal Japanese women with estrogen receptor-positive breast cancer and treated with adjuvant anastrozole were enrolled in this prospective cohort study (SAVS-JP, UMIN000002455). Postmenopausal status was assessed locally of patients with whose last menstruation was more than 1 year previously or who had undergone bilateral oophorectomy. Four patients were enrolled because of amenorrhea induced by chemotherapy. A total of 416 patients were recruited from 28 centers, mostly in the Hyogo area. We obtained PROs from 391 (94.0 %) patients at baseline and reports at one or more time points during treatment from 362 (92.6 %) of the baseline responders. These 362 patients were therefore included in further analyses. This study was approved by the Ethics Committee of Hyogo College of Medicine or each institute. Written informed consent was obtained from each participant.

Data assessment

The patient-reported assessments were obtained at their after-care appointments between August 2009 and April 2012. Patients completed the self-report questionnaire at baseline and at 3, 6, 9, and 12 months. Symptoms were assessed and assigned to one of four categories: none; grade 1: mild ("I feel symptoms, but can easily ignore them"); grade 2: moderate ("I always feel symptoms, but can live as usual"); grade 3: severe ("the symptoms sometimes interfere with my daily activities"). The questionnaires covered joint symptoms (arthralgia, decrease in range of joint motion, and joint stiffness), vasomotor symptoms (hot flashes, night sweats, and cold sweats), and adherence to anastrozole. Pre-existing symptoms were included only if they had worsened from baseline. Clinicopathological characteristics for each patient were also obtained with the case report form.

Statistical analysis

The frequencies of joint symptoms at baseline and during anastrozole treatment were analyzed with the chi-squared test or Fisher's exact test as appropriate. The relationships between joint symptoms and clinicopathological factors were calculated with the chi-squared test, Fisher's exact test, and Mann–Whitney tests. BMI was defined as weight (kg)/[height (m)]^2, and the risk of joint symptoms, based on the results of univariate and multivariate analyses, was determined with the logistic regression method to obtain the odds ratios (ORs) and 95 % confidence intervals (95 % CIs). Statistical significance was set at $P < 0.05$ and JMP10 software (SAS Institute Japan, Tokyo, Japan) was used for all the analyses.

Results

Frequency of joint symptoms associated with aromatase inhibitor

Clinicopatholgical characteristics of the initial 391 participants in this study are listed in Table 1. At baseline, arthralgia (26.1 %), decrease in range of joint motion (14.1 %), and joint stiffness (19.4 %) were recorded for these participants (Table 2). Of the 134 patients who had joint symptoms at baseline, 88 were on medication for hyperlipidemia ($n = 26$), hypertension ($n = 20$), osteoporosis ($n = 12$), rheumatoid arthritis ($n = 8$), diabetes mellitus ($n = 7$), angina pectoris or myocardial infarction ($n = 5$), hypothyroidism ($n = 4$), asthma ($n = 2$), hyperthyroidism ($n = 1$), spinal canal stenosis ($n = 1$), osteoarthritis ($n = 1$), and others ($n = 11$). Tranquilizers or sleep-inducing drugs ($n = 14$), nonsteroidal anti-inflammatory drugs ($n = 8$), and anticoagulants ($n = 4$) were also used by some of these patients. Significantly higher frequencies of these symptoms were identified at any point between 3 to 12 months during treatment with anastrozole. First appearance of symptoms during treatment in patients who had no symptoms at baseline were reported by 161 out of 289 (55.7 %) patients for arthralgia, 139 out of 336 (41.4 %) for decrease in range of joint motion, and 193 out of 315 (61.3 %) for joint stiffness. More than 60 % of these symptoms were grade 1, while grade 3 was experienced by less than 6 % of patients (Table 3). When any of the above three symptoms were defined as joint symptoms, which were observed in 34.3 % at baseline, they had increased to 66.9 % at 12 months (Fig. 1). Of the 260 patients who developed newly occurring or worsening joint symptoms compared to baseline, 138 patients (53.1 %) did so within 3 months, followed by 63 (24.2 %) at 3–6 months, 32

Table 1 Patient background, clinicopathological characteristics and breast cancer treatments

Characteristics	$n = 391$
Age (years)[a]	63.8 (36–86)
BMI (kg/m^2)[a]	23.1 (15.8–39.9)
Age at menarche (years)[a]	13.5 (10–20)
Age at menopause (years)[a]	49.9 (28–59)
Parity	
Yes (%)	382 (83.9 %)
No (%)	61 (15.6 %)
Unknown	2 (0.5 %)
Breast cancer family history[b]	
Yes (%)	78 (19.9 %)
No (%)	311 (79.5 %)
Unknown	2 (0.5 %)
Ovarian cancer family history[b]	
Yes (%)	15 (3.8 %)
No (%)	375 (95.9 %)
Unknown	1 (0.3 %)
Histological type	
Invasive ductal carcinoma	341 (87.2 %)
Invasive lobular carcinoma	10 (2.5 %)
Non-invasive carcinoma	12 (3.1 %)
Others	16 (4.1 %)
Unknown	12 (3.1 %)
Clinical stage	
0	12 (3.1 %)
I	200 (51.2 %)
IIA	115 (29.4 %)
IIB	42 (10.7 %)
IIIA	3 (0.8 %)
IIIB	9 (2.3 %)
IIIC	4 (1.0 %)
Unknown	6 (1.5 %)
Progesterone receptor	
Positive	291 (74.4 %)
Negative	93 (23.8 %)
Unknown	7 (1.8 %)
HER2	
Positive	42 (10.7 %)
Negative	335 (85.7 %)
Unknown	14 (3.6 %)
Chemotherapy	
Pre-operatively[c]	24 (6.1 %)
Post-operatively[c]	68 (17.4 %)
No	300 (76.7 %)
Chemotherapy regimen	
Anthracyclines	19 (20.7 %)
Anthracyclines and taxanes	47 (51.1 %)
TC[d]	25 (27.2 %)
Taxane	1 (1.1 %)
Trastuzumab treatment	
Yes	31 (7.9 %)
No	313 (91.3 %)
Unknown	3 (0.8 %)
Radiation therapy	
Yes	229 (58.6 %)
No	157 (40.2 %)
Unknown	5 (1.3 %)
Anastrozole continuation	
On treatment	368 (94.1 %)
Off treatment	18 (4.6 %)
Unknown	5 (1.3 %)

[a] Mean (range)

[b] 1st and 2nd degree relatives

[c] One case was treated both pre- and post-operatively

[d] Docetaxel and cyclophosphamide

(12.3 %) at 6–9 months, and 27 (10.4 %) at 9–12 months (Fig. 2). The mean time to onset of joint symptoms was 5.4 months, and nearly 80 % of the symptoms occurred within 6 months.

Risk factors associated with joint symptoms

The findings of an analysis of the clinicopathological factors induced by anastrozole are listed in Table 4. Mean age (62.9 years, range 36–82) of patients who developed joint symptoms was significantly ($P = 0.009$) younger than that of patients who did not (65.5 years, range 37–86). Age at menopause of the patients with joint symptoms (50.1 years, range 28–58) was significantly ($P = 0.01$) higher than that of patients without joint symptoms (49.2 years, range 35–59). Number of years after menopause were significantly ($P = 0.0005$) shorter for patients with joint symptoms (12.5 years, range 0–37) than for those without symptoms (16.4 years, range 0–51). In addition, patients treated with adjuvant chemotherapy before starting anastrozole manifested a significantly ($P = 0.003$) higher frequency of joint symptoms (86.4 vs 68.6 %). Next, we categorized BMI into three groups in accordance with previously defined criteria (low <25, intermediate 25–30, high >30 mg/m^2) [5], but could find no significant relationships between BMI and joint symptoms, nor for other factors including previous HRT, suffering from menopausal disorders, neoadjuvant chemotherapy, and radiation therapy.

The relationships of joint symptoms with clinical factors were further analyzed by dividing the symptoms into arthralgia, diminished joint motion, and joint stiffness. Significant associations with age and number of

Table 2 Frequency of joint symptom occurrence for patients at baseline and after anastrozole treatment

	Baseline ($n = 391$)	3 months ($n = 343$)	6 months ($n = 335$)	9 months ($n = 329$)	12 months ($n = 305$)
Arthralgia	102 (26.1 %)	133 (38.8 %)[a]	155 (46.3 %)[b]	163 (49.5 %)[b]	166 (54.4 %)[b]
Decrease of joint motion	55 (14.1 %)	80 (23.3 %)[c]	97 (29.0 %)[b]	91 (27.7 %)[b]	104 (34.1 %)[b]
Joint stiffness	76 (19.4 %)	134 (39.1 %)[b]	157 (46.9 %)[b]	165 (50.2 %)[b]	182 (59.7 %)[b]
New appearance or worsening from baseline					
Arthralgia		84 (24.5 %)	101 (30.1 %)	119 (36.2 %)	114 (37.4 %)
Decrease of joint motion		57 (16.6 %)	76 (22.7 %)	63 (19.1 %)	81 (26.6 %)
Joint stiffness		93 (27.1 %)	122 (36.4 %)	135 (41.0 %)	151 (49.5 %)

Statistical calculations were done with the chi-squared test

[a] $P = 0.0002$

[b] $P < 0.0001$

[c] $P = 0.0012$

Table 3 Maximal grades of joint symptoms developing during anastrozole treatment in patients without joint symptoms at baseline

	Arthralgia	Decrease of joint motion	Joint stiffness
Grade 1	103 (64.0 %)	96 (69.1 %)	122 (63.2 %)
Grade 2	53 (32.9 %)	41 (29.5 %)	61 (31.6 %)
Grade 3	5 (3.1 %)	2 (1.4 %)	10 (5.2 %)
Total	161 (100 %)	139 (100 %)	193 (100 %)

postmenopausal years were consistently recognized irrespective of individual joint symptoms. On the other hand, age at menopause was significantly associated only with joint stiffness ($P = 0.01$), and administration of adjuvant chemotherapy with joint motion ($P = 0.0092$) and joint stiffness ($P = 0.0007$).

Univariate analysis indicated that age, time span after menopause, and adjuvant chemotherapy were significantly associated with development of joint symptoms (Table 5). Multivariate analysis of these factors identified number of years after menopause (OR 0.95, 95 % CI 0.90–0.99; $P = 0.02$) and adjuvant chemotherapy (OR 2.29, 95 % CI 1.06–4.95; $P = 0.03$) as significant independent risk factors for joint symptoms. Next, we combined both chemotherapy and number of years after menopause as shown in Fig. 3, demonstrating that 45 out of 49 (91.8 %) patients with chemotherapy and 0–15 years after menopause onset had developed joint symptoms (Fig. 3). On the other hand, joint symptoms were reported by 62.1 % of the patients with no prior chemotherapy and those with ≥16 years after menopause.

Discontinuation of anastrozole

Eighteen patients discontinued treatment during the first year and eight of them suffered from joint symptoms

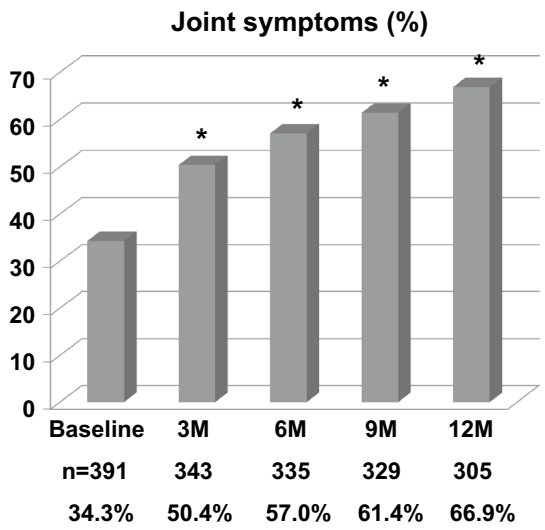

Fig. 1 Frequency of joint symptom occurrences at baseline and 3, 6, 9, and 12 months. Statistical calculations were performed with the chi-squared test. *$P < 0.05$

according to medical records (Table 6). Grade 2 and grade 3 joint symptoms were reported by three (37.5 %) and four (50.0 %) of these patients, respectively.

Discussion

In the present study, the incidence of anastrozole-related joint symptoms (arthralgia, decrease in range of joint motion, and joint stiffness) was 34.3 % at baseline and 66.9 % at 12 months. Nearly 80 % of new or worsening from baseline joint symptoms had developed by 6 months and more than 60 % of these symptoms were grade 1. Multivariate analysis, short time span after menopause, and

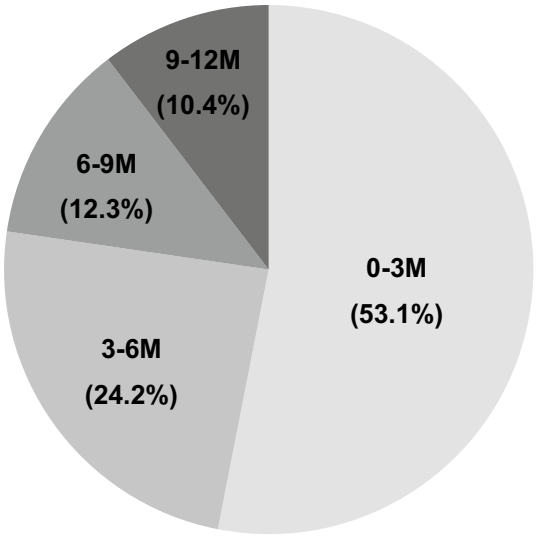

Fig. 2 Appearance of new joint symptoms or worsening of pre-existing joint symptoms

previous adjuvant chemotherapy were significant independent risk factors for joint symptoms. During the 1st year of anastrozole administration, 260 out of 362 (71.8 %) patients reported experiencing first appearance or worse joint symptoms from baseline. This incidence seems to be higher than prevalence rates for symptoms as defined and rated by physicians as published in pivotal clinical trials, which reported 20–35 % frequencies for joint symptoms [2, 3, 5]. Since data obtained by physicians may be underestimated, the incorporation of PROs might yield a more accurate assessment of a patient's actual symptoms. For Sestak et al.'s study [5], anastrozole-related joint symptoms (35.2 %) were collected in free-text format on the case report form but it is not certain whether all joint symptoms were covered. However, self-reported data showed that 47 % of subjects reported suffering joint pain and 44 % joint stiffness [4], while the percentage suffering joint pain was 59.6 % as recorded from PROs [8]. Values obtained from PROs thus tend to be higher than those obtained by physicians or from

Table 4 Clinical risk factors of patients treated with anastrozole and with and without joint symptoms

	With joint symptoms ($n = 260$)	No joint symptoms ($n = 102$)	P value
Age (years)[a]	62.9 (36–82)	65.5 (37–86)	0.009
Body mass index			
<25 kg/m^2	197 (75.8 %)	78 (76.5 %)	0.48
≥25, ≤30 kg/m^2	52 (20.0 %)	17 (16.7 %)	
>30 kg/m^2	11 (4.2 %)	7 (6.9 %)	
Age at menopause (years)[a]	50.1 (28–58)	49.2 (35–59)	0.01
Years from menopause[a]	12.5 (0–37)	16.4 (0–51)	0.0005
Previous hormone replacement therapy			
Yes	21 (8.1 %)	9 (8.8 %)	0.73
No	236 (90.8 %)	93 (91.2 %)	
Unknown	3 (1.2 %)	0 (0 %)	
Experience of menopausal disorders at menopause			
Yes	147 (56.5 %)	49 (48.0 %)	0.21
No	112 (43.1 %)	52 (51.0 %)	
Unknown	1 (0.4 %)	1 (1.0 %)	
Neoadjuvant chemotherapy			
Yes	18 (6.9 %)	4 (3.9 %)	0.28
No	242 (93.1 %)	98 (96.1 %)	
Adjuvant chemotherapy			
Yes	57 (21.9 %)	9 (8.8 %)	0.003
No	203 (78.1 %)	93 (91.2 %)	
Radiation therapy			
Yes	158 (60.8 %)	56 (54.9 %)	0.31
No	100 (38.5 %)	44 (43.1 %)	
Unknown	2 (0.8 %)	2 (2.0 %)	

Statistical calculations were done with the chi-squared test, Fisher's exact test, or Mann–Whitney tests

[a] Mean (range)

Table 5 Univariate and multivariate analyses of risk factors for joint symptoms in patients treated with anastrozole

	Univariate analysis OR (95 % CI)[a]	*P* value	Multivariate analysis OR (95 % CI)[a]	*P* value
Age (years)	0.96 (0.93–0.99)	0.006	1.01 (0.97–1.07)	0.49
Body mass index				
<25 kg/m^2	1.00			
≥25, ≤30 kg/m^2	1.21 (0.66–2.22)	0.53		
>30 kg/m^2	0.62 (0.23–1.66)	0.34		
Age at menopause (years)	1.04 (0.99–1.09)	0.10		
Years from menopause	0.95 (0.93–0.98)	0.0004	0.95 (0.90–0.99)	0.02
Previous hormone replacement therapy	0.92 (0.41–2.08)	0.84		
Experience of menopausal disorders at menopause	1.39 (0.88–2.21)	0.15		
Neoadjuvant chemotherapy	1.82 (0.60–5.52)	0.28		
Adjuvant chemotherapy	2.90 (1.38–6.11)	0.005	2.29 (1.06–4.95)	0.03
Radiation therapy	1.24 (0.78–1.98)	0.36		

Statistical calculations were done with the logistic regression method

[a] Odds ratio (95 % confidence interval)

medical records. Sestak et al. extracted only data for women who had not reported joint symptoms at entry [5], but we collected data for both first appearance and worsening from baseline symptoms. This difference in entry criteria might also help to explain the higher prevalence rates in our study.

Perimenopausal women or with a short-time postmenopausal status are generally frequently aware of menopausal disorders including vasomotor symptoms [9]. Although the exact mechanism of aromatase-related joint symptoms is unknown, they seem to be associated with estrogen deficiency. This speculation might at least partly explain why younger women and those with a short time of postmenopausal status experience joint symptoms, since estrogen deficiency induced by aromatase inhibitors seems to have a stronger effect on these women. Similarly, the fact that higher serum estrogen levels have been noted in obese postmenopausal women [10] suggests that the reduction of estrogen levels by aromatase inhibitors may induce more frequent joint symptoms. Consistent with this speculation, Sestak et al. reported that high BMI (>30 kg/m^2) in women was significantly associated with appearance of joint symptoms (OR 1.33, 95 % CI 1.14–1.55; $P < 0.0001$) [5]. However, Crew et al.'s study [4] and ours found no association of high BMI (>30 kg/m^2) with joint symptoms. Since the number of Japanese women with high BMI in our study was very small (18 women), further studies with larger numbers need to be done. Similarly, Sestak et al.'s study reported a significant association of HRT with high prevalence of joint symptoms (OR 1.53, 95 % CI 1.35–1.74; $P < 0.0001$) [5], but no such association was observed in our study. However, the percentage of previous HRT users was 35.2 % in Sestak et al.'s report, but the ratio for Japanese women was only 8.3 % in our study, such that we cannot reach any conclusion regarding this issue because of the small sample number.

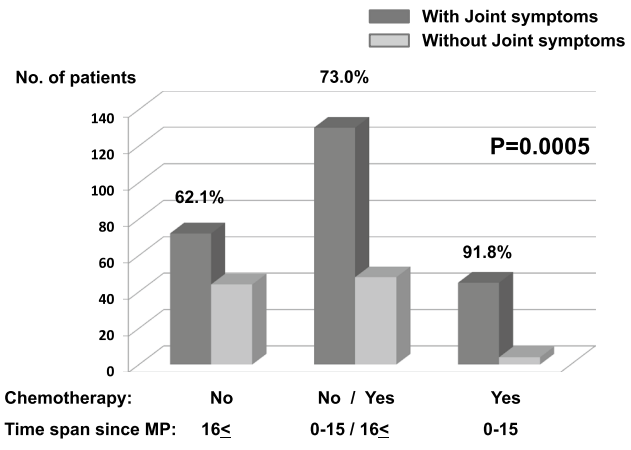

Fig. 3 Effects of chemotherapy and number of postmenopausal years on joint symptoms. Statistical calculations were performed with Fisher's exact test

Table 6 Discontinuation of anastrozole by patients with and without joint symptoms

	3 months ($n = 343$)	6 months ($n = 335$)	9 months ($n = 329$)	12 months ($n = 305$)
Discontinuation				
With joint symptoms	1	2	3	2
Without joint symptoms	3	0	2	1
Not evaluated	3	0	1	0
Total	7	2	6	3

The positive association between previous chemotherapy and joint symptoms is consistent across publications. It is well established that chemotherapy induces joint symptoms including arthralgia and myalgia [11]. The additive or synergistic effects of both chemotherapy and aromatase therapy seem to induce higher prevalence rates of joint symptoms. Interestingly, when joint symptoms were analyzed only for women who experienced new development, chemotherapy was found to have no impact on joint symptoms (53.0 vs 47.0 %). We therefore speculate that deteriorating symptoms are induced by anastrozole in patients who have developed chemotherapy-related joint symptoms. Crew et al.'s study reported that taxane but not doxorubicin chemotherapy was associated with joint pain and joint stiffness [4]. In our study, there was no indication of associations between type of chemotherapy regimen and occurrence of joint symptoms (data not shown). Since the frequency of joint symptoms at baseline was significantly higher for patients using medication, complications associated with patients' backgrounds could have influenced the occurrence of joint symptoms. However, we were able to confirm that there was no significant association between the appearance of new or the worsening of existing joint symptoms and use of medication, so that we believe medication is unlikely to influence such occurrences.

It has been reported that 2.1–7.9 % of women discontinued the use of aromatase inhibitors because of related joint symptoms [7], and 18 patients (4.6 %) in our study stopped using them within 12 months. There was no significant difference between occurrence of joint symptoms and discontinuation of anastrozole. However, since the frequency of discontinuation (16.7 %) among patients with grade 3 joint symptoms was significantly higher than among those with grade 1 (0.7 %) or grade 2 (3.1 %), the patients with grade 3 joint symptoms may have stopped due to the development of joint symptoms. The findings of univariate analyses indicated that the number of postmenopausal years and use of adjuvant chemotherapy were both associated with joint symptoms. However, separate analyses for newly developed joint symptoms and worsening of existing joint symptoms showed that the number of postmenopausal years was the only significant risk factor for the development of new joint symptoms (OR 0.98, 95 % CI 0.95–0.99; $P = 0.047$). Adjuvant chemotherapy, on the other hand, was exclusively and significantly associated with worsening of joint symptoms (OR 1.93, 95 % CI 1.07–3.46; $P = 0.028$). However, these data may not be conclusive due to the small number of samples. Of the 118 patients who had joint symptoms at baseline, 35 (29.7 %) reported improvement of symptoms during the treatment course. The reason for this improvement could not be determined, but only 2 (5.7 %) of these 35 patients were treated with adjuvant chemotherapy. These issues need to be investigated in a future study with a larger number of patients.

In conclusion, we have demonstrated that joint symptoms related to anastrozole occurred at a high frequency within the 1st year. Most of these symptoms started within 6 months and were of mild or moderate intensity. Multivariate analysis identified that previous chemotherapy and short time span after menopause were risk factors for joint symptoms. To the best of our knowledge, this is the first report of a prospective cohort study based on PROs of Japanese postmenopausal women treated with adjuvant anastrozole. These findings should prove useful for counseling before initiating treatment with adjuvant aromatase inhibitors in postmenopausal Japanese women.

Compliance with ethical standards

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Conflict of interest Yasuo Miyoshi has received research funding and honoraria from Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., GlaxoSmithKline K.K., Novartis Pharma K.K., and Taiho Pharmaceutical Co., Ltd. All other authors of this manuscript have no conflict of interest.

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