

# Osteoporosis and musculoskeletal complications related to therapy of breast cancer

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**Abstract:** Aromatase inhibitors (AIs) are the treatment of choice for the majority of postmenopausal women with estrogen receptor (ER) positive breast cancers in early and advanced stage settings. One of most frequent side effects of AIs is bone loss that is of sufficient magnitude to increase risk of osteoporotic fractures. Osteoporosis is primarily a complex genetic disease with few modifiable risk factors. As the lifespan increases, and breast mortality decreases, more women with breast cancer will be at risk of osteoporotic fractures, or falls that result in fractures. The screening, prevention, and treatment of osteoporosis do not differ in women with or without breast cancer. Rather, breast cancer treatments, including AIs, chemotherapy-induced ovarian failure, and gonadotropin-releasing hormone (GnRH) agonists, all decrease estrogen, which causes net bone resorption, leading some women to experience fracture. Occurring in about fifty-percent of women, AI-induced arthralgia is one of the most common side effects, and causes of nonadherence and discontinuation. Registry studies show that nonadherence and discontinuation may contribute to higher breast cancer mortality. Thus, understanding the mechanisms, risk factors, and interventions to mitigate symptoms of AI-induced arthralgia is a high priority.

**Keywords:** Aromatase inhibitor (AI); osteoporosis; arthralgia

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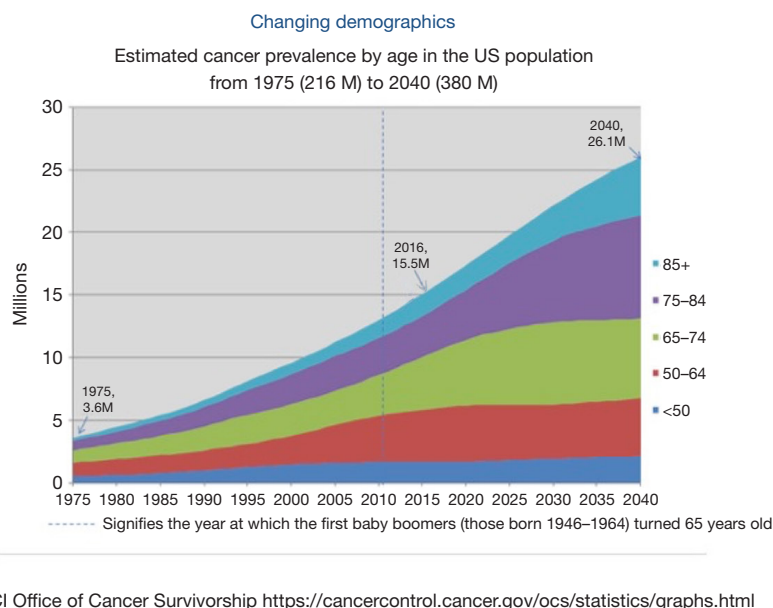
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## Introduction

The majority of women diagnosed today with early-stage breast cancer will be long-term survivors and experience personal cures (1). Hence, awareness, screening, and treating the late and long-term effects of breast cancer treatments are of paramount importance in maintaining health (2). One of the common long-term effects of breast cancer treatments is osteoporosis. Chemotherapy-related ovarian failure, gonadotropin hormone-releasing (GnRH) agonists, and aromatase inhibitors (AIs) all result in bone loss that in some women is of sufficient magnitude to cause osteoporosis and fractures. The risk of osteoporosis is higher in postmenopausal women with breast cancer

receiving AIs (3). Osteoporosis is highly relevant to the 25 million cancer survivors in the United States (US) by the year 2040, the majority of whom will be in their sixth, seventh, and eighth decades (*Figure 1*).

Thus, as both breast cancer and osteoporosis increase with age, screening, prevention, and treatment of osteoporosis in women with breast cancer are high priorities. Postmenopausal women with estrogen receptor (ER)-positive breast cancers (i.e., luminal A and B subtypes (4) representing about seventy-five of all breast cancers. Currently, AIs are an important part of the standard treatment for early stage and advanced ER-positive breast cancers. The focus of this review is on AI-related osteoporosis (5,6), arthralgia, and myalgia (7-9).



**Figure 1** Changing demographics of breast cancer survivor population (reprinted with permission).

## Aromatase

Aromatase (CYP19) is in the family cytochrome P450 enzymes that are responsible for converting adrenal gland-derived androgens to estrogens in postmenopausal women (10). Many tissues including ovarian, adipose, bone, healthy breast, breast cancer, and brain contain CYP19. Inhibiting aromatase results in decreasing estrogen levels lower than the already low estrogen levels of postmenopausal women (11). Anastrozole, exemestane, and letrozole are the three selective AIs in use for the treatment of postmenopausal women with breast cancers expressing the estrogen (ER) and/or progesterone receptor (PR). Randomized trials and meta-analysis show the superiority of AIs over tamoxifen in disease-free and overall survival (12,13).

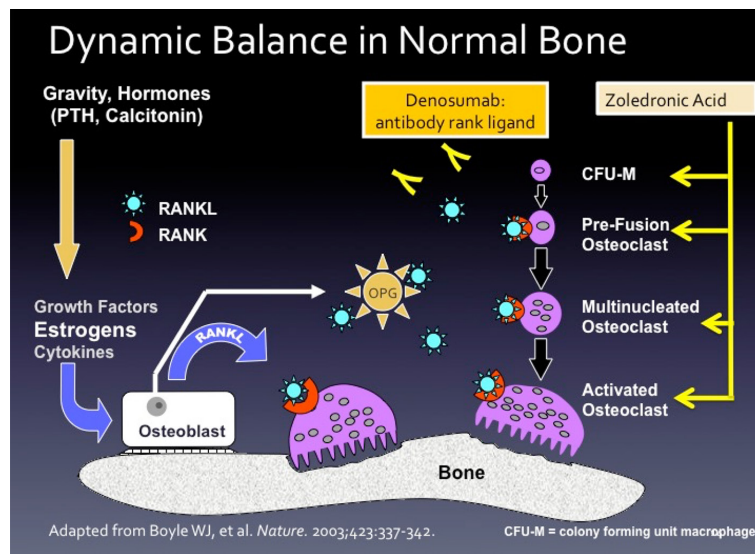
All three AIs have similar benefits (14); they reduce the risks of local, distant recurrence, contralateral breast cancers, and improve overall survival in comparison to tamoxifen. They also have the same spectrum of side effects including possible increases in vasomotor symptoms, arthralgias and myalgias, vaginal dryness, hair thinning, and bone loss leading higher risks of osteoporosis and fractures.

## Aromatase and bone loss: mechanisms of action

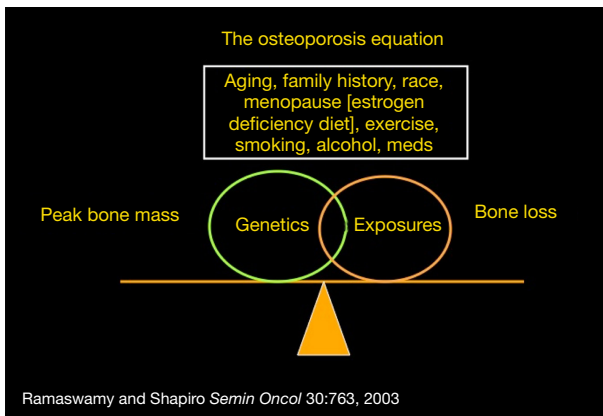
Aromatase regulates estrogen in postmenopausal

women (15), and estrogens and other hormones play a central role in the regulation of bone mass (16). The control of healthy bone mass involves two levels: at a “macro” level, the regulation of healthy bone is through systemic hormones (e.g., androgens, estrogens, calcitonin, and parathyroid hormone), and the mechanical forces imposed by gravity. The “micro” level occurs in the bone-remodeling unit, comprised of two primary cell types. Osteoblasts, derived from mesenchymal precursor cells, are responsible for new bone formation, whereas, osteoclasts derived from hematopoietic precursor cells are responsible for bone resorption.

The dynamic balance between osteoblast and osteoclast function regulates new bone formation and resorption (*Figure 2*) (17). The master regulator is the osteoblast secreting both osteoprotegerin (OPG; also called osteoclastogenesis inhibitory factor, a member of the tumor necrosis factor receptor superfamily), and the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL). When RANKL binds to RANKL receptor located on osteoclast precursor cells, it causes differentiation into mature osteoclasts and stimulates the multiple mechanisms by which bone resorption occurs. The osteoblast also secretes OPG that acts as a decoy receptor for RANKL, thus putting the brakes on osteoclasts. Also, T-cells play critical roles in maintaining bone mass. Estrogen deficiency of normal



**Figure 2** Dynamic balance in the bone remodeling unit, and the actions of the anti-resorption drugs, zoledronic acid and denosumab, modified from reference (17).



**Figure 3** The osteoporosis equation.

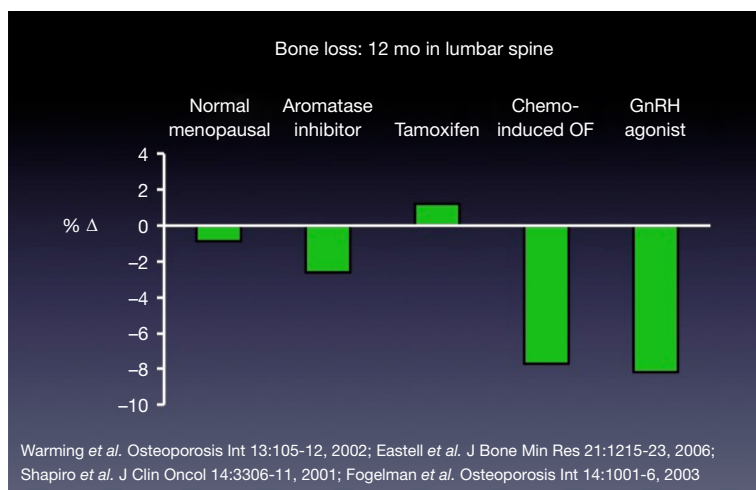
menopause causes T cells to secrete tumor necrosis factor-alpha and RANKL that activate osteoclasts causing bone resorption (18,19).

In healthy women, peak bone mass occurs around age 30 years. After 30 years age-related bone loss in both women and men occurs. The magnitude of bone loss in women (relative to men) is higher due to menopause, where estrogen levels may be decreased by one hundred-fold as compared with premenopausal women. A key point is everyone loses bone after age 30 years. Therefore, osteoporosis is an equation (Figure 3) (20) subtracting the loss of bone mass relating to aging and menopause

from starting bone mass. Although modifiable risk factors include current smoking, excess alcohol consumption of greater than two drinks per day, and chronic steroid use, osteoporosis is primarily a genetic disease with the most influential non-modifiable risk factors being aging, parental history of non-traumatic fracture, low body mass (or weight under 150 pounds) and diabetes (21).

### Genetics of AI-induced osteoporosis and AI-induced myalgias

The genetics of osteoporosis is complex involving single-nucleotide polymorphisms (SNPs) in twenty or more candidate genes (22,23). Several candidate gene SNPs specifically associate with AI-induced bone loss and even associate with response to AIs (24). In postmenopausal women with ER-positive breast cancers receiving AI, SNPs in the ESR1, ESR2, CYP19A1, and CYP11A1 predict decreases in bone density (25-27). The results of an extensive case-cohort genome-wide association study (GWAS) show that three SNPs in or near six genes located on chromosomes 20 (CTS2, SLMO2, ATP5E), chromosome 6 (TRAM2, TRAM14A), and chromosome 2 (MAP4K4) relate to an increased risk of fractures in women receiving AIs (28). In preclinical experiments these six-genes are estrogen-regulated, and knocking down the expression of these genes increased the expression of genes known to



**Figure 4** Percentage change in bone loss in spine at 12 months with various breast cancer treatments.

associate with osteoporosis. Ideally, a blood test of germline DNA would identify SNPs that predict who has higher (or lower) risks of bone loss or fractures before starting AIs. If this were true, one could better tailor treatment either by changing therapy to tamoxifen, which mitigates bone loss in postmenopausal women or by initiating anti-resorptive drugs at same time as AI. However, the literature on this topic is conflicting based on studies that use different methodologies, sample sizes, populations, and other factors. In fact, a recent review concluded “...there are no strong associations between functional SNPs and AI-related adverse events with clinical implications.” (29).

Specific SNPs also associate with AI-induced arthralgia and myalgia. Statistically significant associations with SNPs in OPG, CYP17A1, vitamin D receptor (VDR), and CYP2 predict for higher risks of AI-induced adverse musculoskeletal events (30,31). However, more research is needed before SNPs are used in clinical decision-making (32).

### Screening, risk factors, prevention, and treatment of AI-induced osteoporosis

The detection, prevention, and treatment of osteoporosis fundamentally do not differ in women with and without breast cancer. Routine treatments for breast cancer like gonadotropin-releasing hormone agonists (33), chemotherapy-induced ovarian failure in premenopausal women (34), or AIs in postmenopausal women (6) lower estrogen levels and accelerate bone loss. *Figure 4* (34-37)

describes the relative magnitude of bone loss with different treatments. AIs cause two to three-fold higher bone loss than the rates observed in early postmenopausal bone loss.

### Screening and risk factor assessment

The most common screening for osteoporosis is central dual-energy X-ray absorptiometry (DXA) scans measuring the total spine, hip, and femoral neck (10). The T-score is most crucial outcome variable of DXA scanning because it predicts fracture risk (38). The T-score is the number of standard deviations (SDs) by which bone mineral density (BMD) falls above or below the mean peak BMD for a reference population of healthy 20–29 years old females. For every 1 SD decrease in T-score, relative risk of fracture increases about 1.5 to 2.5-fold. The World Health Organization defines a normal T-score as  $-1.0$  or above, T-scores between  $-1$  and  $-2.5$  as osteopenia, and T-scores below  $-2.5$  or a non-traumatic fracture as osteoporosis (39). The Z score is another outcome variable of DXA scans that is the number of SDs the individual’s bone density falls above or below that of reference population of the same age and sex. The Z-score is useful for considering secondary causes of osteoporosis.

Women initiating AI treatment should receive a baseline DXA scan if they have never had one before or depending on the timing of the last DXA scan. Counseling should occur about modifiable risk factors that not only affect bone health but also influence overall health (e.g., current smoking, daily alcohol intake of three or more drinks, and

increasing physical activity). Routinely checking vitamin 25-OH D levels is controversial. Vitamin D deficiency and insufficiency are prevalent among the general population and in women with breast cancer (40-42), especially in minority populations. Some health care providers routinely check a serum 25-OH vitamin D level before starting AIs. Others (including the authors), use the initial DXA scan as a guide, checking serum 25-OH vitamin D if osteopenia or osteoporosis is present.

Whether supplementing calcium and vitamin D will decrease non-traumatic fractures in postmenopausal women with or without osteoporosis is controversial (39). The most recent Cochrane review concludes that vitamin D alone does not have an impact on fractures (43). Supplementing calcium and vitamin D does lead to a small, statistically significant decrease in risk of hip but not vertebral fractures, and this is dependent on patient population (low versus high risk of osteoporosis) and the setting (outpatient versus institutionalized). However, there is evidence that supplemental calcium and vitamin D decreases postmenopausal BMD loss (39). More recently, there is evidence that calcium and vitamin D supplementation prevents falls by affecting muscle strength (44-46). Preventing fall is essential, as this will reduce fractures in an aging population of women with osteopenia or osteoporosis.

Relatively few trials have evaluated the impact of calcium and vitamin D supplementation in women receiving AI or cancer treatment-induced bone loss. Of those that did, the consensus is that doses of supplemental calcium and vitamin D of 500–1,500 mg and 200–1,000 IU, respectively, do not prevent loss of BMD (47) but mitigate it (45).

There is a broad consensus of policy-making organizations (e.g., National Osteoporosis Foundation, National Academy of Sciences, Institute of Medicine, and US Preventive Services Task Force) that women over age 50 years should receive 1,000–1,200 mg of calcium (including dietary calcium) and 800–1,000 IU vitamin D<sub>3</sub> (cholecalciferol) daily (39). In addition to mitigating BMD loss, there is evidence to support other positive health outcomes, including cancer prevention (48). These doses of calcium and vitamin D supplementation are also the recommendations of several position papers on AI-induced bone loss (5,49).

### Assessing fracture risk

The goal of evaluating fracture risk is preventing non-traumatic fractures of the hip and vertebrae. The primary

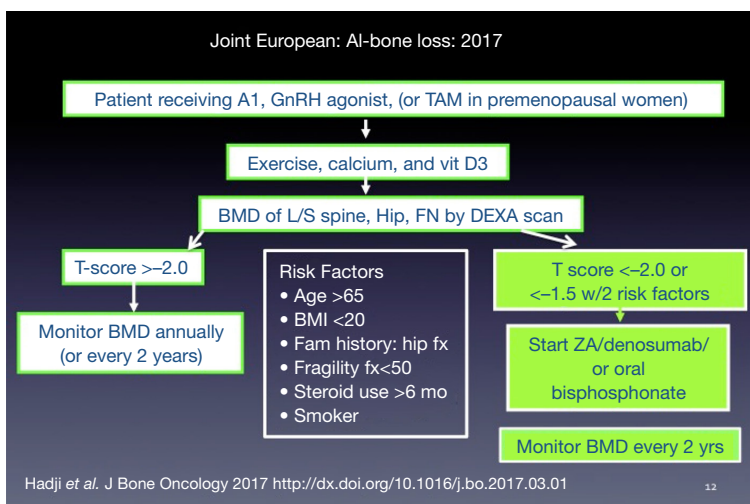
endpoint is reducing fractures when testing osteoporosis drugs. In contrast, few studies have fractures as a primary endpoint in women with breast cancer receiving AIs. Most studies use a surrogate endpoint, BMD, as the primary endpoint and to make decisions when to institute anti-resorptive treatment. In breast cancer, trials are not large enough, and follow-up is too short to detect a reduction in fractures as a primary endpoint.

The fracture risk assessment (FRAX<sup>®</sup>) calculator is commonly used to estimate the ten-year risk of hip and non-hip vertebral fractures ([www.sheffield.ac.uk/FRAX/](http://www.sheffield.ac.uk/FRAX/)) (21,50). FRAX<sup>®</sup> uses age, height, weight, sex, a variety of risk factors (prior fracture, parental hip fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol of 3 or more drinks per day) and optional femoral neck T-score of BMD (51). The FRAX<sup>®</sup> calculator estimates the absolute ten-year risk of hip or non-hip fractures, but also the age-related thresholds for treating or not treating with anti-resorptive drugs. There are versions of FRAX<sup>®</sup> specific for each country.

FRAX<sup>®</sup> has limitations [described extensively in reference (21)]. The principal guideline groups around the world recently published a consensus statement on the management of AI-induced bone loss (49). In the guideline consensus paper, FRAX<sup>®</sup> may underestimate the ten-year fracture risk in women receiving AIs, and the authors provide an algorithm for using anti-resorptive drugs that don't involve FRAX<sup>®</sup> (Figure 5) (49). This contrasts with National Comprehensive Cancer Center Network (NCCN) latest recommendations that suggest using FRAX<sup>®</sup> to estimate risks of hip and non-hip fractures (52).

The trabecular bone score (TBS) is an assessment of bone microarchitecture derived from the DXA lumbar spine measurements. The TBS independently predicts falls and osteoporotic fractures in both men and women (53). In the study by Hans *et al.* incorporating TBS and BMD measurements was better than either alone in predicting osteoporotic fracture risk (54). A retrospective pilot trial of one hundred women with ER-positive breast cancers using BMD, FRAX<sup>®</sup>, and TBS measures at baseline (before starting AI) and two years post-AI treatment (55). The combination of three measurements identified a higher number of women at risk of osteoporotic fractures. Incorporating TBS into FRAX makes sense because it takes into consideration a measure of bone strength. There are not enough data yet to recommend incorporating TBS into routine fracture risk assessment in screening, either for osteoporosis or for women with an AI-induced bone loss.





**Figure 5** Suggested approach of aromatase inhibitor bone loss: Joint European Guidelines 2017 (used with permission).

**Table 1** Fracture rates in randomized controlled of aromatase inhibitor (AI) versus tamoxifen (TAM)

Trial	N	Follow-up (mo)	Treatment	Fractures (%)	P
AI vs. TAM					
ATAC (12)	9,366	100	ANA vs. TAM	11.0 vs. 7.7	<0.001
BIG 1-98 (56)	4,922	60	LET vs. TAM	9.3 vs. 6.5	0.002
AI after 2–3 years of TAM					
TEAM (57)	9,779	61	EXE vs. TAM	5.0 vs. 3.0	0.0001
ABCSG8/ARNO (58,59)	3,224	28	ANA vs. TAM	2.0 vs. 1.0	0.015
AI after 5 years of TAM					
MA-17 (60)	5,187	63	LET vs. placebo	5.2 vs. 3.1	0.02

ANA, anastrozole; LET, letrozole; EXE, exemestane.

**Prevention and treatment with anti-resorptive drugs to prevent fractures in women receiving AIs**

Table 1 describes the fracture rates in the major clinical trials of AI versus tamoxifen. All AI-treatment groups had statistically significant increases fractures relative to tamoxifen (12,56-60). The fractures remain elevated during the five years of AI treatment and decreases to the same rate as tamoxifen-treated patients during years five to ten (12).

The osteoclast inhibitor, zoledronic acid (ZA), and the RANKL inhibitor, denosumab, are the two drugs used to mitigate BMD loss in women receiving women receiving AIs (5,6,49). Table 2 describes ZA and denosumab. The primary differences in these drugs are in their mechanism of actions, routes of administration, toxicities, and the costs (61).

There are no randomized trials directly comparing ZA and denosumab to mitigate BMD loss in women treated with AIs. More recently, a randomized placebo-controlled trial of denosumab 60 mg subcutaneously every six months in postmenopausal women receiving AI was first to show a statistically significant reduction in fractures (62).

Instructive are the results of the ZO-Fast trial (63). Over 1,000 postmenopausal women receiving letrozole 2.5 mg a day were randomized to receive either immediate ZA 4 mg IV every six months for five years or to receive ZA only if the DXA showed a decreasing T-score of less than or equal -2.0, or an osteoporotic fracture occurred. Entry criteria included those women with normal BMD (i.e., T-scores of -1.0 or above) or osteopenia with T-scores of -1.0 to -2.0.

**Table 2** Major differences between zoledronic acid (ZA) and denosumab

Factor	ZA (IV)	Denosumab (SC)
Dose	4 mg	60 mg
Mechanism	Osteoclast inhibitor	RANKL monoclonal antibody
Metabolism	Not metabolized	Not metabolized
Half-life	188 days, the majority goes to bone	28 days
Clearance	Renal (44% of the dose is excreted in urine within 24 hours after administration)	Denosumab is most likely cleared by the reticuloendothelial system with minimal renal filtration and excretion
Common side effects	Fever and chills; muscle, bone or joint pain; nausea; fatigue; and headache	Joint, muscle pains, and hypocalcemia
Rare side effects	Hypocalcemia, renal insufficiency, and osteonecrosis	Osteonecrosis
Cost (\$) <sup>§</sup> (61)	252.00	1,906.00

<sup>§</sup>, cost of drug and administration from the Centers for Medicare and Medicaid Services Reimbursement ([www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/Value-Based-Programs.html](http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/Value-Based-Programs.html)). RANKL, receptor activator of nuclear factor- $\kappa$ B ligand.

As expected the group that was randomized to immediate ZA statistically significantly increased BMD in lumbar while the delayed ZA lost bone. However, after five years, only 27% of delayed ZA group received ZA. Thus, only minority of women on AIs needed anti-resorptive drugs, at least for first five years.

### Anti-resorptive drugs as anti-cancer drugs

Several randomized trials (64-66) and a recent meta-analysis (67) suggest that in postmenopausal women or premenopausal women rendered postmenopausal with a GnRH agonist (64), ZA improves clinical outcomes such as distant recurrence, bone recurrence, and cancer deaths. Included in the meta-analysis were over 11,000 postmenopausal and over 6,000 premenopausal early stage women with breast cancer. In the postmenopausal women only, the ten-year absolute decreases in distant recurrence, bone recurrence, and cancer mortality were 1.5% ( $P=0.10$ ), 2.2% ( $P=0.0002$ ), and 3.3% ( $P=0.002$ ), respectively. In 2017, the Canadian Care Ontario and American Society of Clinical Oncology Clinical Practice Guidelines Focused Update put out a statement on the use adjuvant anti-resorptive drugs. The guideline stated “consider” ZA (4 mg intravenously) every six months for three to five years or oral clodronate 1,600 mg per day (only available in Europe) for three years in high-risk postmenopausal women (68). There is insufficient evidence at present to recommend denosumab as anti-cancer drug. Additional

clinical trials of anti-resorptive drugs specifically in early stage postmenopausal women are needed to confirm the preliminary evidence of the meta-analysis (69).

### AI-induced arthralgia and myalgia

AIs cause musculoskeletal systems including joint pain (arthralgias) and muscle pain (myalgias). Aromatase-induced musculoskeletal symptoms include both arthralgias and myalgias. For the purposes of this review, the reference to AI-induced arthralgias, will often include myalgias, depending on the particular study. AI-induced arthralgia is one of the most common side effects and is a significant contributor to nonadherence and discontinuation of drug (discussed below). The primary criteria that define AI-induced arthralgia are joint pain that develops or worsens while taking an AI, stopping the AI for two weeks and joint pain resolves, and then restarting the AI and joint pain returns (70). Minor criteria include pain affecting the joints symmetrically, pain in the hands or wrists, carpal tunnel syndrome, decreased grip strength, morning stiffness, and improvement with exercise. AI-induced arthralgia tends to occur soon after initiating AI with median onset 1.6 months (range 0.4 to 10 months) (71).

The prevalence of AI-induced arthralgias is about 50% (range 20% to 74%) in a recent systemic review and a meta-analysis (9). In retrospective analyses, independent predictors that increase the risk of developing AI-induced arthralgias include prior taxane use (as opposed to non-

taxane containing chemotherapy), and previous anti-estrogen treatment (as opposed to no prior anti-estrogen therapy), whereas independent predictors of decreased risk are body mass index (BMI) 25–30 (as opposed BMI under 25 or over 30), and stage III breast cancer (as opposed to stage I cancers) (9). In a prospective trial of three hundred ninety-two postmenopausal women receiving anastrozole, independent risk factors for AI-induced arthralgia were shorter time since menopause and prior adjuvant chemotherapy (72). BMI was not a risk factor in this study. The wide variation in the prevalence of AI-induced arthralgias, and the uncertainty of impact of risk factors (e.g., BMI), is in part related to retrospective study designs in majority of the studies, varying definitions of AI-induced arthralgia, as well as the instruments used to assess this side-effect.

The mechanism of AI-induced arthralgia is poorly understood, and there are several hypotheses (70). The MRI may show tenosynovitis with enhancement and thickening of tendon sheaths consistent with an inflammatory process (73,74). One theory invokes suppression of pro-inflammatory cytokines [i.e., interleukin-6 (IL-6)] by the activity of synovial cell aromatase that produces estrogen from androgens. With AI treatment, decreased estrogen levels result in increased levels of IL-6, which causes inflammation and tenosynovitis (70).

AI-induced arthralgia is a significant contributor to nonadherence and drug discontinuation (8). The definition and causes of nonadherence are reviewed in Hugtenburg *et al.* (75). The rates of nonadherence and discontinuation increase over time. In one retrospective study of over 2,000 women receiving care in single health system treated with anti-estrogens (i.e., either tamoxifen, anastrozole, or switching between them), 21% were non-adherent by the end of one year, and after five years 73% were non-adherent (76). There are reports by others of similar non-adherence rates (77–80).

Non-adherence may affect worsening disease-free survival and increases cancer mortality (81,82). Independent risk factors for nonadherence include symptoms (83), and higher co-pays and out of pocket costs (84,85) and negative health beliefs (83,86). Also, poor doctor-patient communication, lack of social support, perceptions of low risk or recurrence, race (i.e., African-American), and older and younger ages (87).

### Treatments for AI-induced arthralgia

There are several systemic reviews and meta-analyses on

treatments AI-induced arthralgia (88,89). The interventions to treat AI-induced arthralgia include drugs, nutritional supplements, acupuncture, relaxation techniques, and physical therapies (including exercise, yoga, tai chi, and walking). Several caveats are important to point out when reviewing interventions for AI-induced arthralgia. The primary outcome is pain in the most studies. The sample size of the majority of studies is one-hundred women or less, and only six of thirty-eight (16%) enrolled randomized controlled trials of more than one hundred women (88). Studies vary in design including randomized controlled trials, prospective cohorts, and retrospective. Also, the entry criteria, and especially the validated instruments, vary greatly between studies. The preceding factors affect study quality, and thus the evidence for the interventions is weak to moderate (90).

One of the simplest and most effective interventions is switching an AI for another or switching to tamoxifen (91,92). About one-third of women will switch to another AI and be able to tolerate the second AI for a median of nearly 14 months (3 to 39 months) (93). One randomized trial of vitamin D3 at 4,000 IU versus 600 IU per day (94), and a second in which women on 600 IU per day plus 1,200 mg/day calcium for a run-in period were then randomized to 30,000 IU vitamin D3 per week versus placebo (95) have been conducted. In the two trials, measures of joint pain, stiffness, or functional ability were not statistically significant between the groups that received the higher vitamin D dosing. A recent randomized placebo-controlled trial of duloxetine in two hundred ninety-nine early-stage postmenopausal women receiving AI with at least moderate joint pains showed statistically significant improvements joint pain, stiffness, pain interference, and physical functions (96). Another randomized, placebo-controlled trial of omega-3 fatty acids in two hundred forty-nine women with similar characteristics to the duloxetine trial showed no statistically significant differences in pain (97). Interestingly, women randomized to placebo experienced more than fifty percent pain relief.

The results of small-randomized trials of acupuncture are conflicting (89). The results in randomized exercise intervention (twice-weekly resistance and supervised aerobic training for twelve months) versus usual care in one hundred twenty-one early stage women with breast cancer receiving AI with least mild joint pain show statistically significant reductions in pain, pain severity, and pain interference, and other validated instruments (98).

There is pressing need for interventions that mitigate



AI-induced arthralgia that are cost-effective and feasible outside the resource-rich Cancer Center and in the community where the majority of women receive treatment for breast cancer. The emphasis should be on randomized controlled trials adequately powered to detect a statistically and clinically significant effect sizes, using standardized instruments to facilitate cross-trial comparisons.

### Suggested approach to AI-induced arthralgias

Before starting AI, weight management and increasing physical activity are part of the routine care for every woman with breast cancer. Increasing physical activity has a wealth of benefits beyond breast cancer, and may mitigate AI-induced arthralgia. It is beyond the scope of this review to discuss all of the “teachable moments” (99), and the ways to affect behavior modification. However, women receiving AIs desire information from their oncology provider about AI-induced arthralgia, in addition to other side effects, and are more likely to increase physical activity if their oncologist recommends it (100).

Before discussing the side effects of AIs, two points deserve emphasis: (I) there are women for whom no to minimal symptoms occur (101), and (II) if symptoms occur there are approaches to mitigate them. If AI-arthralgia is suspected, one can stop the AI for 2–3 weeks. If the joint pain improves, re-challenge with same AI can be considered. If the joint pain reoccurs, options include changing the AI. If the joint pain does not resolve with stopping, it is not likely related to the specific use of AI. A referral to acupuncture, despite conflicting data, will work in some women and allow them to stay on AI. Although it may be the result of a placebo effect, from the individual's point of view, this of no importance (102). Another option is starting duloxetine.

Some women are intolerant of all three AIs. In this case, switching to tamoxifen is option of choice if there are no contraindications to this drug.

### Conclusions

AIs are mainstays in the treatment of postmenopausal women with ER-positive and will be for the foreseeable future. AI-induced arthralgias are common side effects and responsible for nonadherence and discontinuation. Interventions for AI-induced arthralgias are many, but many trials are underpowered and use different instruments in assessing the primary endpoint of joint pain. Switching

the AI is helpful in about 30% of women and is simple to do. More research is needed to understand the mechanisms of AI-induced arthralgia, SNPs that predict that risk, and interventions that are feasible and cost-effective.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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