Cancer Treatment–Induced Bone Loss in Women With Breast Cancer and Men With Prostate Cancer

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Cancer and cancer therapies can have a negative impact on bone health. Because cancer is a common diagnosis, survivorship concerns for osteoporosis and fragility fractures are an important component of care. This review addresses management of bone health in nonmetastatic cancer survivorship with a focus on breast cancer and prostate cancer.

Cancer treatment–induced bone loss refers to the accelerated loss of bone resulting from cancer therapies. It is recognized as an important survivorship issue in cancer care because newer medical therapies extend survival but may render patients at risk for osteoporosis and consequent fractures that can compromise quality of life and longevity. The focus of this review is to discuss the known mechanisms and cancer therapies associated with bone loss and risk of fracture as well as screening and management of bone health in this population. We focus on breast cancer (BCa) and prostate cancer (PCa), which have >400,000 new cases reported annually in the United States. Patients with a history of cancer are commonly seen in the Endocrine/ Osteoporosis, Primary Care and Oncology clinics, with many patients on antihormonal therapies for the management of BCa or PCa. Bone loss may occur due to the underlying cancer itself via complexed mechanisms, but this is not within the scope of this current article, which focuses on bone health in patients without osseous metastases.

1. Methods

A literature review was conducted using a PubMed search to identify recent studies that addressed mechanisms of bone loss and management in early-stage cancers, specifically of the breast and prostate. Guidelines from international and national oncology and bone societies, as well as expert consensus opinion articles, were identified and included in this review.

2. Epidemiology of BCa and PCa

BCa and PCa are among the most common cancers that occur in older women and men and make up 25% of newly diagnosed cancers in the United States and Europe [1]. In the United

States, almost one in eight women will be diagnosed with BCa at a median age of 62 years and at a slightly younger age in black women [2], with over 266,000 new cases diagnosed in 2018 [3]. Premenopausal BCa is much less common and comprises <20% of all newly diagnosed cases of invasive BCa [2]; nonetheless, therapies in this setting pose an important risk to bone health. PCa is the second leading cause of cancer deaths in US men, with an estimated 164,690 new cases in 2018 and over 29,000 deaths annually [3]. The median age at diagnosis is 66 years. It is more common in African American men and in those with a family history of PCa. Greater than 90% of cases are diagnosed at the local stage, with a 98.6% 5-year survival rate [4].

3. Therapies Leading to Bone Loss in BCa and PCa

Bone loss from cancer therapies can be attributed to various mechanisms. These include chemotherapy, hormone ablation therapy leading to sex steroid–induced hypogonadism, antiestrogen therapies, radiation, and medications around treatment such as glucocorticoids that may promote bone loss.

A. Chemotherapy

Chemotherapy may be used in the setting of neo-adjuvant or adjuvant treatment in pre- or postmenopausal BCa as well as in locally advanced PCa. In postmenopausal women chemotherapy has not been studied extensively as an independent factor for bone loss, although it has been associated with lower BMD in a small retrospective analysis [5] and in a 1-year prospective study [6] compared with women not receiving chemotherapy for BCa. However, chemotherapy-induced hypogonadism and bone loss is well documented in premenopausal women. Chemotherapies used to treat cancers injure cells that divide quickly and are often associated with ovarian dysfunction when used in premenopausal women. Hence, menopause occurs about 10 years earlier than average natural menopause due to direct toxicity to the ovaries with interference of follicle maturation [7]. Premature ovarian failure occurs between 40% and 95% of women treated with chemotherapy, depending on the regimen and age at time of treatment [8]. Increasing age appears to be correlated with higher rates of premature ovarian failure [9–11].

Male gonadal hormone production normally decreases with age, but there is no direct parallel to a clear menopausal transition as seen in women. In PCa, chemotherapy is typically used in the setting of metastatic disease where there are often bone metastases. Although docetaxel has been used with androgen deprivation therapy (ADT) in the nonmetastatic setting with some evidence of survival benefit [12], there are insufficient data on the use of chemotherapy for early-stage PCa and its effect on bone health.

B. Hormonal (Endocrine) Therapies

Therapeutic maneuvers to decrease the likelihood of hormone-sensitive BCa or PCa tumor growth include inhibition of gonadal hormone production. Because bone is an endocrine-responsive organ, the decreases in circulating estrogen or androgen can accelerate the rate of bone resorption. In pre- and perimenopausal women, estrogen production may be manipulated by use of gonadotropin-releasing hormone (GnRH) agonists or by surgical removal of ovaries. GnRH agonists are given as intramuscular or subcutaneous injections and lead to regulation of gonadotropin receptors at the level of the anterior pituitary, reducing estrogen and testosterone production [13]. Thus, this is an important mechanism in hormone-sensitive breast tumors (those expressing estrogen/progesterone receptors, ER/PR+) in premenopausal BCa, in which ~60% of cases of BCa are hormone receptor positive, which is less than the ~80% of cases BCa in postmenopausal women [14].

In PCa, androgens stimulate PCa cell growth and proliferation via the androgen receptor. GnRH agonists or GnRH antagonists (also known as ADT) are commonly used therapies.

Since the introduction of GnRH-agonists and antagonists, chemical castration has essentially replaced surgical castration. Typically they can be used with or without androgen receptor blockade in localized disease before (neoadjuvant) or after (adjuvant) surgery or radiation therapy. They are used in men who have a rising prostate-specific antigen after primary therapy has failed (biochemical relapse). In men with PCa, 33% to 70% will receive GnRH-agonists at some point during the course of their disease [15]. More recently, GnRH antagonists, such as degarelix and abarelix, have been approved for use in PCa, although they are used most often in the advanced disease setting. They are direct competitive inhibitors of endogenous GnRH binding to receptors in the anterior pituitary [16]. Antiandrogen medications such as bicalutamide or flutamide, which are competitive inhibitors at the androgen receptor, are often used in conjunction with GnRH agonists or antagonists in "combined" androgen blockade. Estrogen preparations have been historically used in PCa, but, due to cardiovascular and thromboembolic events, they are infrequently used currently.

C. Antiestrogen Therapy in BCa

Antiestrogen therapy has been the mainstay of treatment in hormone receptor–positive BCa. Tamoxifen exerts an antiestrogen effect in the breast regardless of menopausal status and is an estrogen agonist within the bone. Tamoxifen, a selective estrogen receptor modulator, has efficacy regardless of the menopausal status. If tamoxifen is used as the sole adjuvant antiestrogen, the duration of therapy is 10 years [17]. If tamoxifen is sequenced with an aromatase inhibitor (AI), the course of therapy may be shorter, and the duration of therapy is influenced by the use of AIs. Large phase III randomized trials in postmenopausal women and a meta-analysis demonstrated the superiority of adjuvant (curative) AIs such as anastrozole, exemestane, and letrozole over tamoxifen in postmenopausal BCa outcomes [18]. AIs block the conversion of androgen to estrogen, primarily in adipose tissue, by inhibiting the aromatase enzyme, a cytochrome P 450 CYP 19 family member, thus profoundly decreasing serum estrogen levels. Several strategies of AI use can be used, including beginning with an AI for 5 years, using an AI after 2 to 3 years of tamoxifen, or using an AI after 5 years of tamoxifen. In pre- and perimenopausal BCa, an AI is not indicated unless used with surgical or chemical ovarian ablation because AIs do not affect ovarian estrogen production [19]. A summary of endocrine therapies and their common side effects in BCa and PCa is shown in Tables 1 and 2.

D. Radiation Therapy

Radiation therapy is a local therapy that may be applied in conjunction with surgery and/or systemic therapies. Radiation constitutes an effective and indispensable modality in the curative management of patients with cancer with the goal to deprive cancer cells of their

Table 1. Anti-Estrogen Medications and Common Adverse Effects

Anastrozole	Letrozole	Exemestane	Tamoxifen
Arimidex	Femara	Aromasin	Nolvadex
AI	AI	AI	SERM
Nonsteroidal	Nonsteroidal	Steroidal	
		Side Effects	
Hot flashes			Hot flashes
Muscle aches/Joint pains			Urogenital symptoms
Hypertension, dyslipidemia			Mood changes
Less DVT than TAM			DVT, CVA
Osteoporosis			Uterine Ca

Abbreviations: CVA, cerebrovascular accident; DVT, deep vein thrombosis; SERM, selective estrogen receptor modulator.

Table 2. Commonly Used GnRH Agonists and Antagonists for Ovarian Suppression and Androgen Deprivation Therapy and Common Adverse Effects

GnRH Agonists	GnRH Antagonists	Androgen Receptor Antagonists	Androgen Synthesis Inhibitors
Leuprolide	Degarelix	Flutamide	Abiraterone
Goserelin[a]	Abarelix	Bicalutamide	Ketoconazole
Triptorelin		Enzalutamide	Aminoglutethimide
Histrelin		Topilutamide	
		Side Effects	
Symptoms		Signs	
Fatigue		Weight gain	
Decreased muscle mass		Gynecomastia (in men)	
Increased insulin resistance		Reduced testicle size	
Decreased libido/erectile dysfunction		Anemia	
Hot flashes			

[a]Goseralin acetate is most commonly used in women.

mitotic activity. It is estimated that >50% of patients with cancer receive radiation therapy during their treatment [20]. It is commonly used in the treatment of BCa and PCa for local tumor control in early disease and for palliation in advanced disease, including bone metastases. The biologic target of radiation therapy is to induce extensive DNA damage beyond the scope of repair mechanisms in cancerous cells, which eventually induces mitotic cell death [20]. The primary insult in the etiology of these adverse effects is the interruption of the vascular supply to the bone and to the direct effects of hypoxia, which inhibits osteoblast function and a reciprocal increase in osteoclastogenesis [21]. Despite technological advances in this field, patients undergoing therapeutic radiation therapy have been shown to suffer from radiation-related bone-specific toxicities regardless of the type of radiation source. These effects are dose related and associated with bone loss within the field of radiation. Radiation toxicities include osteopenia or osteoporosis with an increased risk of fracture and a risk for avascular necrosis, medullary fibrosis, and secondary malignancies [22].

4. Bone Loss and Fracture Risk in Treatments for BCa and PCa

A. Bone Loss and Fracture Risk in BCa

Therapies used in the treatment of BCa and PCa may accelerate bone loss due to the mechanisms discussed herein, including chemotherapy, endocrine therapies, and radiation. Evidence from the Women's Health Initiative has demonstrated that survivors of BCa have a 15% increased risk of fractures compared with cancer-free women [23]. In postmenopausal women with BCa, tamoxifen is modestly protective against bone loss [24] and has not been associated with the same rate of bone loss as the AIs. Limited data are available regarding fracture risk with tamoxifen in postmenopausal women. However, retrospective data in postmenopausal women have suggested that hip and overall fractures are decreased, and in a prospective BCa prevention trial tamoxifen was associated with a 32% relative risk (RR) reduction in combined spine, hip, and radius fractures compared with the placebo control group [25].

Tamoxifen, a selective estrogen receptor modulator, has both agonist and antagonist effects on the estrogen receptor; the balance is affected by the clinical scenario. Tamoxifen use has been shown to decrease BMD in premenopausal women, even in those who maintain normal menstrual cycles [24, 26]. Ovarian suppression with GnRH agonists, oophorectomy, or premature menopause secondary to cytotoxic chemotherapy diminishes circulating estrogen and leads to accelerated bone resorption and to a subsequent decrease in BMD. This decline is greatest in the first year of treatment and is seen most profoundly in the lumbar

spine [27, 28]. Premenopausal women with chemotherapy-induced ovarian dysfunction have experienced bone loss of 3% to 7% in the lumbar spine and 2% to 4% in the total hip [29]. Amenorrhea in this setting may be reversible, and the women should not be assumed to be menopausal until sufficient time has passed. Studies in premenopausal women differ in rates of bone loss depending on the modality of suppressing ovarian function used. Studies have demonstrated an annual loss of total body BMD of 5% with GnRH agonists [30] and as high as 18% to 19% over 2 years after oophorectomy [31]. Fracture data with these modalities are limited because short-term fracture events are overall low in this younger population. Long-term studies are needed to better define the risk to bone health in these young women treated with curative intent and expected to have decades of life expectancy after completing BCa therapy.

It is well established from numerous phase III randomized studies with AIs in post-menopausal women with BCa that AIs accelerate bone loss (Fig. 1) and fracture risk (32–37). Fracture risk is increased by ~10% in some large trials, although in several case-control studies, prescription analyses, and one randomized controlled trial, the absolute risk of fracture was close to double (18% to 20%) after 5 years of AI treatment [38]. After completion
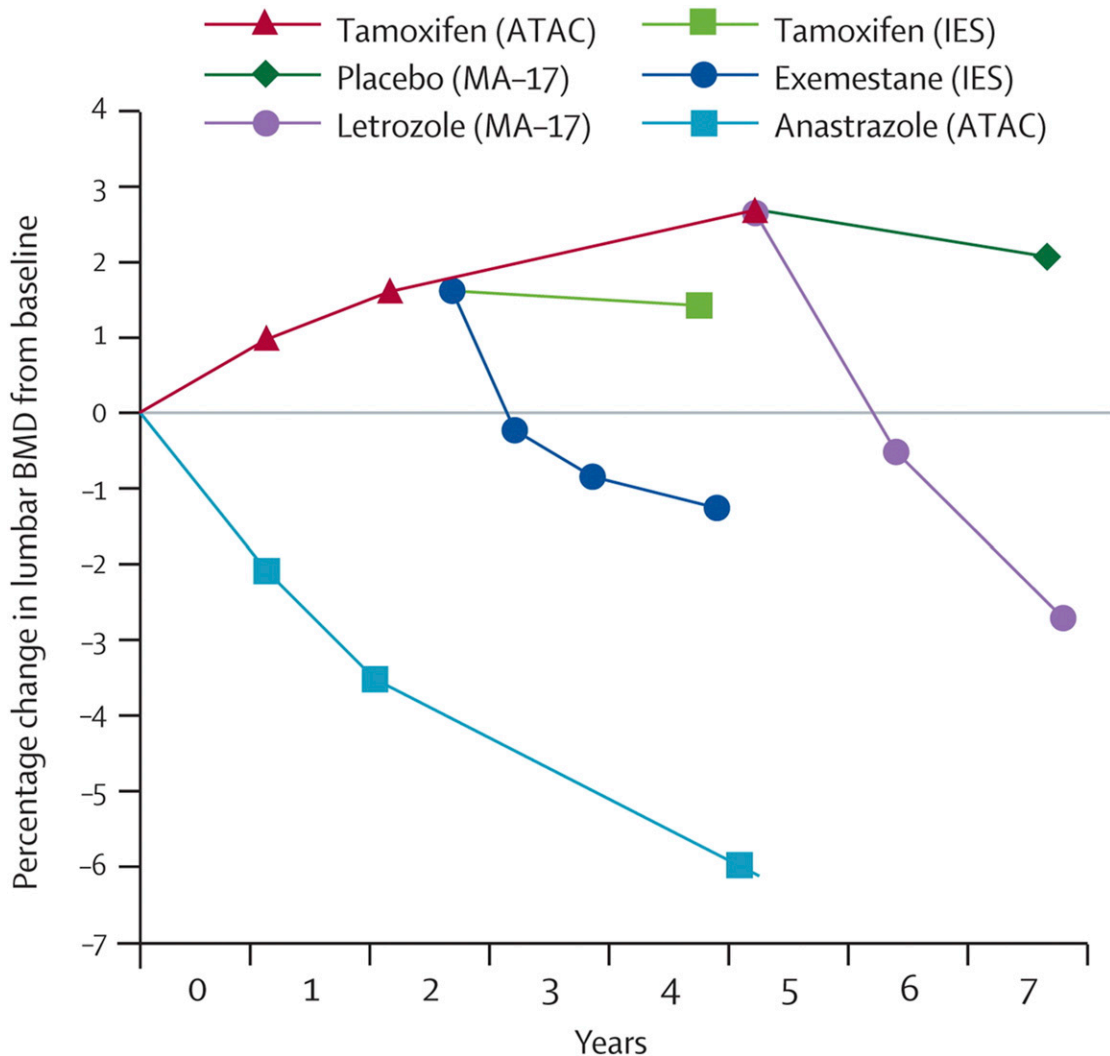

Figure 1. Summary of bone loss from major trials. Data from Shapiro *et al.* [32], Gnant *et al.* [33], Ellis *et al.* [34], Brufsky *et al.* [35], Ryan *et al.* [36], and Smith *et al.* [37].

of AI treatment, bone turnover tends to decrease back to baseline levels, and BMD may even show improvement [39].

Fracture risk may also decline after completion of AI therapy. The Arimidex, Tamoxifen, Alone or in Combination trial reported a similar fracture rate of 2% in the anastrozole group and 1.5% in the tamoxifen group after 5 years of follow-up after discontinuation of treatment [40]. A recent retrospective observational review analyzed fracture data in pre- and post-menopausal women after therapy with tamoxifen or AI with a mean follow-up time of 3.1 years. When women with osteoporosis were excluded, the investigators found an overall 14% fracture incidence, with similar fracture rates in pre- and postmenopausal women regardless of therapy (tamoxifen, AI, or both). However, postmenopausal women had significantly greater major osteoporotic and hip fractures [41]. The Austrian Breast Cancer Study Group's phase III trial (ABCSG-12) of premenopausal women assigned to 3 years of goserelin plus either tamoxifen or anastrozole with or without zoledronic acid (ZOL) and bone outcomes also found a low overall fracture rate of 0.17% during a median follow-up of 48 months [42].

B. Extension of Antiestrogen Therapies and Bone Outcomes

A number of trials evaluating extended antiestrogen therapy in postmenopausal BCa from 5 to 10 years have been published over the past decade. The primary outcome measures are BCa recurrence and survival end points, but several studies have included bone outcomes. In the MA-17B trial, bone health was assessed in women receiving the AI letrozole vs placebo after 5 years of tamoxifen. After 2 years, the women receiving letrozole had substantial declines of BMD of 5.4% at the spine and 3.6% at the hip. More women on letrozole reached the T-score threshold for osteoporosis in the spine than those receiving placebo [43]. A more recent phase III study, MA-17-R [44], demonstrated a modest improvement in BCa outcomes with extended AI use. However, the longer duration of AI therapy was associated with an increased risk of fracture of 14% vs 9% ($P = 0.001$) in those treated with an AI for 10 years vs 5 years, respectively.

C. Bone Loss and Fracture Risk in PCa

In men with PCa, androgen deprivation therapy with GnRH agonists results in a profound decrease in the levels of circulating androgen, which causes high bone turnover. The rate of bone loss can be as high as 4% to 5% in the lumbar spine during the first year of therapy, significantly greater than that of a similar-aged man. On average, there is a range of 1.5% to 5% bone loss depending on the skeletal site considered [45]. The prevalence of osteoporosis in men with PCa has been shown in studies to be as high as 53% in those who have received ADT vs up to 38% in those who have not. Thus, ADT likely worsens baseline bone health. Identification of the presence of osteoporosis is determined by skeletal site measured (*e.g.*, spine or hip), and the degree of bone loss is affected by the duration of ADT, ethnicity, and lifestyle and behaviors [46, 47]. ADT has been associated with fractures in this population, as shown in several epidemiologic studies. In a systematic analysis, an overall RR of fracture of 1.23 [95% confidence interval (CI), 1.10 to 1.38] has been demonstrated, with an RR of vertebral fracture of 1.39 (95% CI, 1.20 to 1.60). The risk is increased with increased doses of ADT [48] and with the addition of antiandrogen therapy to GnRH agonists [49]. Additionally, men with PCa who experience fracture have a significantly increased risk of mortality [50].

C-1. Assessment of patients for risk of fracture at initiation of hormonal treatments

In women and men receiving treatment for BCa and PCa, respectively, the determination of the patient's risk of fracture is best done at the onset of antiestrogen or antiandrogen therapies, particularly because osteoporosis may be a preexisting condition. A number of

bone and oncologic societies have published specific algorithms to guide this [38, 45]; however, clinical judgement after a thorough history and physical examination is critical in decision-making with each patient.

In women with BCa or men with PCa, a thorough history, including personal and family history of fractures, comorbidities, medications, and nutritional factors, should be sought. A physical examination is necessary, particularly to look for spine abnormalities, including kyphosis and significant height loss. A history of prior fragility fractures and secondary causes of bone loss, including hyperparathyroidism, vitamin D deficiency, and hypogonadism, should also be determined in men, all of which are frequent in the older population. Hypogonadism would not be treated with testosterone replacement in the setting of PCa; however, it is a risk factor for low bone density. Ideally, a dual-energy X-ray absorptiometry (DXA) scan should be performed on all women and men to assess BMD. A lateral vertebral assessment to evaluate for prevalent vertebral fractures should be considered, particularly if there is substantial height loss, and can be accomplished on DXA scan or lateral X-ray. When the criteria for osteoporosis are met, treatment with antiresorptive therapy should be initiated at the time of antiestrogen or antiandrogen therapy if not already established.

D. Use of FRAX

The FRAX tool is freely available on-line and can be used to assist clinical decision-making in those who do not meet DXA T-score values for treatment. It calculates the 10-year probability of fracture risk in both men and women and can be used with or without DXA results. When using the FRAX tool, the outputs provided are the absolute 10-year probability of a major osteoporotic or a hip fracture. Guidelines from the World Health Organization and other organizations suggest that treatment should be initiated if the risk for a major osteoporotic fracture is ≥20% or if the risk for a hip fracture is ≥3% [51].

FRAX uses clinical risk factors, including age, height, weight, smoking history, prior fracture history, family history (hip fracture only), and femoral neck BMD, as well as secondary osteoporosis, including diabetes and rheumatoid arthritis, but does not use data on antiestrogen/antiandrogen therapy. When AI therapy is assumed in the "secondary osteoporosis" category of the FRAX tool, it underestimates fracture risk, which is highest while patients are actively receiving AI therapy [38]. The same can be done in men with PCa if one considers ADT therapy as secondary osteoporosis, although it may also underestimate fracture risk because it has not been validated in this population. Recently FRAX has been shown to predict falls in older men, which may be critically important in this population receiving ADT because another effect of this therapy is decreased muscle mass and function [52].

In a recent joint position statements from several international societies addressing anticancer hormonal therapy for BCa and PCa [38, 45], medical treatment was recommended in patients with a T-score less than −2.0 or if two or more clinical risk factors are present, including age >65 years, low body mass index (<20), smoking (current or history), personal history of fracture after 50 years, family history of hip fracture, glucocorticoid (dose not specified) use >6 months, and T-score less than −1.5. When T-scores are greater than −2.0 with no other risk factors, then consideration can be given to monitoring for bone loss every 1 to 2 years [38].

Premenopausal women generally are not considered at high risk for osteoporosis and fracture. However, their risks change in the setting of hormonal manipulation during the course of BCa therapy. Chemotherapy-induced ovarian dysfunction, chemical ovarian suppression with or without tamoxifen or an AI, and tamoxifen without ovarian suppression can increase the risk of bone loss. Some experts support treatment in this patient group with antiresorptive therapy if they have undergone ovarian suppression and are receiving an AI, with a T-score less than −1.0, or with a prevalent vertebral fracture, although data are limited on fractures and on the efficacy of this approach [53].

In terms of biochemical screening, secondary etiologies of bone loss should be sought when clinically indicated. These include serum levels of calcium, phosphorus, 25-hydroxy vitamin

D, (bone formation marker), thyroid-stimulating hormone, complete blood count, and serum protein electrophoresis [38]. We also recommend spot fasting second urine for calcium/creatinine ratio to rule out hypercalciuria as well as serum bone alkaline phosphatase (formation marker) and spot urine *N*-telopeptide (bone resorption marker). Some laboratories use serum C-telopeptide, another marker of bone resorption. The use of bone turnover markers has not been included in most society recommendations; however, clinicians may selectively follow bone metabolism marker trends because they can assist in determining when to initiate therapy or response to treatment.

5. Effect of Antiresorptive Treatments on BMD and Fractures

Phase III studies have demonstrated that the risk of bone loss in women with BCa and men with PCa can be ameliorated by antiresorptive therapies (Fig. 2). The foundation of anti-resorptive treatments includes intake of adequate calcium (1000 to 1200 mg daily, with food sources preferred over supplements) and vitamin D ~800 to 1000 units/d or achievement of a 25-OH vitamin D level between 30 to 40 ng/mL, as is recommended for fall and fracture prevention in the general osteoporosis population [54]. The US Preventive Services Task Force recently reported that there is insufficient evidence to weigh the benefits and harms for calcium and vitamin D when used in supplements to prevent fracture at similar doses [55]. Adequate calcium and vitamin D intake is important in decreasing the risk of hypocalcemia in the setting of antiresorptive therapies. Adequate weight-bearing and resistance exercise is also important and has been shown to limit bone loss in postmenopausal women with BCa [56] and should be encouraged, although fracture risk has not been demonstrated [38]. Men with PCa receiving GnRH agonists experience sarcopenia [57], and thus weight-bearing activities may be important to maintain balance and decrease fall risk.

6. Premenopausal BCa, Antiresorptives, and Fracture

GnRH therapies or oophorectomy used in premenopausal women create a postmenopausal state. With the abrupt change in circulating levels of estrogen, the sudden menopause is associated with a substantial loss of bone mass [58]. Given that these younger women are now iatrogenically menopausal, tamoxifen, a selective estrogen receptor modulator, can diminish the rate of bone loss as well [30]. In this population of women in whom menopause was intentionally induced with GnRH therapy, AIs can be considered as an anticancer therapy. As expected, AIs accelerate loss of bone mass. ZOL has been studied in the setting of treatment-induced ovarian dysfunction in ABCSG-12 [42] and in the CALGB trial [32] and has been demonstrated to mitigate the early, rapid bone loss that can occur.

In a trial in premenopausal women randomly assigned to GnRH agonist/tamoxifen or GnRH agonist/AI, a second randomization with ZOL every 6 months preserved bone density
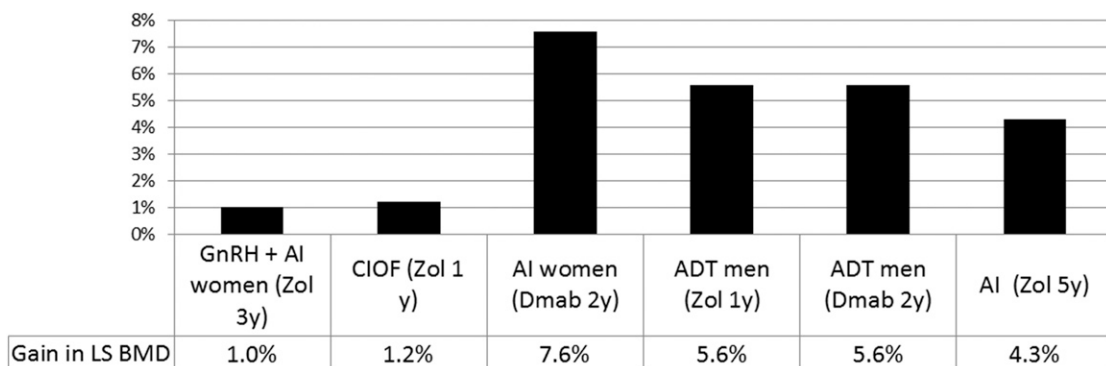

	GnRH + AI women (Zol 3y)	CIOF (Zol 1 y)	AI women (Dmab 2y)	ADT men (Zol 1y)	ADT men (Dmab 2y)	AI (Zol 5y)
Gain in LS BMD	1.0%	1.2%	7.6%	5.6%	5.6%	4.3%

Figure 2. Bone modifying agents can maintain or improve lumbar spine BMD in patients receiving hormonal manipulation for breast or prostate cancer.

in both groups over the 3-year study. In those who did not receive ZOL, BMD decreased by 9% in the GnRH agonist/tamoxifen group and by >13% in the GnRH agonist/AI group [42]. Increases in the number of patients who became osteopenic or osteoporotic were greater in the groups not receiving ZOL, with more in the anastrozole group, as one would expect.

7. Postmenopausal BCa, Antiresorptives, and Fracture

The impact of antiresorptive therapy with bisphosphonates or denosumab is well documented in postmenopausal patients with BCa receiving AI therapy. Oral bisphosphonates, including alendronate, clodronate, ibandronate, and risedronate, have been studied using variable designs and therapy durations of 1 to 5 years. Increases in BMD, particularly at the lumbar spine, were shown regardless of T-score status at onset. BMD hip changes were modest, and there are limited fracture data [38].

In the trial known as Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE), which was designed to examine the impact of ZOL on cancer outcomes, patients were randomized to receive high-dose ZOL or not for 5 years as adjuvant therapy. Assessment of fracture rates at 84 months demonstrated that the ZOL-treated group had a significantly lower overall fracture rate of 6.2%, whereas the control group had a fracture rate of 8.3% [59]. Less intensive dosing of ZOL was used in the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) and Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) studies where postmenopausal women with hormone receptor–positive BCa receiving adjuvant AI therapy were randomized to either upfront use of ZOL (4 mg) every 6 months or delayed use of the ZOL regimen [35, 60]. These studies had parallel designs, and both studies found that the ZOL up-front group had increases in BMD, but fracture rates were not statistically different across the treatment arms.

Denosumab (60 mg) given at 6-month intervals is currently FDA approved for women on AIs at high risk for osteoporotic fracture. The Austrian Breast Cancer Study Group's phase III study (ABCSG-18) examining postmenopausal women with early-stage BCa receiving adjuvant AI therapy randomized 3420 study participants to denosumab (60 mg, subcutaneously) (n = 1711) or placebo (n = 1709) every 6 months [61]. Time to first clinical fracture was decreased in the denosumab-treated group regardless of baseline BMD T-score results (hazard ratio, 0.50; 95% CI, 0.39 to 0.65). At 36 months of follow-up, ~5% of participants on AI plus denosumab experienced a fracture, whereas ~10% of participants on AI plus placebo had a fracture. Most fractures occurred in the forearm or hands. This was followed by fractures in the vertebrae, ribs, ankle or foot, humerus, pelvis or femur, lower leg or knee, and shoulder and sternum. Further morphometric vertebral fractures were decreased, as was worsening of prevalent vertebral fractures. This decreased fracture risk occurred regardless of baseline BMD or age. There were no adjudicated cases of osteonecrosis of the jaw. As expected, denosumab was associated with increasing BMD at the lumbar spine, total hip, and femoral neck. Denosumab is FDA approved for treatment to increase bone mass in women at high risk for fracture receiving adjuvant AI therapy for BCa, although ABCSG-18 enrolled postmenopausal women regardless of preexisting fracture risk. Recently, there has been evolving concern over the risk of worsening fracture risk upon stopping denosumab [62, 63]. Long-term follow-up of the ABCSG-18 participants will be of great interest. There is a growing need to define the practice of discontinuing denosumab and whether to use a bisphosphonate subsequent to denosumab [63]. However, no cancer-specific studies or guidelines have addressed this at present. This is a topic for future research and expert opinions.

In general, the anabolic agents that mimic the effects of parathyroid hormone, teriparatide, and abaloparitide and agents containing estrogen are not used in the management of bone health in patients with BCa due to the concern for stimulating the growth of micrometastatic occult tumor cells and increasing the risk of BCa recurrence. The same concept applies to PCa.

8. PCa Antiresorptives and Fracture

A number of randomized controlled trials have evaluated the efficacy of antiresorptive therapy in preserving bone in men with PCa receiving GnRH agonists. The antiresorptives bisphosphonates and denosumab have proven efficacy in this scenario and in men with idiopathic or age-related osteoporosis [45]. Improvement in BMD has been demonstrated in studies using oral alendronate or risedronate as well as intravenous pamidronate or ZOL. The earlier studies with ZOL used frequent dosing schedules of 4 mg every 3 months. A small, 1-year study demonstrated efficacy at a single dose annually [64]; however, there remains limited evidence for the efficacy in fracture prevention with bisphosphonates in this patient population [65].

Denosumab has been studied in men with PCa treated with GnRH agonist therapy. In a 3-year randomized, controlled trial of over 1400 men, denosumab (60 mg, subcutaneously) vs placebo every 6 months was given. Men treated with denosumab had significant increases in BMD at the lumbar spine, total hip, and distal 1/3 radius by 7.9%, 5.7%, and 6.9%, respectively, compared with placebo ($P < 0.0001$ for each comparison). Further, the denosumab group showed a rate of vertebral fractures of 1.5% at 36 months, whereas 3.9% of the control group experienced new vertebral fractures (RR, 0.72; 95% CI, 0.19 to 0.78; $P = 0.006$) [37]. Denosumab (60 mg, subcutaneously) every 6 months is now FDA approved for men at high risk for fracture receiving ADT for nonmetastatic PCa. There are scant data addressing the impact of stopping denosumab on BMD and fracture risk in men with PCa, and this is an area that needs to be studied.

9. Prevention of Bone Metastases

Detailed discussion of the bisphosphonates and denosumab as adjuvant BCa or PCa therapy is outside the scope of this review; however, there are evolving data that support the use of bisphosphonates or denosumab to improve cancer outcomes in certain subsets.

The meta-analysis by the Early Breast Cancer Trialists' Collaborative Group used the individual patient data from all unconfounded trials in early BCa that randomized between bisphosphonate and control and analyzed for cancer outcomes [66]. There was a wide range of bisphosphonate regimens used, and the regimens were of varying duration. In the entire population (n $>$ 18,000), there was borderline statistical significance for the use of bisphosphonate. However, among the postmenopausal women (n = 11,767), treatment with a bisphosphonate regimen was associated with a statistically significant decrease in risk of BCa recurrence (RR, 0.86; 95% CI, 0.78 to 0.94; $P = 0.002$). Similarly, bisphosphonate treatment was associated with a decrease in distant recurrence, bone recurrence, and BCa mortality (RR, 0.82; 95% CI, 0.73 to 0.93; $P = 0.002$). The meta-analysis did not identify differences by bisphosphonate class, treatment schedule, or tumor characteristics (estrogen receptor expression, lymph node involvement, tumor grade) or concomitant chemotherapy. The meta-analysis did identify a reduction in the risk of bone fractures (RR, 0.85; 95% CI, 0.75 to 0.97; $P = 0.02$)

A series of expert panel guidelines have addressed the use of adjuvant bisphosphonates in postmenopausal women, with general recommendations to consider their use in postmenopausal women who are at high risk for BCa recurrence [67, 68]. The criteria for this practice are not yet well delineated. There are concerns over the existing data, including the lack of a defined mechanism of action for the anticancer effect being selective to postmenopausal women; the lack of formal hypothesis testing in population subsets; and the absence of clarity as to which drug to use, at what dose and interval, and duration of therapy.

Adjuvant denosumab is being studied for potential anticancer effects. The ABCSG-18 study has a secondary endpoint related to cancer outcomes. Preliminary reporting of the study results in 2015 at the San Antonio Breast Cancer Symposium are notable for the addition of denosumab to the use of adjuvant AI, which reduced the risk of BCa recurrence by ~18% [69]. We eagerly await additional updates from ABCSG-18 as well as reporting from the

phase III study known as the Study of Denosumab as Adjuvant Treatment of Women With High Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy, or the DCARE study (clinicaltrials.gov identification number NCT01077154), which randomizes women with BCa to adjuvant denosumab (120 mg, subcutaneously, every 6 months) or to placebo. The primary outcome is bone metastases–free survival, with secondary outcomes including overall survival and other cancer-related events.

The efficacy of antiresorptive therapies to prevent bone metastases in PCa is also being studied. In two studies in men with nonmetastatic, high-risk PCa, ZOL showed no improvement in bone metastases–free survival rates [45]. In contrast, denosumab was shown to delay the onset of bone metastases by 4.1 months in a study of men with castrate-resistant, nonmetastatic PCa [70]. Thus, men in specific high-risk subgroups may benefit from this therapy. However, overall survival rates were not changed in the denosumab-treated men. Osteonecrosis of the jaw was higher in the treated group. Currently, denosumab is not approved to prevent bone metastases in men with PCa without bone metastases.

10. Conclusion

Bone loss and fractures in women with BCa and in men with hormone-sensitive PCa are common complications of the therapies used to treat these conditions. As advancements in treatment have improved survival, emphasis on skeletal health outcomes has become increasingly important. Individual assessment of patients, including cancer treatment history along with well-known established bone-related risk factors, must be taken into consideration to develop a plan of both nonpharmacologic and medical therapy. Collaboration of oncologists and primary care providers with bone health specialists is imperative for optimal patient care. Additional research is indicated to optimally inform clinical guidelines addressing screening, prevention, and treatment of bone health in those affected by cancer and cancer therapies.

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