Arthralgia among Breast Cancer Patients Receiving Adjuvant Aromatase Inhibitors

Alaa Fayed [1]; Mostafa M. Toom [1]; Ahmad Alattar [1]; Abd Almotaleb Mohamad [1]; Khaled A. Mansour [1]; Reham A.Salem [1]; Nabila Hefzi, [1]; Saed M. Yosef [1]; Amal F.Gharib [2]; Wael H. Elsawy [1].

Departments of [1]Clinical Oncology, [2]Medical Biochemistry, Faculty of Medicine, Zagazig University. Egypt
fayed_alaa@yahoo.com

Abstract: The aim of this study was to determine the rate of arthralgia among breast cancer patients who received AI at our institution, to determine the onset of AI-related arthralgia in relation to initiating AI therapy, to explore the clinical and demographic risk factors associated with AI arthralgia, and finally to find out the clinical presentation of AI arthralgia. We carried out a cross-sectional survey that included 200 postmenopausal patients with stages I to III hormone receptor–positive breast cancer who were currently taking a third-generation AI for at least 3 months and were seen between January 2010 and August 2013. Medical and demographic data were collected via medical chart review and using patient self-report data measures that included age, marital status, educational level, current employment status, date of last menstrual period and entry into menopause. The main outcomes were self-report data measures of any joint pain or stiffness before starting or worsened after initiating AI treatment, location of affected joints, severity of joint pain or stiffness on a 0 to10 scale, use of oral medications to relieve joint symptoms, degree of pain relief from these oral medications on a 0 to 10 scale, and use of non-pharmacologic interventions to relieve joint symptoms. Of all patients, AI-related arthralgia was reported in 90 patients (45%): 44 (22%) had new-onset joint pain, and 46 patients (23%) had worsening of prior joint pain after starting adjuvant AI treatment. 62 patients (69%) of those who reported AI-related arthralgia experienced moderate to severe symptoms. Six patients (6.7%) out of the ninety who had AI-related arthralgia reported the start of arthralgia after initiation of AI treatment; another six patients (6.7%) reported the onset within the first week of treatment, thirty two (35.6%) recorded the onset within the remaining first month, twenty four (26.6 %) within the first 3 months, eight (8.9%) within the first 6 months 14 (15.5 %) noticed the onset after the first 6 months. Thus, about 75% of AI-related arthralgia has been recorded within the first 3 months after the initiation of treatment. Younger age, full-time employment status, rebound level of serum estrogen and fewer years since last menstrual period were associated with greater AI-related arthralgia in bivariate analyses. However, time since last menstrual period was the only factor associated with reporting AI related arthralgia in the multivariate analyses. The wrist/hand (61.5%) followed by knee (58%), were the most common sites of joint pain. Our study suggests that AI-arthralgia is more prevalent than what has been estimated previously in clinical trials. The success of AI therapy depends on patients' ability to adhere to treatment recommendations; therefore, additional studies of interventions that may alleviate these symptoms are needed.
[Alaa Fayed, Mostafa M. Toom, Ahmad Alattar, , Abd Almotaleb Mohamad, Khaled A. Mansour, Reham A.Salem, Nabila Hefzi, Saed M. Yosef, Amal F. Gharib, Wael H. Elsawy. **Arthralgia among Breast Cancer Patients Receiving Adjuvant Aromatase Inhibitors.** *Life Sci J* 2013; 10(4): 2303-2310]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 307

Key words: Arthralgia, Breast Cancer, Aromatase Inhibitors

1.Introduction

The aromatase inhibitors (AIs) are now a standard of care in the management of postmenopausal women with hormone receptor–positive breast cancer.[1] AIs suppress plasma estrogen levels in postmenopausal women by inhibiting the enzyme responsible for the conversion of androgens to estrogens in peripheral tissues (skin, muscle, fat, and benign and malignant breast tissue).[2]Although their exact etiology is unknown, AI-associated arthralgia are likely related, at least in some degree, to estrogen deprivation, given estrogen's role in collagen maintenance and modulation of pain perception.[3]

Adverse effects of AIs include a higher risk for bone fractures and arthralgia, the latter being a clinical symptom defined as nonspecific pain in the joints. In one of the first reports of arthralgia associated with anastrozole treatment, 16% of women with metastatic breast cancer developed joint pain within 2 months of starting treatment. [4]

The incidence of musculoskeletal (msk) symptoms in phase III clinical trials of anastrozole, letrozole, and exemestane has been reviewed, and women on those AIs have shown significantly higher rates of arthralgia than are seen with tamoxifen. In a specific study investigating arthralgia in 200 patients on AIs, 47% of patients reported AI-related joint pain, and 44% reported stiffness. [5] Typically, patients on AIs experience stiffness, achiness, or pain that is frequently symmetric, occurring in the hands, arms, knees, feet, and pelvic and hip bones. In addition,

patients on AIs may develop tenosynovial changes, including fluid in the tendon sheath, increased tendon thickness, trigger finger, and carpal tunnel syndrome (CTS). [6]

In AI trials in which the intensity of pain was reported (Breast International Group 1-98, for example), pain was usually mild, with 58% of women on letrozole experiencing pain categorized as grade 1, and 33% grade 2.[7]The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial reported that pain symptoms resolved within 6–18 months (50% and 75% of patients respectively). [8] Nevertheless, pain has a considerable impact on quality of life in women on AI therapy. In a prospective study of 100 patients on either letrozole or exemestane, 45.4% developed joint symptoms meeting criteria for rheumatology referral. Median time to development of symptoms was 1.6 months, and 13% of patients discontinued therapy after a median period of 6.1 months.[6] Discontinuation rates on account of pain have not been reported in large clinical trials, but rates as high as 20% have been noted in studies outside of such trials.[9]

Few studies have carried out to determine the risk factors that may be associated with onset of arthralgia in women on AI therapy. In the ATAC trial, risk factors for arthralgia (regardless of whether patients were on anastrozole or tamoxifen) included previous chemotherapy, previous hormone replacement therapy, hormone receptor positivity, and obesity.[10] In a study carried out by Crew et al. investigating the prevalence of pain in women with early-stage breast cancer on AI therapy, those who had received prior taxane therapy had a likelihood of experiencing pain that was increased by a factor of 4.[5]

Because there is increasing awareness that poor compliance due to AI arthralgia may compromise the future effectiveness of therapy, we conducted this study to better identify the characteristics of AI related arthralgia. Thus the aim of this study was to determine the rate of arthralgia among breast cancer patients who received AI at our institution, to determine the onset of AI-related arthralgia in relation to initiating AI therapy, to explore the clinical and demographic risk factors associated with AI arthralgia, and finally to find out the clinical presentation of AI arthralgia.

2. Study Design and Patients

We carried out a cross-sectional survey at the Clinical Oncology and Nuclear Medicine department in Zagazig University. The survey included all postmenopausal women with stages I to III hormone receptor–positive breast cancer who were currently taking a third-generation AI (anastrozole, letrozole, or exemestane) for at least 3 months and were seen between January 2010 and August 2013. Additional inclusion criteria were the patient's ability to understand and provide written informed consent in Arabic. Using a cross-sectional design, 231 patients screened for the study, 4 (1.7%) declined enrollment, 12 (5.2%) were ineligible due to discontinuation of AI therapy or development of metastatic disease, and 15 (6.5%) did not show up for their scheduled follow-up, leaving a total of 200 patients. After obtaining an informed consent, each patient was given a self-administered 25-item survey in Arabic. All patients were unaware of the study hypothesis, but were told that the survey was being conducted to assess for potential adverse effects related to their cancer treatments.

Measurement of outcome

Medical and demographic data were collected via medical chart review and using patient self-report data measures. Patient self-report data measures included age, marital status, educational level, current employment status, date of last menstrual period (LMP) and entry into menopause. Medical data included height, weight, body mass index, date of breast cancer diagnosis, stage at diagnosis, tumor size, axillary lymph node status, tumor grade, hormone receptor status, time on AI therapy, and previous/current cancer treatment (i.e., surgery, chemotherapy, radiation therapy, and hormonal therapy).

The main outcomes were self-report data measures of any joint pain or stiffness before starting or worsened after initiating AI treatment, location of affected joints, severity of joint pain or stiffness on a 0 to10 scale, use of oral medications to relieve joint symptoms, degree of pain relief from these oral medications on a 0 to 10 scale, and use of non-pharmacologic interventions to relieve joint symptoms. The questions on pain or stiffness severity and degree of pain/stiffness relief were adapted from the Brief Pain Inventory Short Form.[10] Also assessment of location of affected joints was adapted from standard geriatric pain assessment scales. On the 11-point scale, patients were categorized as having mild symptoms if they reported a score of 1 to 4, moderate symptoms if they reported a score of 5 to 7, and severe symptoms if the score was 8 or more. To determine the presence of AI-related arthralgia, women were asked, "Have you had any joint pain/stiffness in the past week?" and then subsequently asked, "Did this joint pain/stiffness get worse after initiating treatment with an aromatase inhibitor?" and "Did you have joint pain/stiffness which started after starting treatment with an aromatase inhibitor?"

Serum estrogen (E2) was measured using a specific immunometric assay kit (Immulite; Diagnostic Products Corporation, Los Angeles, CA, USA).The serum levels of E2 were assayed before administration of the AI and then at 3, 6, 9, and 12 months after starting the AI treatment. The laboratory's standard value for the postmenopausal levels of this hormone is 10–40 pg/mL. If the patient is maintained E2 at ≥5 pg/mL for more than 6 consecutive months following treatment with AI, such patient was categorized as "rebound" cases while all other patients were categorized as "decreased" cases. "Decreased" cases were also categorized If E2 was transiently increased or did not decreased initially after treatment with AI but decreased with 6 months from AI treatment.

Statistical Analysis

Epi Info™ 7 (7.1.2), was used for data analysis. Descriptive statistics and bivariate analyses were performed initially, after that multivariate logistic regression was created to determine the influence of each variable on AI related arthralgia. Chi-square analyses were done to compare patients with AI-related arthralgia and those without. Statistical tests were 2-sided, and *P* values <.05 indicated significance except in the exploratory analyses for joint-specific arthralgias.

3. Results:

Patient's characteristics:

Patient's characteristics are described in Table 1. The median age was 59 years (range, 45 to 70 years).40 patients (20%) reported having had their LMP within the 5 years before entry into the study, 64 patients (32%) had their LMP between 5 years and 10 years before entry, and 96 patients (48%) had their LMP >10 years. Natural menopause was experienced in 122 patients (61%), radiation induced menopause was underwent in thirty six (18%) and chemically induced menopause was reported in forty two patients (21%).

The median duration of AI treatment was 18 months (range 3 to 66 months), the majority of patients received anastrozole, one hundred and fourteen patients (57%), 44 patients (22%) received letrozole while exemestane was received by 42 patients (21%).

Of all patients, AI-related arthralgia was reported in 90 patients (45%): 44 (22%) had new-onset joint pain, and 46 patients (23%) had worsening of prior joint pain after starting adjuvant AI treatment. 62 patients (69%) of those who reported AI-related arthralgia experienced moderate to severe symptoms.

Six patients (6.7%) out of the ninety who had AI-related arthralgia reported the start of arthralgia after initiation of AI treatment; another six patients (6.7%) reported the onset within the first week of treatment, thirty two (35.6%) recorded the onset within the remaining first month, twenty four (26.6 %) within the first 3 months, eight (8.9%) within the first 6 months 14 (15.5 %) noticed the onset after the first 6 months. Thus, about 75% of AI-related arthralgia has been recorded within the first 3 months after the initiation of treatment.

Predicting Factors for aromatase inhibitor-related arthralgia

Younger age, full-time employment status, rebound level of serum estrogen and fewer years since LMP were associated with greater AI-related arthralgia in bivariate analyses (Tables 1, 2). However, time since LMP was the only factor associated with reporting AI related arthralgia in the multivariate analyses (Table 3). Patients who had their LMP within the last 5 years were significantly more likely to report AI-related arthralgia than women who had their LMP >10 years previously (adjusted OR, 3.34; 95% CI, 1.19-9.37; *P* = .02).The probabilities of reporting AI-related arthralgia after Adjusting for covariates were 0.73 (95% CI, 0.59-0.84) for LMP within 5 years, 0.48 (95% CI, 0.37-0.58) for LMP between 5 years and 10 years, and 0.35 (95% CI, 0.28-0.44) for LMP >10 years.

Joint-Specific Aromatase Inhibitor-Related Arthralgia

We examined manifestations of AI-related arthralgia in specific joints because arthralgia in different joints may have different underlying pathophysiologic mechanisms and differential impact on function and quality of life. The wrist/hand (61.5%) followed by knee (58%), were the most common sites of joint pain in patients who had AI-related arthralgia followed in decreasing frequency by joints of the back (53.4%), ankle/foot (50.7%), and hip (43%).The average number of joints affected in patients with joint pain was greater in individuals who had AI-related arthralgia than who did not (3.7 affected joints vs. 2.3 affected joints; *P* < .001).The knee (24%) and the wrist/hand (21.7%) joints showed the worst arthralgia related to AI followed by the joints of the back (17.1%), the ankle/foot (12.9%), and the hip (10%). Compared with the patients who did not have AI-related arthralgia, the patients who reported AI-related arthralgia were significantly more likely to report arthralgia in the wrist/hand (relative risk [RR], 1.91; 95% CI, 1.49-2.51), the elbow (RR, 1.75; 95% CI, 1.40-2.20), the ankle/foot (RR, 1.69; 95% CI, 1.32-2.12), and the knee (RR, 1.49; 95% CI, 1.18-1.97) (Table 4).

Table 1: Demographic characteristics (N=200)

Characteristics	No. of patients	No. of patients with arthralgia	%	*P**
Total	200	90		
Age, years				
< 55	42	26	62	0.012
55-65	76	36	47	
> 65	82	68	34	
Marital status				
Married	184	80	43.5	0.62
Single	16	10	62.5	
Educational level				
Less than high school	68	28	41	
High school graduate	62	30	48	0.27
College graduate	42	20	48	
Post college education	28	12	43	
Employment				
Employed	68	28	41	0.04
Not employed	132	62	47	

* Values based on chi square test

Table 2: Clinical and treatment characteristics (N=200)

Characteristics	No. of patients	No. of patients with pain	%	*P**
Total	200	90		
Time since LMP, y				
<5	40	30	75	**<0.001**
5-10	64	28	47	
>10	96	32	33	
Body mass index, kg/m2				
<25	74	34	46	0.67
25-30	62	28	45	
>30	64	28	44	
Stage				
I	68	28	41	0.39
II	98	48	49	
III	34	14	41	
Chemotherapy				
None	74	30	40	0.08
Chemotherapy But no taxane	68	28	41	
Chemotherapy included taxane	58	32	55	
Previous tamoxifen				
None	108	48	44	0.59
Yes	92	42	45	
AI				
Anastrozole	114	48	42	0.71
Letrozole	44	22	50	
Exemestane	42	20	47	
Duration of AI therapy, y				
<1	76	36	47	0.14
1-3	60	26	43	
>3	64	28	44	
Entry to menopause				
Natural	122	54	44	0.19
Radiotherapy or chemotherapy	78	36	46	
Change of serum estrogen				
Rebound	52	24	46	0.04
decreased	148	64	68	
Previous arthritis				
None	138	64	46	0.29
Yes	62	26	42	

* Values based on chi square test

Table 3: multivariate adjusted odds ratios for the association of AI-related arthralgia with demographic and clinical characteristics

Patient characteristics	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	AOR (95% CI)	*P*
Age, y				
<55 (reference group)	1		1	
55-65	0.51 (0.38-1.00)	0.05	0.93 (0.40-2.13)	0.90
>65	0.34 (0.14-0.60)	<0.001	0.75 (0.25-2.27)	0.61
Employment				
Full time (reference group)	1		1	
Part time	0.61 (0.33-1.32)	0.20	0.59 (0.26-1.41)	0.24
Not currently	0.39 (0.22-0.68)	<0.001	0.60 (0.31-1.09)	0.11
Time since LMP, y				
>10 (reference group)	1		1	
5-10	1.54 (0.91-2.60)	0.07	1.05 (0.51-2.19)	0.72
<5	4.59 (2.24-9.51)	<0.001	3.34 (1.19-9.37)	0.02
Chemotherapy				
None (reference group)	1		1	
Chemotherapy but no taxane	1.45 (0.83-2.48)	0.13	1.01 (0.51-1.91)	0.84
Chemotherapy included taxane	1.89 (1.05-3.45)	0.03	1.06 (0.51-2.13)	0.83
No. of comorbid conditions				
None (reference group)	1		1	
1	0.71 (0.41-1.29)	0.35	0.93 (0.47-1.86)	0.89
≥2	0.51 (0.35-0.93)	0.04	0.90 (0.44-1.74)	0.79
Duration of AI therapy, y				
<1 (reference group)	1		1	
1-3	1.02 (0.50-1.89)	0.34	0.90 (0.44-1.81)	0.69
>3	0.55 (0.13-2.29)	0.29	0.23 (2.12)	0.79
Prior tamoxifen				
No (reference group)	1		1	
Yes	0.77 (0.36-1.61)	0.33	0.41 (0.14-1.17)	0.51
Change of serum estrogen				
Rebound	1		1	
decreased	2.52 (1.01-6.62)	0.04	2.28 (0.70-7.40)	0.67
Aromatase inhibitor				
Anastrozole (reference group)	1		1	
Letrozole	1.39 (0.55-3.49)	0.89	1.54 (0.60-3.41)	0.82
Exemestane	1.31 (0.51-3.11)	0.41	1.67 (0.61- 2.06)	0.61

OR indicates odds ratio; CI, confidence interval; AOR, adjusted odds ratio; LMP, last menstrual period.

Table 4: Joint specific AI-related arthralgia

Joint location with pain	RR (95% CI)*	*P*
Upper extremity		
Shoulder	1.15 (0.88-1.49)	0.20
Elbow	1.75 (1.40-2.20)	<0.001
Wrist/hand	1.91 (1.49-2.51)	<0.001
Core body		
Neck	1.21 (0.9101.52)	0.12
Back	1.46 (1.13-1.86)	0.001
Lower extremity		
Hip	1.43 (1.13-1.81)	0.002
Knee	1.49 (1.18-1.97)	<0.001
Ankle/feet	1.69 (1.32-2.12)	<0.001

RR indicates relative risk; CI, confidence interval.

* The RRs are based on chi-square comparisons between breast cancer survivors with and without aromatase inhibitor-related arthralgia.

4. Discussion

In the present study, we tried to evaluate AI-related arthralgia according to the patient's perceptions. Forty-five percent of patients in included in the present study developed AI-related arthralgia, although arthralgia in a postmenopausal breast cancer patient is usually multifactorial in nature. The majority of patients reported arthralgia within the first 3 months from the starting of AIs, and 69% of them classified their arthralgia as moderate or severe. When evaluating the demographic and clinical factors that may contribute to AI-related arthralgia, we noticed that the time from LMP was related inversely to the report of AI-related arthralgia, and those with less than 5 years from their menopause had a 3-folds increase in the likelihood of complaining of AI-related arthralgia compared with those who were 10 years post-menopause. Furthermore, we found that multiple joints can be affected, wrists/hands, elbows, ankles/feet, and knees may be the most vulnerable to AI-related arthralgia.

In postmenopausal patients with early-stage hormone-sensitive breast cancer, AI became the standard of care. Several studies show that 23% to 40% of women discontinue tamoxifen early despite its known benefits.[11] AIs have a better adverse effect profile compared with tamoxifen, but its associated musculoskeletal events may leads to poor compliance, a lower quality of life and suboptimal adherence to treatment. In study analyzing medical and pharmacy claims data found that adherence to adjuvant anastrozole therapy decreased from 69% to 78% in year 1 to 50% to 68% in year 3.[12]

The pathogenesis of AI-related arthralgia is unknown, but it is thought to be due to estrogen deprivation. Cecil and Archer [13], 80 years ago first described “arthritis of the menopause” as the rapid development of hand and knee osteoarthritis (OA) coinciding with cessation of menses. In addition, studies of the incidence and prevalence of OA in postmenopausal women with and without hormone replacement therapy (HRT) has provided strong support for a protective effect of estrogens in OA.[14, 15]HRT reduces the incidence of radiologic knee OA, and increases tibial cartilage volume.[16] In a randomized controlled trial of HRT, the Heart and Estrogen/Progestin Replacement Study found no difference in the prevalence of knee pain with or without HRT (24.1% and 26.1%, respectively).[17] But the Women’s Health Initiative recently reported a difference in the incidence of any joint pain or swelling in postmenopausal women taking estrogen compared with those who were not taking estrogen (70.6% v 77.2%; *P*=.01).[18]

The clinical characteristics of AI-related arthralgias have not been well described. Morales *et al.* [20] examined 12 consecutive non-metastatic breast cancer patients taking AIs who reported severe musculoskeletal pain. They reported characteristic teno-synovial joint changes on joint ultrasound and magnetic resonance imaging, which included fluid in the digital flexor tendon sheaths on ultrasound and tendon sheath enhancement and thickening on magnetic resonance imaging in their series. Until now there are no standard measures to specifically assess AI induced joint symptoms, which limit the interpretation of all studies.

Some of the limitations of our study that we did not included patients who discontinued therapy early due to adverse effects and only included patients who were actively receiving adjuvant AI treatment, also some patients may not attribute their joint symptoms to AI treatment. Therefore our study may have underestimated the prevalence and severity of AI-related arthralgia like all other studies.

Our findings with regard to the rapid onset of symptoms confirm similar findings of Donnellan *et al.*[21] These findings may suggest early follow-up for patients who start AIs to explain the potential onset of arthralgia, so that early detection and management can occur to prevent premature discontinuation, which has been reported as high as 20%. [9]

Predicting factors for AI-arthralgia are not well determined. In the present study, prior use of tamoxifen and higher weight seems to be associated with a lower risk of AI-arthralgia, whereas prior taxane chemotherapy was associated with increased risk. Although this were not statistically significant (*P* = .08).Theses differ with the study of Crew *et al.*[5] and this may be attributed to subtle underlying differences in the study populations.

With regard to the relation between serum estradiol and AI-arthralgia, the incidence was lower in patients with serum estrogen rebound. Although multivariate analysis did not reveal any significant difference between AI-arthralgia and decrease in serum estrogen. Our results support the results of Junko *et al.* where they explain that a decrease in serum estrogen causes some other secondary change(s) in joints, which is followed by manifestation of joint symptoms.[22]

In the current study, the duration after menopause (measured as the time from last menstrual period) was the only significant predicting factor that was associated with AI-related arthralgia and these results were similar to study done by Miyuki *et al.*[23] We hypothesize that those individuals who most recently have transitioned into menopause may have

higher residual circulating estrogen; thus, the exposure to AIs may cause a more precipitous absolute drop in estrogen, leading to greater symptom experience. Several studies have cited estrogen deprivation caused by AIs as a potential cause for AI-arthralgia. [24,25] The effect of estrogen withdrawal on the clinical syndrome of AI-arthralgia may be multifactorial, acting both centrally and peripherally. Centrally, acutely reducing estrogen levels may decrease endogenous opioid generation, thereby decreasing pain threshold. Thus, some individuals with subclinical osteoarthritis may experience a rise in AI-associated symptoms because of a decreased pain threshold and an increased awareness of arthralgia, leading some patients to attribute the ''cause'' of arthralgia to AIs. Peripherally, estrogen withdrawal may up-regulate inflammatory cytokines like interleukin-6 and tumor necrosis factor-a, which may accelerate bone loss and bone aging, thereby leading to pain. Prospectively measuring appropriate biomarkers (e.g., reproductive hormones, drug metabolites, and inflammatory cytokines) in addition to subjective symptom measurement may help elucidate the biology underlying this unexplained clinical phenomenon. [24]

The pattern of joint pain at certain joints provides important data for both clinical care and future development of specific intervention. Site-specific joint symptoms may have different effect on functions and quality of life and therefore treatment and rehabilitation.[26] Several studies have suggested that pain medications and exercise may be helpful for AI-arthralgia.[24,25]

To summarize, our results have thrown light on AI-related arthralgia and have identified the duration of menopause as possible predicting factor for this adverse event of AI. More studies should explore the clinical characters, the pathogenesis, natural history and radiological characteristics to better understand and manage this unwarranted adverse effect of AI. The long term effects of profound estrogen suppression in breast cancer patients taking AIs are unknown. Therefore, targeted interventions that relieve AI-induced musculoskeletal pain are needed. However, until interventions are identified, patients who suffer severe adverse effects should be reassured that the clinical benefit of AIs compared with tamoxifen is modest, so that for some, changing therapy may be a reasonable solution.

References:

1. Early Breast Cancer Trialists' Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-years survival: an overview of the randomized trials. Lancet 2005; 365:1687–1717.
2. Nelson L.R..andBulun S.E.: Estrogen production and action. J Am Acad Dermatol, 2001; 45:S116-S124.
3. Riggs B.L. and Melton L.J. III: The prevention and treatment of osteoporosis. N Engl J Med1992; 327:620- 627, [Erratum: N Engl J Med 1993; 328:65].
4. Donnellan P.P., Douglas S.L., Cameron D.A. and Leonard R.C.: Aromatase inhibitors and arthralgia. J Clin Oncol 2001; 19:2767.
5. Crew K.D., Greenlee H., Capodice J., *et al.* Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J ClinOncol 2007; 25:3877–3883.
6. Henry N.L., Giles J.T., Ang D., *et al.* Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat 2008; 111:365–372.
7. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B., Keshaviah A., Coates A.S., *et al.* A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005; 353:2747–2757.
8. Buzdar A.U. on behalf of the ATAC Trialists Group. Clinical features of joint symptoms observed in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [abstract 551]. J ClinOncol 2006; 24.
9. Fontaine C., Meulemans A., Huizing M., *et al.* Tolerance of adjuvant letrozole outside of clinical trials. Breast 2008; 17:376–381.
10. Cleeland C.S. and Ryan K.M.: Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore1994; 23:129-138.
11. Partridge A.H., Wang P.S., Winer E.P., *et al.*: Non-adherence to adjuvant tamoxifen therapy in women with primary breast cancer. J ClinOncol 2003; 21:602-606.
12. Partridge A.H., La Fountain A., Taylor B.S., *et al.*: Adherence with adjuvant anastrozole therapy among women with early-stage breast cancer. Presented at San Antonio Breast Cancer Symposium, December 14-17, 2006, San Antonio, TX.
13. Cecil R.L. and Archer B.H.: Arthritis of the menopause. JAMA 1925;84:75-79.
14. Spector T.D., Nandra D., Hart D.J., *et al.*: Is hormone replacement therapy protective for hand and knee osteoarthritis in women? The Chingford Study.Ann Rheum Dis1997; 56:432-434.

15. Nevitt M.C., Cummings S.R., Lane N.E., *et al.*: Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women: Study of Osteoporotic Fractures Research Group. Arch Intern Med 1996; 156:2073-2080.
16. Wluka AE, Davis SR, Bailey M, *et al.*: Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis2001; 60:332- 336.
17. Nevitt M.C., Felson D.T., Williams E.N., *et al.*: The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. Arthritis Rheum2001; 44:811- 818.
18. Chlebowski R.T., Johnson K.C., Kooperberg C., *et al.*: The Women's Health Initiative randomized trial of calcium plus vitamin D: Effects on breast cancer and arthralgias. J ClinOncol 24:2s, 2006 (suppl; abstr LBA6).
19. Høegh-Andersen P., Tanko L.B., Andersen T.L., *et al.*: Ovariectomized rats as a model of postmenopausal osteoarthritis: Validation and application. Arthritis Res Ther2004; 6:R169-R180.
20. Morales L., Pans S., Paridaens R., et al.: Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: Associated tenosynovial changes on magnetic resonance imaging. Breast Cancer Res Treat 2007 Jul;104(1):87-91.
21. Donnellan P.P., Douglas S.L., Cameron D.A., Leonard R.C. Aromatase inhibitors and arthralgia [letter]. J ClinOncol.2001; 19:2767.
22. Junko H., Miyuki K., Misako N. *et al.*: Joint Symptoms, Aromatase Inhibitor-Related Adverse Reactions, Are Indirectly Associated with Decreased Serum Estradiol: International Journal of Surgical Oncology Volume 2011, Article ID 951260.
23. Miyuki k., Masami m., junko H. *et al.*: The time since last menstrual period is important as a clinical predictor for non-steroidal aromatase inhibitor-related arthralgia. BMC Cancer 2011, 11:436.
24. Burstein H.J.: Aromatase inhibitor-associated arthralgia syndrome. Breast.2007; 16:223-234.
25. Coleman R.E., Bolten W.W., Lansdown M., *et al.*: Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. Cancer Treat Rev. 2008; 34: 275-282.
26. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the M-SACRAH, a modified, shortened version of SACRAH (Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands). Rheumatology (Oxford). 2004;4+3:1409-1413.

11/12/2013