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OSTEOPOROSIS AND CANCER (P TAXEL, SECTION EDITOR)

Skeletal Manifestations of Treatment of Breast Cancer on Premenopausal Women

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Abstract With increasing use of screening mammography and more effective adjuvant systemic therapies, the majority of women diagnosed with early stage breast cancer will be long-term survivors and experience personal cures. Among the common side effects of adjuvant therapies is treatment-related bone loss, primarily as a result of estrogen deprivation. Whereas this occurs in both postmenopausal and premenopausal women, this brief review will focus on pre- or perimenopausal women when initially diagnosed with breast cancer. An important distinction is between those women who retain ovarian function despite cancer or preventative treatments and the more common situation of premenopausal women who as result of cancer treatments undergo ovarian failure or early menopause. Some women with treatment-related ovarian failure will have sufficient treatment-related bone loss to be at increased risks of subsequent nontraumatic fractures and/or osteoporosis and will be candidates for antiresorptive treatments. The noncancer treatment risk factors, screening and treatments for the management of osteopenia and osteoporosis are generally the same in postmenopausal women with and without breast cancer. However, premenopausal women with relatively rapid onset of treatment-related ovarian failure and bone loss pose several challenges. Awareness of treatment-related bone loss and risks of subsequent osteoporosis is a high priority in an ever-increasing population of breast cancer survivors.

Keywords Breast cancer · Premenopausal osteoporosis · Chemotherapy-induced ovarian failure

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Endogenous Estrogens, Normal Bone Remodeling and Age- and Menopausal-Related Bone Loss

The primary source of endogenous estrogens differs in pre- and postmenopausal women. In premenopausal women, the ovaries are the major source. In postmenopausal women, androgens synthesized in the adrenal glands and adipose tissue are converted to estrogens by actions of the aromatase enzyme. Anti-estrogen drugs are mainstays in the prevention and treatment of breast cancers that are estrogen and/or progesterone receptor positive. The mechanisms of action of these drugs are either to block estradiol (ie, ligand) from binding to the estrogen receptor, or to reduce circulating endogenous estrogens. Table 1 describes breast cancer treatments and their mechanisms of action.

Osteoporosis may be thought of as an equation. On one side of the equation is the peak bone mass attained by age 30 and determined by genetics, dietary, and lifestyle factors. On the other side are normal age-related bone loss and the bone loss caused by menopause because of declining endogenous estrogen levels [1]. In normal bone remodeling, there is a dynamic balance between bone formation and bone resorption that is regulated by systemic hormones [2, 3], the immune system [4, 5], and by the receptor activator factor-kappa β ligand (RANKL) pathway [6]. Briefly, RANKL is produced by osteoblasts and binds to RANK receptors on pre-osteoclasts to stimulate osteoclastogenesis and thus bone resorption. In contrast, osteoprotegerin (OPG), also secreted by osteoblasts, inhibits osteoclast activation by acting as a decoy

Table 1 Breast cancer treatments associated with bone loss

Treatment	Class	Mechanism	Premenopausal	Postmenopausal
Tamoxifen	SERM	Block ER	Bone loss [20]	Maintain bone
Raloxifene	SERM	Block ER	ND	Maintain bone
Fulvestrant	SERD	Degrade ER	ND	ND
GnRH agonist	OF	Lower estrogens	Bone loss [66, 67]	ND
Oopherectomy	OF	Lower estrogens	Bone loss [68]	ND
Adjuvant Chemotherapy	OF	Lower estrogens	Bone loss [37, 69, 70]	Bone loss?
Aromatase Inhibitor	SEEM	Inhibit aromatase	ND	Bone loss [13, 71, 72]

ER estrogen receptor, *ND* no data, *OF* ovarian failure, *SEEM* selective estrogen enzyme modulator, *SERD* selective estrogen receptor down regulator [73], *SERM* selective estrogen receptor modulator.

receptor for RANKL, thus, preventing bone resorption. Normally, the RANKL and OPG ratio is balanced such that periods of bone resorption are counterbalanced with new bone formation. When endogenous estrogens decline, either through natural menopause or several breast cancer treatments, net bone resorption rate is greater than bone formation leading to bone loss, and in some women an increased fracture risk.

There are several risk factors for osteoporosis (Table 2). A family history of osteoporosis, smoking, alcoholism, and chronic corticosteroid treatment all increase risk for osteoporosis [7••]. More recently, candidate genes that are associated with increases in fracture risk have been identified [8, 9]. Breast cancer treatments associated with bone loss are described in Table 1 and Fig. 1. As there are several recent reviews concerning the mechanisms, screening, and treatment of bone loss in postmenopausal breast cancer survivors [10, 11••, 12, 13], this topic will be not discussed except where it is directly relevant to premenopausal women who relatively rapidly become postmenopausal from treatment.

How Breast Cancer Treatments Affect Menopausal Status

Whether a premenopausal woman develops secondary ovarian failure as a result of breast cancer treatment or retains menstrual function is a critical factor in assessing bone health. An excellent review of this important topic was published recently [14]. The difficulty in assessing menopausal status is related to several factors including a lack of a standard definition of chemotherapy-induced ovarian failure in clinical trials. Women often become transiently amenorrheic during chemotherapy, and some will subsequently reestablish ovarian function with or without menses. Biochemical markers of menopause such as estradiol or follicle-stimulating hormone are often themselves affected by ongoing anti-estrogen therapy [15], and, thus, are of limited value in determining menopausal status. Several newer markers such as anti-Mullerian hormone, a marker of ovarian reserve, show promise in determining ovarian failure in a small prospective trial, but additional studies are required [14].

Table 2 Osteoporosis risk factors*

Genetic	Lifestyle	Secondary risk factors
Parental fragility fracture	Current smoking	Rheumatoid arthritis
Sex	Alcohol >3 drinks/day	Hypogonadism (primary or secondary eg, cancer treatment)
Low body mass index	Steroids >3 mo	Inflammatory bowel
Prior fragility fracture	Immobility	Diabetes
		Hyperthyroidism

*Adapted from Kanis et al [7••].

Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen and Raloxifene

Tamoxifen is a partial agonist acting as an estrogen or an anti-estrogen depending on the target tissue and hormonal milieu. Food and Drug Administration (FDA) approved indications for tamoxifen are the prevention of breast cancer in high-risk women [16, 17], and treatment of breast cancer, irrespective of menopausal status [18]. Tamoxifen maintains bone in postmenopausal women in the low endogenous estrogen environment relative to premenopausal patients (Fig. 1) [12, 19]. In contrast, tamoxifen causes bone loss in premenopausal women in a small placebo-controlled trial [20]. The mean percent decrease in the lumbar spine per year in premenopausal women was 1.44 % and 0.24 % for the tamoxifen and placebo, respectively.

Is tamoxifen-induced bone loss a major problem in the clinic? No, because the majority of premenopausal women over 40 years of age who receive adjuvant chemotherapy develop Chemotherapy-induced ovarian failure (CIOF), or if they retain menstrual function become menopausal at earlier ages than those who did not receive chemotherapy [21]. In addition, for those under 40 years of age who retain menstrual function, the proximity to the age of peak bone mass (ages 30–

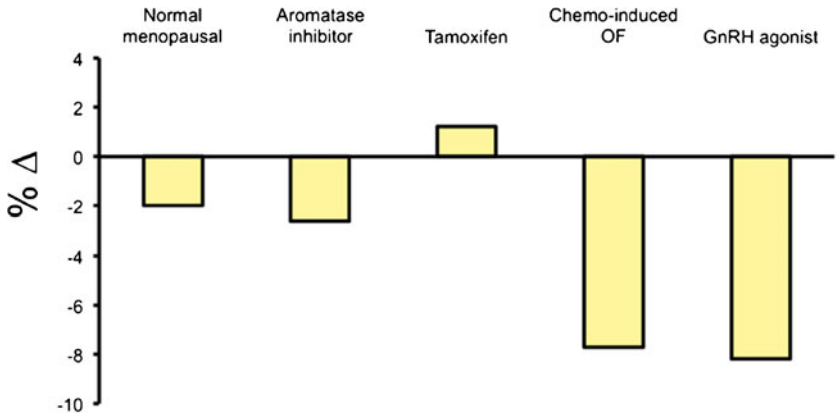

Fig. 1 Percentage change in bone mineral density over one year in the lumbar spine with various breast cancer treatments. Adapted from ref 11

35 years) is such that losses due to tamoxifen may be of little clinical significance. For premenopausal women who have underlying risk factors for osteoporosis (Table 2) and are placed on tamoxifen for prevention or treatment of breast cancer, measurement of bone mineral density (BMD) should be considered.

Raloxifene is FDA approved for prevention of breast cancer in postmenopausal women [22, 23], and is approved for the treatment of osteoporosis in postmenopausal women based on a statistically significant reduction in vertebral fractures, but not nonvertebral fractures [22, 24–26]. Raloxifene and tamoxifen have similar side effects such as increased vasomotor symptoms and slight increases in the risks of major thromboembolic events. However, unlike tamoxifen, raloxifene does not cause endometrial hyperplasia or a slightly increased risk of endometrial cancer. Although approved for the prevention of breast cancer in postmenopausal women, raloxifene does not have an indication for the treatment of breast cancer and should not be used after tamoxifen based on the potential for cross-resistance of similar SERMS. There are several newer promising SERMS in clinical development for osteoporosis and breast cancer prevention [27].

Fulvestrant is a selective estrogen receptor down-regulator FDA approved for postmenopausal women with ER positive metastatic breast cancer [28]. Data is lacking concerning the effects of fulvestrant in premenopausal women in general, and specifically in bone.

Premenopausal Women Who Develop Ovarian Failure and are Rendered Postmenopausal by Breast Cancer Treatments

Oophorectomy and Gonadotropin-Releasing Hormone (GnRH) Agonists

Both oophorectomy and GnRH agonist either alone, or in combination with tamoxifen or aromatase inhibitors, are used to treat premenopausal women with ER positive breast cancers. Both oophorectomy and GnRH agonists cause bone loss by decreasing ovarian estrogens. Treatments with GNRH agonist for 2 years or cyclophosphamide, methotrexate and fluorouracil (CMF) adjuvant for 6 months were directly compared in a randomized trial of over 1600 premenopausal women with early stage breast cancer, 75 % of whom were ER positive [29]. The therapeutic efficacy of the 2 treatments was comparable. In a smaller substudy at 2 years, the mean decline in BMD at the lumbar spine was -10.5 % and -6.5 % ($P=0.0005$); at the femoral neck -6.4 % and -4.5 % ($P=0.04$) in the GnRH and CMF-treated groups, respectively [30]. Ninety-five percent of the GnRH agonist group was amenorrheic for 2 years (the entire 2-year, correct) whereas 60 % of CMF-group was amenorrheic at 2 years (the entire 2-year, correct) [29]. Less bone loss was observed in the CMF group because approximately 40 % of them did not develop CIOF whereas virtually the entire GnRH agonist-treated group had their circulating estrogens reduced to postmenopausal levels.

The Austrian Breast Cancer Study Group Trial 12 is another illustrative trial in over 1800 premenopausal women with early stage breast cancer that received GnRH agonist and were randomized to either tamoxifen or aromatase inhibitor for 5 years with a secondary randomization to zoledronic acid 4 mg every 6 months for 3 years or no zoledronic acid [31]. Over 400 women participated in a bone sub-study that measured BMD at baseline (or time 0), 6, 12, 24, and 36 months [32]. The Trial 12 results showed the mean difference in T scores measured at 36 months decreased more in the anastrozole treated group than in the tamoxifen treated group, but even more important was how many women made the transition from normal BMD to osteopenia to osteoporosis over the 3-year treatment period. Among 16 % defined to be osteopenic in the tamoxifen + GNRH agonist group at the baseline evaluation, 46 % were osteopenic at 3 years, and none were osteoporotic. In contrast, 24 % in the anastrozole + GnRH agonist were osteopenic at baseline, with 56 % osteopenic, and 25 % osteoporotic at 3 years. Zoledronic acid virtually eliminated the bone loss in both treatment arms.

Chemotherapy-Induced Ovarian Failure

Premenopausal women adjuvant chemotherapy may develop ovarian failure due to the direct effect of chemotherapy on the ovary [33]. Risk factors for CIOF include age, with older premenopausal women more likely to develop CIOF than younger women [34], and the specific type of chemotherapy (ie, alkylating such as cyclophosphamide have higher risks of CIOF than the taxanes), as well as higher doses and prolonged durations of chemotherapy [35]. In populations of premenopausal women, the risks of CIOF can be estimated, but for the individual woman there is no current method for predicting CIOF.

Trials that prospectively defined CIOF [36, 37], or observed prolonged periods of amenorrhea greater than 3 years after chemotherapy [38], were associated with a greater magnitude of bone loss [36–39] relative to trials in women who retained menstrual function or in those trials in which bone loss was reported irrespective of menstrual status [40]. Percentage decrease in BMD in the lumbar spine at 1 year ranged from 4 %–8 % for those with CIOF or prolonged amenorrhea, whereas women who retained menstrual function had no loss of bone. Managing this acute bone loss is made more difficult since virtually all the guidelines for screening and managing osteoporosis are based on the experiences of postmenopausal women.

Screening for Osteoporosis in Premenopausal Women

Dual energy x-ray absorptiometry (DEXA) scan is used routinely to measure BMD and screen for osteoporosis. Guidelines for anti-resorptive treatments based primarily on T-scores are well established in men and postmenopausal women without cancer [7••, 41, 42], in addition to several guidelines in postmenopausal women receiving aromatase inhibitor treatment [10, 43, 44]. However, there are relatively few data to inform screening recommendations for premenopausal women that develop ovarian failure due to breast cancer treatments.

There are several important points to consider in evaluating premenopausal osteoporosis in general [45–48] and in particular, premenopausal women with bone loss due to breast cancer treatments [49••]. The majority of premenopausal women with osteoporosis or low BMD will have some secondary cause, although about one-third of them are idiopathic [47, 50, 51]. If the secondary cause is treatable, the BMD often improves. The Z-score, or the number of standard deviations compared with an age-matched control population, as opposed to the T-score, is preferred in premenopausal women [52]. Z-scores of ≤ -2.0 are defined as below the expected range for age, whereas Z-scores > -2 are within the expected range for age. Although there is some controversy surrounding the use of bisphosphonates in premenopausal women [45, 47], there are data to support the use of these drugs in premenopausal with treatment-related ovarian failure [31, 37].

The FRAX Assessment Tool, which estimates the 10-year fracture risk with or without BMD measurements [53], (http://www.shef.ac.uk/FRAX/tool) is indicated for men age 50 and older and postmenopausal women although it has some inherent limitations in these populations [7••]. There is no experience with FRAX in premenopausal women with treatment-related bone loss. Lastly, the role bone turnover markers that reflect bone resorption and bone formation is not as yet established in any population for routine clinical management.

It is important to remember that reductions in fractures are the endpoint in clinical trials designed to evaluate drugs to prevent or treat osteoporosis [54]. In contrast, trials of treatment-related ovarian failure rely on a BMD endpoint because fractures are uncommon in premenopausal women. Even in the largest clinical trials the sample sizes are too small and the duration of follow-up too short to detect a decrease in fracture rates. While BMD changes serve as surrogate endpoint for fractures in postmenopausal women, there is more uncertainty when using BMD changes to predict who will experience fractures among premenopausal women.

Bisphosphonates

Both zoledronic acid and denosumab are FDA approved for the treatment of skeletal metastases in breast cancer and other solid tumors. Zoledronic acid has been the predominant bisphosphonate used in clinical trials in premenopausal women with treatment-related ovarian failure performed in the last ten years [31, 37, 40]. Zoledronic acid eliminates the bone loss due to CIOF or GnRH agonist with tamoxifen or anastrozole. Zoledronic acid is not FDA approved for use in premenopausal women with treatment-related ovarian failure but is compendia listed as an accepted use for “osteopenia, secondary to ovarian dysfunction induced by adjuvant chemotherapy in premenopausal women with early-stage breast cancer.”

The optimal schedule and duration of treatment of zoledronic acid is unknown. Four mg intravenously (IV) administered either every 3 or 6 months for 1 or 2 years was used in the clinical trials. An annual dose of 5 mg (IV) of zoledronic acid is approved for use in postmenopausal women [55], and a small single-arm trial showed statistically significantly improved BMD and decreased bone resorption markers in osteopenic cancer survivors [56]. With respect to oral bisphosphonates, clodronate 1600 mg/d for 2 years prevented BMD loss [39, 57], however, clodronate is not FDA approved in the United States. In contrast, oral risedronate at 35 mg/d for 1 year had no statistically significant effect on BMD in a placebo-controlled trial [58]. There are no randomized trials

of oral alendronate or ibandronate in premenopausal women with treatment-related ovarian failure. Denosumab, the rank ligand inhibitor, is FDA approved for postmenopausal osteoporosis, the treatment of skeletal metastases from breast cancer and aromatase inhibitor-induced bone loss [59, 60]. There are no results as yet for denosumab in the prevention of bone loss due to treatment-related ovarian failure.

The side effects of zoledronic acid include acute fever, muscle aches and pain (on initial infusion), potential renal dysfunction, and osteonecrosis. Osteonecrosis is defined as necrotic bone for more than 6 weeks in an area normally covered by mucosa, prior or current bisphosphonate (or denosumab), and no prior history of radiation. In trials of oral bisphosphonates in postmenopausal women or zoledronic acid prescribed for bone loss, the incidence of osteonecrosis is extremely low on the order of 0.2 % or less [61]. Denosumab is currently being evaluated in early stage breast cancer. When denosumab or zoledronic acid are used monthly for extended durations of time to treat skeletal metastases the incidence of osteonecrosis is between 1 %–1.5 % [62].

Suggested Approach and Recommendations

The American Society of Clinical Oncology (ASCO) update on bisphosphonates and bone health in women with breast cancer [63], and the National Cancer Center Network (NCCN) Task Force Report on bone health in cancer care [64••], both consider treatment-related ovarian failure as a risk factor bone loss. Figure 2 illustrates a suggested approach and recommendations for premenopausal women with breast cancer to optimize bone health. All premenopausal women with early stage breast cancer that receive either adjuvant chemotherapy or ovarian ablation should be evaluated for osteoporotic risk factors and counseled regarding lifestyle changes that promote bone health. These include adequate intake of calcium and vitamin D, lifelong participation in regular weight-bearing and muscle-strengthening exercise, cessation of tobacco use, identification and treatment of alcoholism [42]. Those that have treatment-related amenorrhea for more than 1 year should have BMD assessed by central DEXA. If T score is ≤ -2.0 and/or the Z-score is ≤ 2.0, we recommend a vitamin 25-OH D level and parathyroid hormone level should be obtained to rule out secondary causes of bone loss. The threshold for initiating bisphosphonate in premenopausal women with breast cancer receiving treatment varies [49••, 63, 64••]. The recommendations vary from T scores of ≤1.5 with osteoporotic risk factors to ≤2.5, but none has been validated or correlated with increased fracture risk in the premenopausal women with early treatment-induced ovarian failure.The schedule of zoledronic acid in trials of treatment-induced ovarian failure is 4 mg every 3-6 months for 1-2 years. [37, 40] Oral bisphosphonates, denosumab or one

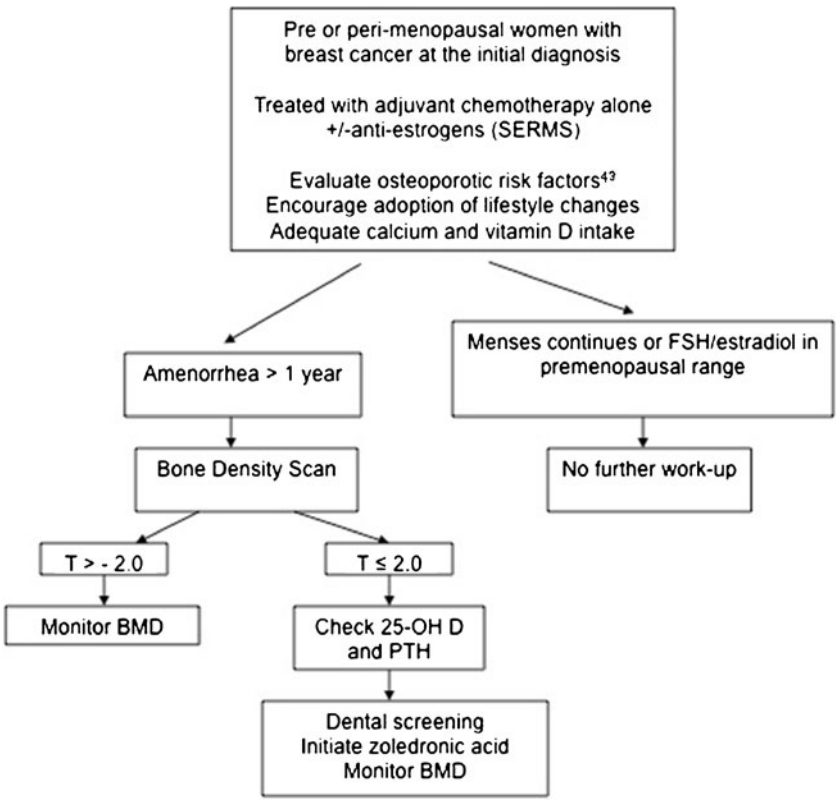

Fig. 2 Suggested algorithm for maintaining bone health in premenopausal women with breast cancer receiving treatments. (Adapted and synthesized from references [11••, 49••, 63, 64••])

annual dose of zoledronic acid may be used, however, there are no data in treatment-induced ovarian failure.

Conclusions

The majority of women diagnosed with premenopausal breast cancer will be long-term survivors and will experience personal cures. Thus, maintaining optimal health is a high priority for this population. Chemotherapy or ovarian ablation causes relatively rapid bone loss in premenopausal patients, some of whom will be at risk for nontraumatic fractures in subsequent decades. Whereas the guidelines to screen, prevent, and treat osteoporosis for postmenopausal women are evidence-based, there is uncertainty in regarding the management of premenopausal women with treatment-induced ovarian failure, and guidelines in this population are primarily consensus recommendations. More important than consensus-based guidelines that are not presently evidence-based, is the awareness among health care providers and premenopausal women with breast cancer that treatment-induced ovarian failure can cause bone loss and the potential for osteoporosis. Studies suggest that education is lacking concerning this problem [65]. In addition, local practice patterns vary such that the medical oncologist, endocrinologist, gynecologist, or primary care physician may assume the responsibility for bone health. It is important that breast cancer survivors understand the potential of treatment-related ovarian failure and bone loss and who among the health care providers is going take responsibility for this problem.

Compliance with Ethics Guidelines

Conflict of Interest L Doo declares that she has no conflicts of interest. CL Shapiro declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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