Aging and Osteoporosis in Breast and Prostate Cancer

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Abstract

As people with cancer survive longer, and as the US population ages, skeletal effects of cancer treatment are becoming more pronounced. This is particularly true for breast and prostate cancer survivors because of the high average age of patients with these malignancies, the propensity of older adults in general toward the development of osteoporosis, and the wide use of therapeutic agents in these cancers that negatively impact bone health. Various therapies used in the treatment and prevention of cancer may cause decreases in bone mineral density and an increased risk of debilitating fracture, even in the absence of bone metastases. Aging is both a baseline risk factor in the development of osteoporosis and bony fracture, as well as a predictor of poor outcome after fracture. A variety of mechanisms may be responsible for the development of bone loss in patients with breast or prostate cancer. Cytotoxic chemotherapy may directly exert long-term toxic effects on bone. Chemotherapy and endocrine therapy can induce hypogonadism, leading to an increased rate of bone loss. The risk of skeletal events in older adults due to cancer therapy should be appreciated by all oncologists, geriatricians, and internists. The following review may serve as a guide to the skeletal side effects of cancer therapy in older adults with breast or prostate cancer, how to screen for treatment-related bone loss, and how to best prevent and/or treat skeletal events. CA Cancer J Clin 2011;61:139–156. © 2011 American Cancer Society, Inc.

Introduction

Osteoporosis and cancer are primarily diseases of aging. This is particularly true for breast cancer (median age at diagnosis and death is 61 years and 68 years, respectively) and prostate cancer (median age at diagnosis and death is 67 years and 80 years, respectively).1 The types of therapies used in the treatment of these cancers may compound the inherent risk of osteoporosis and fracture.2 Osteoporosis is associated with hormonal and age-related changes in bone microarchitecture, a decline is bone mineral density (BMD), increased bone fragility, and a propensity to develop bone fractures.2,3

Aging alone tends to be associated with a rate of bone loss of between 0.5% and 1% per year in both men and women starting from middle age.3,4 Bone loss in women occurs most rapidly immediately after menopause at an annual rate of 3% to 5% over 5 years, mostly due to a decrease in circulating estrogens.3 Osteoporosis is estimated to affect approximately 1 in every 3 postmenopausal women worldwide.5 White women have an estimated 40% lifetime risk of developing an osteoporotic fracture.6 Osteoporotic fractures may also result in a significantly increased risk of mortality. Although men are less likely than women to develop osteoporosis, men have significantly higher mortality rates after osteoporotic fractures.7 Men who suffer an osteoporotic fracture of the hip have been reported to have a 1-year mortality rate of 36%.2,8 Women have an estimated 1-year mortality risk after hip fracture of 21%.8 Geriatric syndromes such as a propensity toward falls, delirium, dementia, and incontinence can predispose both toward osteoporotic fractures as well as increase morbidity and mortality and lengthen recovery time from fractures.9

To understand the relation between breast and prostate cancer therapy, aging, and bone health, studies evaluating the incidence and prevalence of treatment-related bone loss in older adults with breast and prostate cancer and trials
evaluating the role of treatments of bone loss in the setting of these cancers were identified by a search of the PubMed database through the end of August 2010. Additional studies were identified by cross-referencing the reference lists in retrieved articles, and further information was obtained from recent scientific meetings.

**Chemotherapy-Related Bone Loss**

Survivors of many types of cancer are at risk of bone loss due to direct effects of cancer therapy on bone resorption and formation. High-dose methotrexate, for example, inhibits bone formation and increases bone resorption in rat models and human osteoblasts in vitro,\textsuperscript{10} and osteopenia has been observed as a long-term side effect in children and young adults treated with methotrexate for osteosarcoma.\textsuperscript{11} Methotrexate is used as a part of adjuvant therapy in breast cancer. Doxorubicin, a drug commonly used to treat breast cancer both in the adjuvant and metastatic setting, has inhibitory effects on bone formation both in vitro and in animal models.\textsuperscript{10,12,13} Cyclophosphamide, also widely used in breast cancer, has been shown to decrease the number of osteoblasts and osteoclasts on bone surfaces in animal models.\textsuperscript{14}

Glucocorticoids are commonly used as supportive therapy in solid tumors, including both breast and prostate cancers. When given over long periods, glucocorticoids such as prednisone and dexamethasone are known to cause rapid bone loss through a number of pathways, including decreased osteoblastic activity,\textsuperscript{15} increased bone resorption, changes in muscle strength, changes in calcium absorption and excretion, and interference with growth hormone and growth factor pathways.\textsuperscript{16} In patients taking long-term glucocorticoids (> 7.5 to 15 mg of prednisone per day for >5 years) for reasons other than cancer treatment, it has been estimated that up to 30% will experience osteoporotic fractures regardless of age or menopausal status.\textsuperscript{17} It is not clear, however, whether the use of pulse steroids given as supportive care in breast and prostate cancer produces these detrimental effects on bone. Although data from hematologic malignancies may provide some guidance, studies in patients taking high-dose steroids for hematologic malignancies have failed to show increased bone loss due to steroids. Ratcliffe et al compared 50 young women treated for lymphoma with chemotherapy and high-dose steroids with 78 healthy controls.\textsuperscript{18} They found that only those women who went through treatment-induced early menopause had a decrease in BMD. Those who did not develop treatment-induced menopause did not have lower BMD compared with the general population, despite the high doses of steroids received.\textsuperscript{18} These findings suggest that short courses of steroids may not have a substantial impact on bone health; however, a larger study would be necessary to identify a small effect.\textsuperscript{10}

**Endocrine-Related Bone Loss**

Survivors of breast and prostate cancer are also at risk of bone loss due to hypogonadal states induced by cancer therapy, either as an intended result of therapy (as in the treatment of hormone-dependent tumors) or as an unintended side effect (such as with the use of alkylating agents). Early menopause is associated with lower bone density and increased fracture risk later in life.\textsuperscript{19,20} In patients with breast and prostate cancer, osteoporosis at older ages may be accelerated through a number of mechanisms, including premature menopause resulting from chemotherapy, hypoestrogenemia as a result of aromatase inhibition, deliberate ovarian ablation, or medical or surgical castration.\textsuperscript{21-24}

**Ovarian Ablation**

Ovarian ablation (either medical or surgical) accelerates bone loss in premenopausal women. It is thought that the earlier in life menopause occurs, the lower BMD will be later in life. Older adults with a history of premenopausal breast cancer may therefore be at an increased risk of osteoporosis compared with adults of similar age.\textsuperscript{20} A subset analysis of a large study compared the changes in BMD among women treated with a gonadotropin-releasing hormone (GnRH) agonist (goserelin acetate) versus standard chemotherapy for early breast cancer. The 53 women treated with goserelin had an average of 10.5% bone loss in the spine 2 years after starting treatment, compared with only 6.5% bone loss in those who received standard chemotherapy. Bone density improved after goserelin was withdrawn and many women recovered menses.\textsuperscript{25} Another study of a cohort of 463 patients who underwent oophorectomy for benign conditions showed an almost doubling of the risk of vertebral fractures and a 50% increase in forearm fractures after a median follow-up of 15.3 years in comparison with population-based, age-specific normative data.\textsuperscript{26}
Even after natural menopause, ovarian ablation with oophorectomy may be associated with increased numbers of skeletal events. Melton et al studied 340 postmenopausal women who underwent bilateral oophorectomy for benign ovarian conditions between 1950 and 1987. After a median follow-up of 16 years, 194 women had more than 500 fractures. The osteoporotic fracture rate was significantly increased when compared with the standardized incidence ratios (SIRs) of the population at large (SIR, 1.54; 95% confidence interval [95% CI], 1.29-1.82).27 However, data are conflicting on this point. Antoniucci et al reported on the 6295 women in the Study of Osteoporotic Fractures. The authors found that there was no increased incidence of fracture between those 583 women who underwent postmenopausal oophorectomy and those 5712 who did not (hip fracture hazard ratio [HR], 1.1 [95% CI, 0.9-1.5]; vertebral fracture HR, 0.7 [95% CI, 0.5-1.2]).28

Tamoxifen
Tamoxifen, a selective estrogen receptor modulator (SERM), is a widely used endocrine treatment for hormone receptor–positive breast cancer.29 Although tamoxifen is generally an estrogen antagonist, it may also have estrogen-like properties in some tissues. In postmenopausal women, tamoxifen acts as an estrogen agonist in bone, resulting in increased bone formation compared with controls.30,31 This is in contrast to observations in premenopausal women, in whom tamoxifen is associated with bone loss compared with controls,32,33 with an annual change in BMD of -1.4% per year compared with baseline in one study conducted over a 3-year period.33

Fracture risk is also affected by tamoxifen use in older adults. In a population-based, case-control study of women age 50 years or older, with or without breast cancer, who suffered a first osteoporotic fracture, current use of tamoxifen was associated with a significant decrease in fracture risk (HR, 0.68; 95% CI, 0.55-0.84) compared with controls. Although menopausal status is not reported, one might assume that very few patients were premenopausal, because only 14% of patients were younger than age 60 years.34

Aromatase Inhibitors
Aromatase inhibitors (AIs), prescribed in both the adjuvant and metastatic setting for the treatment of postmenopausal women with hormone receptor-positive breast cancer, are potent inhibitors of estradiol production and hence markedly decrease circulating levels of estrogen.29 The depletion of estrogen has a negative effect on bone density.21,29,35 Three AIs are currently in common use: anastrozole, letrozole, and exemestane. Exemestane has weak androgenic activity and it had been postulated that it might have the most favorable bone profile as a result.36,37 However, in the LEAP trial (letrozole [L], exemestane [E], and anastrozole [A] pharmacodynamics trial), the effects of all 3 AIs were compared in postmenopausal women, and no significant difference was found with regard to biochemical bone markers or parathyroid hormone.38

A number of phase 3 clinical trials reporting on the adjuvant use of AIs have reported differences in the risk of fracture between patients taking AIs versus tamoxifen. Bone subprotocols of these large studies have been performed as well, which measured BMD and other markers of bone turnover among a subset of the population in the larger studies. At least one large retrospective cohort study compared fracture rates between patients taking AIs versus controls in the general population. All these trials had median ages of older than 60 years at the time of enrollment. Comparisons between the different trials are presented in Table 1.39-52 The common finding in the studies comparing AIs with tamoxifen was an increased risk of bone loss and an increased risk of fractures in women taking AIs. Among the few trials that compared AIs with placebo, there was at least a trend toward increased fracture rates in patients taking AIs compared with age-matched controls.39-52

Androgen Ablation
Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer.53 Survival in men with nonmetastatic prostate cancer treated with ADT is long, with a median survival of greater than 7 years.54 Hence, long-term effects on bones are of particular concern. At least one study has also suggested skeletal fractures as an adverse predictor of overall survival in men with prostate cancer.55

Even at baseline, men with prostate cancer who have not received ADT have a higher incidence of osteoporosis than the general age-matched population.56 Effects of hormone treatment most likely compound the problem.21
| STUDY                      | NO. OF PATIENTS | STUDY TYPE                  | MEDIAN AGE | PATIENT CHARACTERISTICS                          | AGENTS COMPARED                       | MEDIAN FOLLOW-UP TIME | BMD CHANGES<sup>a</sup>                                                                 | FRACTURES                                                                 |
|---------------------------|-----------------|-----------------------------|------------|--------------------------------------------------|--------------------------------------|-----------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Eastell 2008<sup>39</sup> and Forbes 2008<sup>40</sup> (ATAC) | 6186 (197 in bone substudy) | Double-blind randomized controlled | Core study: 64 y (SD, 9 y) Bone substudy: 64 y (25%-75% range, 57 y-71 y)<sup>41</sup> | Postmenopausal early breast cancer | Anastrozole × 5 y v vs tamoxifen × 5 y | 100 mo                  | BMD substudy (after 5 y of treatment): Anastrozole: -6.08% in L-spine, -7.24% in total hip Tamoxifen: +2.77% in L-spine, +0.74% in total hip 
<sup>P</sup> < .0001<sup>19</sup> | Anastrozole during 5 y of treatment: 2.93% per y 
Tamoxifen during 5 y of treatment: 1.90% per y 
<sup>P</sup> < .0001 |
|                           |                 |                             |            |                                                  |                                      |                       | Letrozole 8.6% over entire follow-up period Tamoxifen: 5.8% over entire follow-up period 
<sup>P</sup> < .001 | Letrozole after 5 y of treatment: 1.56% per y Tamoxifen after 5 y of treatment: 1.51% per y 
<sup>P</sup> = NS<sup>10</sup> |
| Coates 2007<sup>42</sup> (BIG 1-98) | 4922            | Double-blind randomized controlled | 61 y (range, 38 y-90 y) | Postmenopausal early stage breast cancer | Letrozole × 5 y vs tamoxifen × 5 y | 51 mo                  | NR                                                                                       |                                                                                     |
|                           |                 |                             |            |                                                  |                                      |                       | Letrozole 24 mo after completion of tamoxifen: 3.6% at hip, -5.35% at lumbar spine Placebo 24 mo after completion of tamoxifen: -0.71% at hip (<sup>P</sup> = .04) -0.70 at lumbar spine (<sup>P</sup> = .008) | Letrozole: 3.6% from time of completion of tamoxifen Placebo: 2.9% from time of completion of tamoxifen 
<sup>P</sup> = .24 |
| Goss 2003<sup>43</sup> and Perez 2006<sup>44</sup> (MA-17) | 5187 (226 in bone substudy) | Double-blind randomized controlled | Core study: 62 y (26% aged ≥ 70 y) Bone substudy: 61 y (19% aged ≥ 70 y) | Postmenopausal early stage breast cancer | Letrozole vs placebo after completing 5 y of tamoxifen therapy | 28.8 mo after completing tamoxifen (24 mo in bone substudy) | Letrozole: -2.17% per y in L-spine at 24 mo -2.72% per y in femoral neck at 24 mo Placebo: -1.84% per y in L-spine, -1.48% in femoral neck 
<sup>P</sup> = NS in L-spine 
<sup>P</sup> = .024 in femoral neck | After 1 y off therapy, no significant differences were noted. |
| Geisler 2006<sup>45</sup> and Lonning 2005<sup>46</sup> | 147             | Double-blind randomized controlled | 60 y (range, 46 y-73 y) | Postmenopausal early breast cancer | Exemestane for 2 y vs placebo followed by 1 additional y of follow-up | 36 mo                  | Exemestane: -2.17% per y in L-spine at 24 mo -2.72% per y in femoral neck at 24 mo Placebo: -1.84% per y in L-spine, -1.48% in femoral neck 
<sup>P</sup> = NS in L-spine 
<sup>P</sup> = .024 in femoral neck | NR |
| STUDY | NO. OF PATIENTS | STUDY TYPE | MEDIAN AGE | PATIENT CHARACTERISTICS | AGENTS COMPARED | MEDIAN FOLLOW-UP TIME | BMD CHANGES | FRACTURES |
|-------|----------------|------------|------------|-------------------------|-----------------|----------------------|-------------|-----------|
| Coombes 200747 and Coleman 200748 (IES) | 4724 (200 in bone substudy) | Double-blind randomized controlled | Core study: > 60 y (42.8% between ages 60 y-69 y, 25% aged ≥ 70 y); Bone substudy: NR | Postmenopausal early breast cancer | Tamoxifen × 2 to 3 y followed by exemestane × 2 to 3 y vs tamoxifen × 5 y | 58 mo from start of tamoxifen (median exposure to exemestane, 30 mo) | Exemestane after tamoxifen: -2.7% at spine 6 mo after switching from tamoxifen, -3.6% 2 y after switching from tamoxifen | Tamoxifen alone: No change value not given |
| Hadji 2009 (for TEAM trial)49 | 161 | Double-blind randomized controlled | 61 y (SD, 7.3 y) | Postmenopausal early breast cancer | Exemestane × 5 y vs tamoxifen × 2 to 3 y followed by exemestane × 2 to 3 y | 12 mo | Exemestane (from beginning of intervention): -2.8% at spine at 12 mo | Tamoxifen (from the beginning of intervention): +0.5% at spine at 12 mo P = .0008 NR |
| Jones 2008 (for TEAM trial)49 | 167 | Double-blind randomized controlled | Tamoxifen: 66 y (range, 42 y-87 y); Exemestane: 63 y (range, 40 y-87 y) | Postmenopausal early breast cancer | Exemestane × 5 y vs tamoxifen × 2 to 3 y followed by exemestane × 2 to 3 y | 24 mo | Exemestane at 24 mo from beginning of intervention: -3.0% at spine | Tamoxifen at 24 mo from beginning of intervention: +1.2% at spine P = .02 Exemestane: 3.3% from the beginning of intervention | Tamoxifen: 3.4% from the beginning of intervention P = NS |
| Mincey 200651 | 12,368 | Retrospective cohort | Aromatase inhibitor: 65.7 y (SD, 11.2 y); Control: 63.5 y (SD, 12.6 y) | Breast cancer with no documented history of tamoxifen use or bone metastases | Aromatase inhibitors vs no aromatase inhibitors | 20 mo | Aromatase inhibitors: 6.0 new diagnoses of osteopenia or osteoporosis per 100 person-y; 8.7% developed new osteopenia or osteoporosis over entire follow-up period; Controls: 4.7 new diagnoses of osteopenia or osteoporosis per 100 person-y; 7.1% developed new osteopenia or osteoporosis over entire follow-up period P = .001 | Aromatase inhibitors: 8.6 per 100 person-y 13.5% over entire follow-up period; Controls: 6.4 per 100 person-y 10.3% over entire follow-up period P = .01 |
| Burnett-Bowie 200952 | 69 | Double-blind randomized placebo controlled | 66 y (SD, 4 y) | Men aged ≥ 60 y with borderline or low testosterone levels and hypogonadal symptoms | Anastrozole vs placebo | 12 mo | Anastrozole: -1.7% at spine over 1 y Placebo: +0.1% over 1 y (P = .001) | NR |

BMD indicates bone mineral density; ATAC, Anastrozole, Tamoxifen, Alone or in Combination trial; SD, standard deviation; NS, not significant; BIG 1-98, Breast International Group 1-98; NR, not reported; MA-17, National Cancer Institute of Canada Clinical Trials Group Trial MA.17; IES, Intergroup Exemestane Study; TEAM, Tamoxifen Exemestane Adjuvant Multicentre trial.

*Unless otherwise indicated, P values reflect the level of significance of the difference between the aromatase inhibitor and its comparator, not between the aromatase inhibitor and baseline.
A Danish case-control registry study compared more than 15,000 men aged older than 50 years who had fractures with 45,000 men who did not. The authors found that a diagnosis of prostate cancer was associated with an increased odds ratio (OR) for fracture of 1.8 (95% CI, 1.6–2.1) and ADT was associated with an increased OR of 1.7 (95% CI, 1.2–2.5). It was noted that the increased risk became apparent soon after diagnosis and persisted even in long-term survivors.57

Retrospective cohort studies of men who have survived prostate cancer for many years have demonstrated that ADT therapy is associated with an increase in fracture risk (Table 2).58-65 Shahinian et al performed a Surveillance, Epidemiology, and End Results (SEER) database study of 50,613 men who were diagnosed with prostate cancer between 1992 and 1997. Five years after starting treatment, 19.4% of survivors who received ADT developed a fracture at any site, whereas only 12.6% of survivors not receiving ADT developed a fracture.58 Dickman et al studied almost 18,000 men who were treated for prostate cancer with bilateral orchiectomy, and compared their fracture risk with that of approximately 360,000 healthy controls. The authors found that those who had undergone orchiectomy had a fracture risk over 10 years of 12% at the femoral neck alone, compared with 5% in the general population.60 Smith et al conducted a claims-based retrospective cohort study of 3887 men with nonmetastatic prostate cancer receiving GnRH agonists compared with 7774 who did not receive these agents. GnRH agonists were associated with an increased clinical fracture risk (7.88 clinical fractures per 100 person-years in the GnRH group vs 6.51 per 100 person-years in controls; relative risk [RR], 1.21; 95% CI, 1.14–1.29 [P < .001]).59 However, these studies are limited in that fractures were not designated as osteoporotic versus pathologic, and no relation with BMD was performed.

Prospective studies show an apparent negative impact of long-term prostate cancer therapy on bone health.61 Although prospective cohort studies have evaluated treatment-related bone loss as a result of ADT, only a few of these studies have followed patients for at least 2 years after the initiation of therapy.62-65 Likewise, all of these studies have been performed in small numbers of patients. Table 2 summarizes studies performed on the association between ADT, BMD, and fracture.58-65

Further information regarding the natural history of bone loss secondary to ADT can be derived from control arms of randomized clinical trials that investigated the use of bisphosphonates in this setting. Although the control groups tended to show varying degrees of bone loss, none of the studies to date have reported on patients followed for longer than one year on ADT alone, and thus the long-term effects on BMD remain poorly elucidated. Table 3 provides further information on these studies.66-80

Assessment of Bone Loss

Despite the evidence that cancer treatments increase bone loss and fracture risk in patients with various cancers, there remains debate on how best to define those patients at risk, and how to best treat them.35,81-83 Individuals with a history of cancer have been shown to have a poor understanding of osteoporosis and its risk factors,84 underscoring the need for patient education and provider vigilance.

Osteoporosis has been defined by the World Health Organization (WHO) as BMD less than 2.5 standard deviations (SDs) below that expected for a healthy young woman (T score of < -1.0, ≥ -2.5). The most widely validated method of evaluating BMD is with dual-energy x-ray absorptiometry (DEXA) scans.85,86 Osteopenia is defined as bone loss that is more than 1 SD below that of a healthy young woman (T score < -1.0, ≥ -2.5), but that does not meet criteria for osteoporosis.

The US Preventive Services Task Force (USPSTF) recommends screening for osteoporosis in all women aged 65 years and older, and in women ages 60 to 64 years who are considered at higher risk of osteoporosis.87 In addition, the American College of Physicians has recommended screening for men older than age 50 years who have an increased risk of developing osteoporosis.88 The question of who is considered high risk remains unresolved and is noted to be the subject of some disagreement. Potential high-risk factors in women were noted by the USPSTF to include increasing age, low calcium and vitamin D intake, family history of osteoporosis, no concurrent usage of hormone replacement therapy, current or past smoking, weight loss, decreased physical activity, and high alcohol or caffeine intake.87 However, the authors comment that low
| STUDY               | NO. OF PATIENTS | STUDY TYPE       | MEDIAN AGE | PATIENT CHARACTERISTICS                                                                 | AGENTS COMPARED | MEDIAN FOLLOW-UP TIME | BMD CHANGES$^a$                                                                 | FRACTURES                                                                 |
|--------------------|-----------------|------------------|------------|-----------------------------------------------------------------------------------------|-----------------|----------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Shahinian 2005     | 50,613          | Retrospective    | NR (all patients aged > 65 y, 76% aged ≥ 70 y) | Men aged > 65 y with prostate cancer surviving > 60 mo from time of diagnosis | ADT vs no treatment | 60 mo                | 6.92% of all patients reported new diagnosis of osteoporosis 12 to 60 mo after diagnosis, but breakdown by treatment type NR | ADT: 19.4% No ADT: 12.7% < .001 |
| Smith 2005         | 3887 in treatment group 7774 controls | Retrospective cohort | NR (all patients aged ≥ 65 y, 84% aged ≥ 70 y) | Men aged ≥ 65 y with nonmetastatic prostate cancer | ADT vs no treatment | 4.7 y for ADT group 5.4 y for control group | NR                                                                             | ADT group: 7.88 per 100 person-y Control group: 6.51 per 100 person-y HR, 1.21 P < .001 |
| Dickman 2004       | 17,731 in orchietomy group 362,354 population controls | Retrospective cohort | 75 y (treatment group) 74 y (control group) | Men with prostate cancer who underwent orchietomy and population controls without prostate cancer | Orchiectomy within 6 mo of diagnosis vs no treatment | NR | Rates NR Relative risk of orchietomy, 2.11 (95% CI, 1.94-2.19) |
| Mittan 2002        | 15 in treatment group 13 controls | Prospective cohort | 75 y (treatment group) 70 y (control group) | Men with prostate cancer and no bone metastases and age-matched controls without prostate cancer | ADT vs no treatment | 12 mo                | ADT: -3.3% at total hip -5.3% at distal radius -2.8% at spine -2.3% at femoral neck Population controls: No bone loss P < .001 at hip and radius P = NS at femoral neck and spine | NR |
| Morote 2006        | 31 in treatment group 31 controls | Prospective cohort | 70 y (treatment group) 69 y (control group) | Men with nonmetastatic prostate cancer either with biochemical progression (study group) or no biochemical progression (controls) | ADT vs no treatment | 12 mo                | ADT: Between -2.3% and -5.5% depending on site Controls: Between -0.68% and -1.68% depending on site P = NS (compared with baseline) P NR between groups | NR |
| Miyaji 2004        | 27              | Prospective observational | 72 y (range, 62 y-88 y) | Men with nonmetastatic prostate cancer | ADT vs baseline | 24 mo                | ADT: 0.937 g/cm$^2$ Baseline 0.966 g/cm$^2$ (calculated difference: -3.0%) P = .047 | NR |
| Daniell 2000       | 26 in treatment group 12 controls | Prospective cohort | 73.8 y (treatment group) 74.3 y (controls) | Men with advanced or recurrent prostate cancer | Orchiectomy or chemical ADT vs no treatment | NR (range, 6 mo-42 mo) | Orchiectomy after 24 mo: -7.6% at femoral neck Chemical ADT after 24 mo: -6.5% Controls: +0.1% P value not given | NR |
body weight (<70 kg) appears to be the single best predictor of low BMD. This association between low body weight and decreased BMD has been reported in both men and women. Potential etiologies for this finding include decreased load on weight-bearing bones, a lower number of estrogen-producing fat cells, and possibly decreased calcium and nutrient intake.

It must be noted that the most clinically relevant endpoint is the development of osteoporotic fractures, rather than measures of BMD alone. As such, an algorithm has been developed by the WHO to take into account other possible risk factors of osteoporotic fracture. Known as FRAX, this fracture risk assessment tool estimates the 10-year risks of any major fracture and hip fracture based on age, race, nationality, body mass index, medications, medical history, family history, smoking and alcohol consumption, and BMD. Only a few of these factors need to be entered for an accurate assessment, and it is of note that BMD data are not necessary for the calculation. The calculator may be found at http://www.shef.ac.uk/FRAX/ (accessed July 27, 2010) together with instructions for its use. However, the FRAX calculator was not developed to take into account cancer-related bone loss. Although it is possible to qualify patients who have a history of cancer and cancer treatment as those with “secondary osteoporosis” in the calculator, future research is needed to more accurately assign the fracture risk associated with specific cancers and cancer treatments.

Prevention and Treatment of Bone Loss

Consensus guidelines recommend the routine use of calcium, vitamin D, and weight-bearing physical activity in high-risk patients for the prevention of osteoporosis and osteoporotic fractures. The National Comprehensive Cancer Network (NCCN) recommends that all patients with cancer and a high risk of bone loss receive calcium, vitamin D, and counseling regarding lifestyle modifications. In addition, these patients should undergo BMD screening and treatment based on the results. Agents approved by the US Food and Drug Administration (FDA) for the prevention and treatment of osteoporosis are summarized in Table 4.
### TABLE 3. Studies of Bisphosphonate Effects on BMD and Fracture Risk in Patients With Breast and Prostate Cancer

| STUDY | NO. OF PATIENTS | STUDY TYPE | MEDIAN AGE | PATIENT CHARACTERISTICS | AGENTS COMPARED | MEDIAN FOLLOW-UP TIME | BMD CHANGES* | FRACTURES |
|-------|-----------------|------------|------------|-------------------------|-----------------|-----------------------|--------------|-----------|
| Brufsky 2009\(^1\) and Brufsky 2007\(^2\) (2-Fast) | 301 in treatment group and 301 controls | Randomized controlled study | 60 y | Postmenopausal women with early stage, hormone receptor-positive breast cancer receiving adjuvant letrozole | Upfront zoledronic acid starting concurrently with start of letrozole (4 mg iv every 6 mo × 5 y) vs delayed zoledronic acid (starting only when T score < -2.0 at total hip or lumbar spine, or nontraumatic fracture) | 36 mo | 6.7% increased BMD at L-spine (compared with delayed group) at 36 mo | Upfront group: 5.7% Delayed group: 6.3% \(P = NS\) (study not powered to detect difference) |
| Bundred 2008 (ZO-FAST) | 532 in treatment group and 533 controls | Randomized controlled study | Upfront group: 57 y, Control group: 58 y | Postmenopausal women with early stage, hormone receptor-positive breast cancer receiving adjuvant letrozole | Similar to 2-Fast study (except delayed treatment additionally began if asymptomatic fracture discovered at 36-mo point) | 12 mo | 5.7% increased BMD at L-spine (compared with delayed group) at 12 mo | Upfront group: 1.8% Delayed group: 1.7% \(P = NS\) |
| Hines 2009 | 395 | Randomized controlled study | 59.4 y | Postmenopausal women starting letrozole after completing tamoxifen | Upfront zoledronic acid (4 mg iv every 6 mo) concurrently with start of letrozole vs delayed zoledronic acid (starting if T score < -2.0 or if fracture) | 12 mo | Upfront arm: +3.6% at L-spine, Delayed arm: -1.6% \(P < .001\) | NR |
| Confavreux 2007\(^6\) | 118 | Prospective open cohort | Treatment group: 62 y, Surveillance group: 60.5 y | Postmenopausal women with early stage, hormone-dependent breast cancer being treated with anastrozole | Risedronate in osteoporotic patients vs surveillance in nonosteoporotic patients | 12 mo | Risedronate: +4.1% (95% CI, 2.3%-5.9%) at spine, \(P = .008\) (compared with baseline), Surveillance: -3.3% (95% CI, -4.3% to -2.3%) at spine \(P < .0001\) | NR |
| Greenspan 2008 (REBBeCA)\(^7\) | 87 | Randomized placebo controlled study | Treatment group: 50.1 y, Placebo group: 49 y | Newly postmenopausal women after chemotherapy for breast cancer | Risedronate vs placebo | 24 mo | Risedronate: +0.9% at total hip +0.1% at lateral spine, Placebo: -1.6% at total hip -2.4% at lateral spine \(P < .001\) at total hip \(P = .048\) at lateral spine | NR (not powered to detect fracture differences) |
| STUDY                          | NO. OF PATIENTS | STUDY TYPE                      | MEDIAN AGE          | PATIENT CHARACTERISTICS                  | AGENTS COMPARED                                      | MEDIAN FOLLOW-UP TIME | BMD CHANGES | FRACTURES                  |
|-------------------------------|----------------|---------------------------------|---------------------|------------------------------------------|------------------------------------------------------|------------------------|-------------|----------------------------|
| Markopoulos 2010 (ARBI)       | 213            | Mixed prospective cohort and randomized study | Mean, 64.1 y⁹       | Postmenopausal women with hormone receptor-positive breast cancer scheduled to receive anastrozole | Low-risk BMD: Anastrozole alone                       | 24 mo                  | Moderate-risk group: Risedronate and anastrozole: +5.7% at L-spine +1.6% at hip Anastrozole-alone group: -1.5% at L-spine -3.9% at hip P = .006 at L-spine P = .037 at hip | No fragility fractures noted |
| Van Poznak 2010 (SABRE)       | 234            | Mixed prospective cohort and double-blinded, placebo-controlled randomized study | Mean, 64.2 y⁹       | Postmenopausal women with hormone receptor-positive, early stage breast cancer scheduled to receive anastrozole | Low-risk BMD: Anastrozole alone                       | 24 mo                  | Moderate-risk group: Risedronate and anastrozole: +2.2% at L-spine +1.8% at total hip Anastrozole and placebo group: -1.8% at L-spine -1.1% at total hip P < .0001 at both sites | 4 fractures noted in anastrozole and placebo group No fractures noted in risedronate and anastrozole group However, not powered to detect differences |
| Lester 2008 (ARIBON trial)    | 131            | Mixed prospective cohort and randomized, double-blinded, placebo-controlled study | Mean, 65.3 y⁹       | Postmenopausal women with early stage breast cancer | Normal BMD group: Anastrozole alone                   | 24 mo                  | Osteopenia group: Ibandronate and anastrozole: +2.98% at L-spine +0.60% at hip Anastrozole and placebo group: -3.22% at L-spine -3.90% at hip P < .01 at both sites | No fragility fractures noted |
| Smith 2003                   | 106            | Double-blinded, randomized, placebo-controlled study | Treatment group: 73.0 y | Men with nonmetastatic prostate cancer beginning ADT | Zoledronic acid (4 mg iv every 3 mo) vs placebo       | 12 mo                  | Treatment group: +5.6% at L-spine Control group: -2.2% at L-spine P < .001 | NR |
| Ryan 2006 (Zometa US09)       | 120            | Double-blinded, randomized, placebo-controlled study | Treatment group: 73 y | Men with nonmetastatic prostate cancer receiving ADT for ≤12 mo | Zoledronic acid (4 mg iv every 3 mo) vs placebo       | 12 mo                  | Treatment group: +1.4% at total hip +4.6% at L-spine Control group: -2.4% at total hip -2.1% at L-spine P < .0001 at both sites | NR |
| STUDY                               | NO. OF PATIENTS | STUDY TYPE                          | MEDIAN AGE | PATIENT CHARACTERISTICS | AGENTS COMPARED | MEDIAN FOLLOW-UP TIME | BMD CHANGES* | FRACTURES |
|-------------------------------------|-----------------|-------------------------------------|------------|-------------------------|-----------------|------------------------|--------------|-----------|
| Michaelson 2007                      | 40              | Double-blinded, randomized, placebo-controlled study | Treatment group: 66 y | Men with nonmetastatic prostate cancer receiving ADT | Zoledronic acid (4 mg iv annually) vs placebo | 12 mo | Treatment group: +4.0% at L-spine +0.7% at total hip | NR |
| Israeli 2007                         | 215             | Double-blinded, randomized, placebo-controlled study | Treatment group: 74 y Placebo group: 73 y | Men with nonmetastatic prostate cancer receiving ADT for <12 mo | Zoledronic acid (4 mg iv annually) vs placebo | 12 mo | +5.6% at L-spine (compared with placebo) +3.7% at total hip (compared with placebo) | NR |
| Greenspan 2007                       | 112             | Double-blinded, randomized, placebo-controlled study | Mean, 71.5 y\(^b\) | Men with nonmetastatic prostate cancer receiving ADT | Alendronate (70 mg orally wk) vs placebo | 12 mo | Treatment group: +3.7% at spine +1.6% at femoral neck | Not powered to detect differences in fracture frequency |

BMD indicates bone mineral density; Z-FAST, Zometa-Femara Adjuvant Synergy Trial; iv, intravenously; NS, not significant; ZD-FAST, Zometa-Femara Adjuvant Synergy Trial, Europe; NR, not reported; 95% CI, 95% confidence interval; REBBeCA, Risedronate’s Effect on Bone loss in Breast Cancer Study; ARBI, Arimidex Bone Mass Index and Oral Bisphosphonates; SABRE, Study of Anastrozole with the Bisphosphonate Risedronate; ARIBON, Arimidex/Boniva (anastrozole/ibandronate); ADT, androgen deprivation therapy.

\(^a\)Unless otherwise indicated, \(P\) values reflect the level of significance of the difference between the bisphosphonate and its comparator, not between the bisphosphonate and baseline.

\(^b\)Calculated using weighted averages of subgroups.
| CLASS AND DRUG       | FORM               | DOSE/FREQUENCY                        | APPROVED POPULATIONS                                                                 |
|---------------------|--------------------|---------------------------------------|--------------------------------------------------------------------------------------|
| **Bisphosphonates** |                    |                                       |                                                                                      |
| Alendronate         | Oral               | Prevention:                           | Prevention: Postmenopausal women                                                      |
|                     |                    | 5 mg d                                 | Treatment: Postmenopausal women                                                       |
|                     |                    | 35 mg wk                               | Men                                                                                    |
|                     |                    | 10 mg d                                | Long-term corticosteroid induced                                                     |
|                     |                    | 70 mg wk                               |                                                                                      |
| Ibandronate         | Oral               | Prevention and treatment:             | Prevention and treatment: Postmenopausal women                                        |
|                     |                    | 150 mg mo                              |                                                                                      |
|                     | Intravenous        | Prevention and treatment:             | Prevention and treatment: Postmenopausal women                                        |
|                     | injection          | 3 mg every 3 mo                       |                                                                                      |
| Risedronate         | Oral               | Prevention and treatment:             | Prevention: Postmenopausal women                                                      |
|                     |                    | 5 mg d                                 | Long-term corticosteroid use                                                          |
|                     |                    | 35 mg wk                               | Men                                                                                    |
|                     |                    | 70 mg twice mo                         | Postmenopausal women                                                                 |
|                     |                    | 150 mg mo                              | Long-term corticosteroid induced                                                     |
| Zoledronic acid     | Intravenous infusion| Prevention and treatment:             | Prevention: Postmenopausal women                                                      |
|                     |                    | 5 mg y or every 2 y                    | Long-term corticosteroid use                                                          |
|                     |                    |                                        | Patients with recent low-trauma hip fracture                                         |
|                     |                    |                                        | Treatment: Postmenopausal women                                                       |
|                     |                    |                                        | Long-term corticosteroid induced                                                     |
|                     |                    |                                        | Men                                                                                    |
| Calcitonin          | Nasal spray        | 200 IU daily                           | Prevention: Not approved                                                               |
|                     | Injection          |                                      | Treatment: Postmenopausal women at least 5 y beyond menopause                         |
| Calcitonin          | Injection          | Varies                                | Prevention: Not approved                                                               |
|                     |                    |                                        | Treatment: Postmenopausal women at least 5 y beyond menopause                         |
| Hormone therapy     |                    |                                       |                                                                                      |
| Estrogen            | Oral               | Daily, doses vary                      | Prevention: Postmenopausal women, but FDA recommends consideration of other agents     |
|                     |                    |                                        | Treatment: Not approved                                                               |
| Estrogen            | Transdermal        | Twice/wk or weekly, doses vary         | Prevention: Not approved                                                               |
| SERM                |                    |                                       |                                                                                      |
| Raloxifene          | Oral               | Prevention and treatment:             | Prevention and treatment: Postmenopausal women                                        |
|                     |                    | 60 mg d                                |                                                                                      |
| Anabolic agent      |                    |                                       |                                                                                      |
| Teriparatide        | Injection          | Daily                                  | Prevention: Not approved                                                               |
|                     |                    |                                        | Treatment: Postmenopausal women                                                       |
|                     |                    |                                        | Men at high risk of fracture                                                          |
|                     |                    |                                        | Long-term corticosteroid induced                                                     |
| RANKL inhibitor     | Subcutaneous       | Treatment:                            | Prevention: Not approved                                                               |
| Denosumab           | injection          | 60 mg every 6 mo                       | Treatment: Postmenopausal women with one of the following:                            |
|                     |                    |                                        | Previous osteoporotic fracture                                                       |
|                     |                    |                                        | Several other risk factors for fracture                                              |
|                     |                    |                                        | Intolerance of other agents                                                          |
|                     |                    |                                        | Lack of benefit from other agents                                                    |

FDA indicates US Food and Drug Administration; SERM, selective estrogen receptor modulator; RANKL, receptor activator of nuclear factor-κB ligand.
Calcium
Calcium is an essential component of bone formation and has been recommended on the basis of many studies for persons at risk of developing osteoporosis. The recommended dose is usually between 1.0 to 1.5 g of elemental calcium daily. Calcium or calcium in combination with vitamin D has been demonstrated to reduce the rate of bone loss and decrease the rate of fractures, particularly when compliance with treatment regimens is high. However, the efficacy of calcium supplementation alone has recently come into question. A large systematic review of meta-analyses and randomized trials assessing various pharmacological interventions for the treatment or prevention of osteoporosis failed to find any randomized controlled study that demonstrated that the administration of calcium decreased the risk of fractures, despite widespread improvement in BMD. However, it is likely that adherence to calcium was poor in these trials, and one study reported in a subanalysis that those patients who had high adherence to calcium (defined as taking > 60% of recommended doses) did show a statistically significant decrease in fracture rates compared with the group receiving placebo. In addition, although calcium supplementation has been extensively studied in the elderly, it has been less well studied in individuals with cancer.

Vitamin D
Although low doses of vitamin D supplementation have not been shown to decrease fracture rates, higher doses of vitamin D (cholecalciferol or ergocalciferol) and its analogs (700-800 IU daily) have been associated with a lower risk of osteoporotic fractures in some randomized controlled trials. However, the data remain complex, because a number of other randomized trials of vitamin D analogs have failed to find this decrease in fracture risk. In postmenopausal women receiving AIs for breast cancer who have become amenorrheic on therapy, the risk of fracture is increased despite the high bone density (BMD) levels at baseline compared with women without vitamin D deficiency, and high doses of vitamin D (16,000 IU every 2 weeks) can correct the deficiency, although effects on BMD are unknown. Due to the findings in the general population, vitamin D supplementation with cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) at high daily doses (600-800 IU daily) remains a part of recommendations for bone loss prevention and treatment in patients with cancer.

Weight-Bearing Physical Activity
Many trials have shown a clear benefit from certain types of weight-bearing physical activity on BMD. The effect of physical activity may be more pronounced in spinal BMD rather than femoral neck BMD, although the results of trials are conflicting and simple walking may be effective for hip BMD. One trial in older men has shown that a multicomponent physical activity program improved femoral neck BMD. One recent meta-analysis failed to find significant improvement in bone strength in adult women using supervised programs of weight-bearing physical activity. Bone strength takes into account bone mass and morphology in addition to bone mineralization as determinants of fracture risk. However, measures of bone strength are not uniform, and it is unclear whether they can be compared across trials.

Bisphosphonates
Bisphosphonates are chemically stable analogs of inorganic pyrophosphate with the ability to inhibit osteoclast activity in bone. Bisphosphonates include many agents currently in use for the treatment of osteoporosis (Table 4). At the molecular level, bisphosphonates exert their antiresorptive effects by inhibiting farnesyl pyrophosphate synthase activity within osteoclasts. In general, these agents are well tolerated. However, potentially rare but serious side effects can include osteonecrosis of the jaw, and possibly atypical fractures of the femur. Randomized, placebo-controlled clinical trials have demonstrated that bisphosphonate therapy leads to improvement in BMD in both premenopausal women with breast cancer who have become amenorrheic on therapy as well as in postmenopausal women taking AIs (Table 3). Despite these findings, there has not been sufficient follow-up to show whether there is a decrease in the more clinically relevant outcome of fracture risk in any of the above studies with the prophylactic addition of bisphosphonates. Randomized clinical trials demonstrate that bisphosphonates confer protection against ADT-related bone loss at the 1-year point in men with prostate cancer. The most commonly studied agent
has been zoledronic acid given intravenously every 3 months. Those patients receiving zoledronic acid have consistently demonstrated improved BMD from baseline, whereas those receiving ADT without zoledronic acid showed bone loss over the same period.\textsuperscript{66,68-71} Zoledronic acid has also been found to improve BMD when given yearly in patients with prostate cancer taking ADT.\textsuperscript{68} Other bisphosphonates, including oral alendronate, have shown effectiveness as well.\textsuperscript{67} However, long-term data are lacking, and no bisphosphonate trial has been powered to detect improvements in fracture rates.\textsuperscript{71}

### Other Treatments

Estrogen has been shown to decrease the risk of the development of osteoporosis in postmenopausal women.\textsuperscript{101} However estrogen, when combined with progesterone, has been shown to confer a greater likelihood of breast cancer recurrence compared with controls and is therefore contraindicated in women with a history of hormone receptor-positive breast cancer.\textsuperscript{113,114} Whether estrogen-alone preparations confer a lower rate of disease recurrence compared with estrogen plus progesterone is unclear and at the current time neither is widely used in the setting of breast cancer.\textsuperscript{115} Even in women with a history of other types of cancer, menopausal hormone therapy is controversial, and its use has been significantly curtailed since the Women’s Health Initiative Hormone Estrogen Replacement Study II (HERS II) study reported an increased risk of cardiovascular disease and breast cancer in postmenopausal women taking such therapy.\textsuperscript{116}

In men, androgen antagonists that are used for the treatment of prostate cancer, such as bicalutamide, compete with testosterone and bind irreversibly to testosterone receptors in tissue. At least 2 randomized controlled trials have suggested that if bicalutamide is given as monotherapy for prostate cancer, treatment-related bone loss is negligible, at least after 1 to 2 years of therapy,\textsuperscript{117,118} although such use is not uniformly recommended due to concerns over whether this is the most efficacious means of treating the cancer.\textsuperscript{119}

Intermittent dosing of ADT (luteinizing hormone-releasing hormone antagonists) may also confer bone protection versus standard continuous dosing.\textsuperscript{120,121} In one study, patients receiving intermittent ADT had BMD loss similar to patients receiving continuous ADT by years 2 and 4, but by year 6 there was less bone loss in the intermittent compared with the continuous group,\textsuperscript{121} although it must be noted that the efficacy of intermittent versus continuous dosing is still being studied.\textsuperscript{53}

### Selective Estrogen Receptor Modulators

Raloxifene, an agent approved for the prevention and treatment of osteoporosis in postmenopausal women, has been shown to prevent ADT-associated bone loss in men with prostate cancer. Smith et al studied 48 men with nonmetastatic prostate cancer who were receiving ADT. The subjects had a median age of 70 years, and were randomized to receive raloxifene or ADT alone. Raloxifene was associated with significantly higher BMD compared with the ADT-alone group at the total hip and trochanter (\(P < .001\) at both sites).\textsuperscript{122}

Toremifene, a second-generation SERM, may soon also be a relevant agent in the prevention of bone loss in older men receiving ADT for prostate cancer. Toremifene appears to mimic the effects of tamoxifen in bone. In a study of 1392 men with prostate cancer who were receiving ADT, patients were randomized to placebo versus daily toremifene for 24 months. A planned interim analysis of 197 patients with a mean age of 77 years demonstrated a difference in BMD of 1.5% at the femoral neck and 2.3% at the lumbar spine between the intervention group and controls.\textsuperscript{123}

### Denosumab

The monoclonal antibody denosumab, an antagonist of the receptor activator of nuclear factor-\(\kappa B\) ligand (RANKL), inhibits maturation of osteoclasts and has recently been shown to limit bone loss in patients with breast cancer who are taking adjuvant AIs. Women received either placebo (\(n = 125\)) or 60 mg of subcutaneous denosumab every 6 months. All patients were required to have evidence of low bone mass, but not osteoporosis, at enrollment, and the median age was 59 years. Lumbar spine BMD showed an increase of 5.5% at 12 months compared with the placebo group (4.8% vs -0.7%; \(P < .001\)).\textsuperscript{124} This difference was slightly more pronounced in adults aged younger than 65 years compared with those aged 65 years and older, although both groups showed statistically significant improvement over placebo.\textsuperscript{125} However, completed trials using denosumab
in women with breast cancer were not powered to examine fracture rates, and the drug is not yet approved by the FDA for AI-related bone loss, although it has been approved for postmenopausal women with demonstrated osteoporosis by BMD screening.

Denosumab has also been studied in men taking ADT for nonmetastatic prostate cancer. At 24 months, the 734 men in the denosumab group showed an increase of 5.6% in BMD at the lumbar spine, compared with a 1.0% loss in the 734 men who received placebo ($P < .001$). Although all-site fractures were not significantly different between the 2 groups, vertebral fracture reduction was seen with denosumab compared with placebo, with a fracture incidence of 3.9% over 36 months in the placebo group compared with 1.5% in the denosumab group (RR, 0.38; 95% CI, 0.19–0.78 [$P = .006$]).

Consensus Panel Recommendations

Various clinical recommendations exist for the screening and treatment of cancer-related bone loss and fracture prevention, although consensus has not been reached across groups.

The American Society of Clinical Oncology has recommended an algorithm for the management of breast cancer treatment-related bone loss. Women with a history of breast cancer considered to be at high risk are those aged older than 65 years, those aged older than 60 years with other risk factors of osteoporosis, postmenopausal women of any age receiving an AI, or premenopausal women with therapy-induced premature menopause. All women at high risk are recommended to have annual DEXA scans of the spine and hip and to take calcium and vitamin D supplements. If the osteoporosis threshold (T score of $< -2.5$) is reached, the addition of a bisphosphonate is recommended. For patients with osteopenia, the decision to use bisphosphonates should be individualized.

An algorithm has also been proposed by a United Kingdom Expert Group, with recommendations for the more liberal use of bisphosphonates in patients with a history of breast cancer. The group recommends bisphosphonates in all women with a history of breast cancer aged older than 75 years with one or more risk factors of osteoporotic fracture, regardless of BMD measurement. They recommend that a bisphosphonate be initiated in women with a T score of less than or equal to -2 rather than less than -2.5. For premenopausal women taking a combination of ovarian suppression and an AI, the group recommends a T score cutoff of less than or equal to -1.

The NCCN Task Force Report on bone health in cancer care recommends that all cancer patients for whom planned therapy includes medications that will lower levels of sex hormones undergo baseline screening for osteoporosis followed by evaluation by DEXA scan every 2 years. The NCCN also suggests some form of screening for all cancer patients, regardless of cancer type, who are at an increased risk of fracture due to age. The NCCN recommends that at-risk patients undergo lifestyle modifying behaviors, such as weight-bearing physical activity, avoidance of tobacco and alcohol use, and ensuring adequate intake of calcium and vitamin D. Based on BMD screening, the NCCN recommends individualizing treatment, with bisphosphonates reserved only for those patients at the highest risk of fracture.

The NCCN Guidelines Panel for Prostate Cancer recommends calcium and vitamin D supplementation for all men with prostate cancer who are older than age 50 years, and recommends consideration of bisphosphonate therapy with either weekly oral alendronate or annual intravenous zoledronic acid in those receiving ADT who are at high risk of fracture. High risk is defined as a 10-year risk of hip fracture of greater than or equal to 3% or a 10-year probability of major osteoporotic fracture of greater than or equal to 20% as calculated using the FRAX algorithm. For example, a 75-year-old American Caucasian man of average height and weight with a femoral neck T score of less than -2.0 taking ADT would warrant bisphosphonate therapy using the FRAX algorithm regardless of other risk factors. ADT is taken into account as “secondary osteoporosis.”

Conclusions

Bone loss related to the treatment of breast and prostate cancer in older adults is an important potential adverse side effect. Older adults with bone loss are more likely to have increased risks of falling, fracture, disability, and even mortality. Calcium, vitamin D, and weight-bearing physical activity strengthen bones and decrease the risk of the development of osteoporosis. Effective screening strategies should be used to best identify those older adults at risk of treatment-related...
bone loss, and treatment should be administered if risk factors are identified. Research is needed to understand the interaction between cancer, cancer therapies, and aging to identify optimal screening approaches and targeted interventions to maintain bone health and decrease fracture risk.

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