Hormone ablation therapy is a mainstay in the treatment of breast and prostate cancers. However, aromatase inhibitors (AIs) used in postmenopausal women with breast cancer and androgen-deprivation therapy (ADT) used in men with prostate cancer contribute to substantial bone loss, thereby increasing the risk of osteoporotic fractures. Evidence-based guidelines, therefore, urge oncology practices to screen these patients for bone loss and, if needed, provide treatment to maintain bone health. In addition to lifestyle modification and calcium or vitamin D supplementation, bone protection strategies include treatment with bisphosphonates and denosumab, a monoclonal antibody against RANK ligand. Identification of patients at greater risk for bone loss and fracture and proper interventions can reduce fracture rates. Oncology nurses can play an important role in screening these patients. The purpose of this article is to inform oncology nurses about the effects of cancer treatment on bone health, review current prevention and treatment options for cancer treatment–induced bone loss, and discuss recommendations for identifying high-risk individuals.

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Breast and prostate cancers are among the most common malignancies in the United States, with an estimated 232,670 women and 233,000 men, respectively, being diagnosed in 2014 (Siegel, Ma, Zou, & Jemal, 2014). Significant improvements in survival coupled with prolonged cancer therapy have heightened the need for long-term monitoring and prevention of treatment-related complications in these patients (Limburg, 2007). In particular, loss of bone mineral density (BMD) is an important complication of therapy associated with bone fractures (Maxwell & Viale, 2005). Cancer treatment–induced bone loss (CTIBL) can result from several treatment modalities that exert their antitumor effects by reducing circulating levels of estrogen, particularly hormone ablation therapies such as aromatase inhibitors (AIs) for breast cancer and androgen-deprivation therapies (ADTs) for prostate cancer (Hirbe, Morgan, Uluc¸an, & Weilbaecher, 2006; Maxwell & Viale, 2005). This article discusses the pathophysiology of CTIBL, the impact of CTIBL on patients with breast and prostate cancer, the risk factors for developing CTIBL, and currently available treatment options, with a focus on the implications of this information for oncology nurses.

Physiology of Bone Remodeling

Physiologic bone remodeling reflects a balance between two complementary processes: bone mineral resorption by osteoclasts and bone mineral formation by osteoblasts. Pathologic conditions such as postmenopausal osteoporosis result from a loss of equilibrium between these two processes, with the rate of bone resorption exceeding bone mineral formation (Kearns, Khošla, & Kostenuik, 2008). Osteoblasts play an important role in regulating osteoclast function by releasing factors such as
Estrogens play an important role in regulating bone homeostasis by suppressing the differentiation and maturation of osteoclasts during bone remodeling while having a direct stimulatory effect on osteoblasts (see Figure 2). Therefore, estrogen has the net effect of promoting bone formation over resorption and reducing bone loss (Perez & Weilbaecher, 2006; Wickham, 2011). In men, both estrogen and testosterone play an important role in reducing bone resorption and increasing bone mass; however, the relative contribution of the two hormones is unclear (Sinnesael, Boonen, Claessens, Gielen, & Vanderschueren, 2011).

**Cancer Treatment-Induced Bone Loss**

**Mechanism**

Estrogen deprivation from cancer treatment disrupts the balance between bone formation and bone resorption, resulting in net bone loss and decreased bone quality. Estrogen deficiency results in a dysregulation of the RANK ligand pathway and a subsequent increase in osteoclast activity and bone resorption, as well as a corresponding decrease in osteoblast activity and bone formation (Kearns et al., 2008; Tsourdi et al., 2011; Wickham, 2011).

Cancer therapies that contribute to hormone deprivation are known to contribute to CTIBL (Maxwell & Viale, 2005). In breast cancer, such therapies include AIs, which are considered the standard of care in postmenopausal patients with hormone receptor-positive early-stage breast cancer. AIs block the activity of aromatase, a key enzyme in estrogen synthesis, directly reducing estrogen levels and accelerating the bone loss already occurring in postmenopausal women (Perez & Weilbaecher, 2006). In prostate cancer, ADT includes gonadotropin-releasing hormone (GnRH) agonists, antiandrogens with GnRH agonists, or orchiectomy. ADT reduces estrogen levels in men by blocking the production of androgens (e.g., testosterone), which are precursors for estrogen biosynthesis via the aromatase enzyme (Guise et al., 2007).

**Clinical Consequences**

Patients with osteoporosis are at an increased risk for fractures, which are associated with morbidity and mortality (Marks, 2010). Osteoporotic fractures, which frequently occur at the spine, hip, and wrist, can cause chronic pain and an impaired ability to perform activities of daily living. Patients also can suffer from kyphosis, impaired mobility, disability, and deformity, which can have a negative emotional impact and affect patient well-being (Guise et al., 2007; Maxwell & Viale, 2005).

Treatment with AIs is known to accelerate natural bone loss by as much as a 2.5-fold increase in postmenopausal women, and combined therapy with an AI and a GnRH agonist is known to accelerate bone loss by as much as a 7-fold increase (Hirbe et al, 2006). In one large trial, AIs were associated with bone mineral loss of 4% during a two-year period in both the hip and lumbar spine; the incidence of fracture was increased by 15% relative to control groups receiving either placebo or tamoxifen (Hadji et al., 2008).

ADT is associated with a 5- to 10-fold increase in the rate of bone loss and increased rates of fracture (Greenspan et al., 2005). In addition, the prevalence of fracture also appears to increase with longer duration of ADT. Overall, fracture rates ranged from 6%-20% in men on ADT for 1–4 years, but rose to 45% and 73%, respectively, in men on ADT for an average of 7 and 15 years (Guise et al., 2007). External beam radiation to the pelvic area also is known to increase the risk of hip fracture by 75% in men with prostate cancer, and this effect is additive: men receiving both ADT and external beam radiation are 145% more likely than controls to experience a hip fracture (Elliott et al., 2011). Fractures at any location are known to double the risk of mortality in men receiving ADT for prostate cancer (Beebe-Dimmer et al., 2012).

**Identifying At-Risk Patients**

Given the negative impact that osteoporosis and its sequelae can have on quality of life and mortality, clinicians should be familiar with common risk factors for bone loss and fracture...
Prior fragility fracture

DXA T score below –2.5

Clinical Journal of Oncology Nursing  •  Volume 18, Number 2  •  Prevention and Treatment of Bone Loss 225

(Hadji et al., 2008; Kanis et al., 2008) (see Figure 3) and implement routine BMD screening in high-risk patients.

Dual-energy X-ray absorptiometry (DXA or DEXA), the most common method for assessing BMD, produces a raw measurement of bone mineral mass per area of skeleton (g/cm²), which is then generally compared with the measurement for a gender-matched healthy young adult to generate a T score (Limburg, 2007). Comparison of T scores to World Health Organization (WHO) criteria allows a diagnosis of clinical osteoporosis that serves to guide treatment decisions (WHO, 1994; Wickham, 2011) (see Table 1).

BMD is a strong independent predictor of fracture risk among men and women. Men often are perceived as being at lower risk than women for osteoporosis and its consequences, but that belief is inaccurate (Guise et al., 2007). In one study of patients with prostate cancer, a 20% rate of osteoporosis prior to initiation of ADT rose to 90% after 10 years of ADT (Morote et al., 2007).

Evidence-based guidelines for the assessment of CTIBL in patients with breast cancer recommend baseline BMD screening and periodic BMD measurement follow-ups in postmenopausal women receiving AI therapy, and in premenopausal women who experience early menopause from cancer therapy (Gralow et al., 2009; Hadji et al., 2011; Hillner et al., 2003; International Osteoporosis Foundation [IOF], 2007) (see Table 2). Similarly, guidelines for prostate cancer recommend baseline and periodic follow-up screening of BMD in all patients receiving either pharmacologic or surgical ADT (Aapro et al., 2008; IOF, 2007; National Comprehensive Cancer Network [NCCN], 2013) (see Table 3). These consensus guidelines underscore the importance of comprehensive baseline risk assessment for fractures before treatment initiation, highlighting the active role that oncology nurses can play in screening and identifying patients at risk for CTIBL.

Lifestyle Modifications

All patients with breast or prostate cancer treated with hormonal therapies also should receive education on lifestyle and dietary changes that can minimize bone loss and decrease the risk of fracture (Guise, 2006; Limburg, 2007; Wickham, 2011). Effective interventions include diet modifications and weight-bearing exercise. These should be implemented at the initiation of AI therapies or ADT.

Diet modification strategies include adequate protein consumption to maintain muscle strength and body weight. In addition, patients should be encouraged to eat foods rich in calcium (e.g., dairy products such as low-fat milk, yogurt, cheese; calcium-fortified orange juice; tofu; dark green leafy vegetables including broccoli, spinach, collard greens, bok choy) and vitamin D (e.g., vitamin D-fortified milk, herring, salmon, tuna, vitamin-fortified cereal). In addition, calcium and vitamin D supplementation is recommended for these patients. A regular exercise program helps to strengthen muscles and bones while slowing down bone loss (Guise, 2006; Limburg, 2007; Wickham, 2011). The exercise regimen should include weight-bearing aerobic exercise, such as walking, jogging, and stair climbing, as well as muscle-strengthening exercises (e.g., weightlifting, exercise machines). Ideally, patients should exercise for at least 30 minutes per day for four to five days per week.

Other lifestyle changes that can help slow down bone loss include smoking cessation, limitation of alcohol intake, and avoidance of excessive caffeine. Interventions that help maintain a high level of function generally will reduce the risk of falling and fractures (Guise, 2006; Limburg, 2007; Wickham, 2011). In addition to lifestyle changes, many patients with breast or prostate cancer will require pharmacologic interventions to treat CTIBL, which include the currently available bisphosphonates and denosumab (Body, 2010).

Pharmacologic Interventions

Bisphosphonates: Although bisphosphonates are not currently approved for the treatment of CTIBL, they are widely used to maintain BMD in patients with nonmetastatic breast or prostate cancer treated with hormone ablation therapies. Bisphosphonates are pyrophosphate analogs that are assimilated into bone mineral surfaces at sites of active remodeling and, subsequently, taken up by osteoclasts. The bisphosphonate uptake disrupts a number of cellular processes, including signal transduction and cholesterol biosynthesis, thereby inhibiting osteoclast function and possibly inducing apoptosis (Eastham, 2007).

Several IV and oral bisphosphonate regimens, including zoledronic acid, alendronate, and risedronate, have been

<table>
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<th>TABLE 1. Classification of Bone Loss and Treatment Guidelines</th>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Low bone mass (osteoopenia)</td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Severe osteoporosis</td>
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<tr>
<td>BMD—bone mineral density; DXA—dual energy X-ray absorptiometry; SD—standard deviation</td>
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<td>Note. Based on information from World Health Organization, 1994.</td>
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<th>FIGURE 3. Risk Factors for Hip Fractures in Men and Women</th>
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<tr>
<td>Note. Based on information from Hadji et al., 2008; Kanis et al., 2008.</td>
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</table>
evaluated in large randomized clinical trials for the prevention of CTIBL in patients with either breast or prostate cancer, and have demonstrated that bisphosphonates improve BMD from baseline in patients receiving hormone ablation therapies (Bruisky et al., 2012; Eidtmann et al., 2010; Gnant et al., 2008; Greenspan, Nelson, Trump, & Resnick, 2007; Israeli et al., 2007; Llombart et al., 2012; Van Poznack et al., 2010) (see Tables 4 and 5). A growing body of evidence indicates that bisphosphonate therapy must be initiated early to achieve optimal protection against CTIBL in patients with breast and prostate cancer. The Z-FAST, ZO-FAST, and E-ZO-FAST trials showed that women in whom bisphosphonates were initiated at the start of hormonal therapy exhibited improved lumbar spine BMD compared to women in whom therapy was delayed until the occurrence of a fracture or a substantial decrease in bone loss (Body, 2010; Brufksy et al., 2012; Eidtmann et al., 2010; Llombart et al., 2012). Similarly, in 112 men given ADT for nonmetastatic prostate cancer, both patient subsets who received either early or late alendronate therapy showed improvements in BMD after one year of therapy; however, the improvements in late starters were significantly smaller than those seen in early starters (Greenspan et al., 2007).

The trials evaluating bisphosphonates for CTIBL in patients with breast and prostate cancer also have raised several unanswered questions. First, although these trials have consistently demonstrated improvements in BMD, the impact of bisphosphonate therapy on fracture rates is currently unknown (Body, 2010).

The ongoing RADAR trial is designed to address this question and is expected to randomize 1,000 men with prostate cancer to ADT and radiation with or without IV zoledronic acid; follow-up is expected to be completed in 2018 (ClinicalTrials.gov, 2012). Based on the premise that more-intensive dosing might be required for CTIBL compared to age-related osteoporosis because of the observed increased rate of bone loss, several trials have evaluated a more-frequent bisphosphonate schedule compared to the currently approved dosing schedule (Bruisky et al., 2012; Ellis et al., 2008; Gnant et al., 2008). These trials have found standard bisphosphonate-dosing regimens approved for osteoporosis to be effective for treating CTIBL (Greenspan et al., 2007).

Although bisphosphonates are not approved for the treatment of CTIBL, their use in this setting is recommended by a number of clinical practice guidelines (Aapro et al., 2008; Gralow et al., 2009; Hadji et al., 2011; Hillner et al., 2003; NCCN, 2013). Although all evidence-based guidelines generally recommend bisphosphonate therapy in patients who exhibit low T scores on DXA screening, it also has been recommended for patients who exhibit intermediate T scores along with additional risk factors, such as age older than 65 years or personal or family history of fractures (Body, 2010). Bisphosphonate therapy is generally well tolerated; however, several safety concerns—including acute phase reactions, nephrotoxicity, gastrointestinal ulcers, hypocalcemia, and osteonecrosis of the jaw—may limit its use (Aapro et al., 2008; Wickham, 2011). Because of the potential negative impact of these treatment-related adverse events on planned dose delivery

<table>
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<tr>
<th>Guideline</th>
<th>Assessment</th>
<th>Treatment</th>
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<tr>
<td>American Society for Clinical Oncology (Hillner et al., 2003)</td>
<td>Provides algorithm for identifying high-risk patients Annual DXA screening for • Postmenopausal women on AI therapy • Premenopausal women with early menopause from cancer therapy • All women aged 65 years and older • Women older than age 60 years with other family or personal risk factors</td>
<td>For women with T score of –1.5 to –2.5: Routine bisphosphonate therapy is not supported by evidence, but treatment may be considered on individual basis. For women with a T score lower than –2.5: Bisphosphonate therapy is recommended.</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (Gralow et al., 2009)</td>
<td>Baseline and periodic BMD screening • Women on AI therapy • Premenopausal women with early menopause from cancer therapy</td>
<td>Bisphosphonate therapy recommended for women with low BMD (no T score threshold defined). Dental examination with preventive dentistry prior to initiation of bisphosphonate therapy to prevent osteonecrosis of the jaw.</td>
</tr>
<tr>
<td>Practical guidance for prevention and management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer (Hadji et al., 2008)</td>
<td>Baseline screening of BMD and other risk factors at initiation of AI therapy Periodic rescreening of BMD and risk factors • Patients not on bisphosphonates: Rescreen at one year. • Patients on IV bisphosphonates: Rescreen on an individual basis. • Patients on oral bisphosphonates: Rescreen every one to two years, and consider switch to IV bisphosphonate if poor compliance of falling BMD is observed.</td>
<td>For those with a T score of –2 or greater and no additional risk factors: Exercise, calcium, and vitamin D supplements Any two risk factors (T score less than –1.5, older than aged 65 years, BMI less than 20 kg/m², family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use greater than six months, current or history of smoking): Exercise, calcium, and vitamin D supplementation; bisphosphonate therapy T score less than –2: Exercise, calcium, and vitamin D supplementation; bisphosphonate therapy Relative recommendations on drug therapy • IV bisphosphonate (particularly zoledronic acid every six months) is best supported by evidence. • Oral bisphosphonate therapy and subcutaneous denosumab are supported by lesser levels of evidence.</td>
</tr>
</tbody>
</table>

Al—aromatase inhibitor; BMD—bone mineral density; BMI—body mass index; CTIBL—chemotherapy treatment–induced bone loss; DXA—dual energy x-ray absorptiometry
and treatment adherence, strategies to manage these adverse events should be considered.

**Denosumab**: Denosumab is a targeted monoclonal antibody directed against RANK ligand, a promoter of bone resorption that is upregulated in states of estrogen deficiency, such as those induced by hormone ablation therapies. By preventing RANK ligand from binding to its receptor, denosumab blocks bone resorption by inhibiting the differentiation and maturation of osteoclasts, the resorptive function of mature osteoclasts, and osteoclast survival (Kearns et al., 2008; Tsourdi et al., 2011).

Several clinical trials have evaluated the efficacy of denosumab, administered subcutaneously at a dose of 60 mg once every six months, in preventing bone loss or fractures. Two placebo-controlled clinical trials demonstrated that denosumab improved BMD at multiple skeletal sites in patients with nonmetastatic breast cancer and prostate cancer treated with AI and ADT, respectively (Ellis et al., 2008; Smith et al., 2009). Importantly, the trial of 1,468 patients with prostate cancer also showed a statistically significant reduction in new vertebral fractures for patients treated with denosumab, compared to those receiving placebo (1.5% versus 3.9% at 36 months, p = 0.006) (Smith et al., 2009).

The combined analyses of more than 7,000 patients with postmenopausal osteoporosis have indicated a higher incidence of hypocalcemia, osteonecrosis of the jaw, serious infections, and skin disorders associated with denosumab. The incidence of these adverse events was comparable in the denosumab trials of patients with nonmetastatic breast or prostate cancer (Amgen Inc., 2013a; Ellis et al., 2008; Smith et al., 2009).

Based on these results, denosumab 60 mg every six months was approved in the United States as a treatment to increase bone mass in women at high risk for fracture who are receiving adjuvant AI therapy for breast cancer, as well as in men at high risk for fracture who are receiving ADT for nonmetastatic prostate cancer (Amgen Inc., 2013a). It should be noted that denosumab also is available in the United States at a higher dose of 120 mg, which is approved for the treatment of bone metastases from solid tumors (Amgen Inc., 2013b).

### TABLE 3. Guidelines for Assessment and Treatment of CTIBL in Patients With Prostate Cancer

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<tr>
<th>Guideline</th>
<th>Assessment</th>
<th>Treatment</th>
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<tr>
<td>International Osteoporosis Foundation, 2007</td>
<td>Measurement of BMD in patients with risk factors, including men who have undergone orchietomy or are deficient in androgens for other reasons</td>
<td>Calcium (1,000 mg daily), vitamin D (800 IU daily) Bisphosphonate therapy</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network, 2013</td>
<td>In men undergoing pharmacologic or surgical ADT • Consideration of baseline BMD assessment • Calculation of 10-year fracture risk using WHO assessment tool FRAX®, consider ADT-related osteoporosis as “secondary” under the FRAX algorithm</td>
<td>Men with 10-year absolute risk (calculated by FRAX) of 3% or greater for hip fracture: Calcium, vitamin D₃ and antiresorptive therapy Men with 10-year absolute risk (calculated by FRAX) of 20% or greater for any major osteoporotic fracture: Calcium, vitamin D₃ and antiresorptive therapy All men older than age 50 years: Calcium (1,200 mg daily) plus vitamin D₃ (800–1,000 IU daily) Recommended antiresorptive regimens • SQ denosumab, 60 mg every six months • IV zoledronic acid, 5 mg annually • Oral alendronate, 70 mg weekly</td>
</tr>
</tbody>
</table>

ADT—androgen-deprivation therapy; BMD—bone mineral density; CTIBL—chemotherapy treatment–induced bone loss; FRAX—fracture risk assessment tool; SQ—subcutaneous; WHO—World Health Organization

### Nursing Implications

The threat of CTIBL and fracture in patients with nonmetastatic breast or prostate cancer requires attention by the healthcare team to identify high-risk patients as early as possible (Limburg, 2007; Wickham, 2011). Oncology nurses play an important role in identifying such patients and ensuring proper education, instituting interventions, and making referrals.

### Screening and Monitoring for Bone Loss

Techniques that measure BMD, such as DXA, can identify the majority of patients at risk for fracture; however, BMD measures alone fail to identify patients below a defined threshold, and BMD assessment techniques may not be available for some patients. Therefore, patients must be routinely assessed for other clinical factors that increase the risk or severity of CTIBL (Limburg, 2007). Several factors increase fracture risk independent of low BMD, including a susceptibility to falls, unstable gait, poor visual acuity or depth perception, peripheral neuropathy or poor proprioception, low proximal muscle strength, depression, and use of medications such as sedatives, opioid analgesics,

### Implications for Practice

- Educate patients about lifestyle modifications and dietary changes that can decrease bone loss and reduce the risk of fracture.
- Become familiar with currently available treatment options for cancer treatment–induced bone loss (CTIBL) in patients with nonmetastatic breast or prostate cancer, including bisphosphonates and denosumab, a human monoclonal antibody against RANK ligand.
- Play an active role in screening and identifying patients at risk for CTIBL by conducting a comprehensive risk assessment for fractures before treatment is initiated.
or anxiolytics (Wickham, 2011). Individual patient models, such as the WHO’s fracture risk assessment tool or the FRAX® algorithm (www.shef.ac.uk/FRAX®), may be useful tools that oncology nurses can use for risk assessment.

**Patient Education**

Oncology nurses should recognize the potential difficulties posed by lack of awareness of CTIBL among patients with non-metastatic breast and prostate cancer. A Mayo Clinic survey showed that 39% of patients thought cancer treatment strengthened bones or did not know about the effect of treatment on bone health, and another 39% thought that osteoporosis almost never occurred in men (McKean et al., 2008). That knowledge deficit concerning bone health underscores the need for oncology nurses to take a proactive approach to educating patients about bone health in cancer—beginning, in many cases, with alerting them to the risk of CTIBL and lifestyle changes they can make to prevent or reduce this risk.

**TABLE 4. Randomized Clinical Trials Evaluating Bisphosphonates and Denosumab for Prevention of CTIBL in Women With Breast Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Comparison</th>
<th>Endpoint</th>
<th>Results&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td><strong>Denosumab</strong></td>
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<tr>
<td>Ellis et al., 2008</td>
<td>Hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy</td>
<td>Denosumab 60 mg every six months SQ (n = 127) versus placebo (n = 125)</td>
<td>Percent change in BMD at two years at lumbar spine, total hip, femoral neck, trochanter</td>
<td>+ 7.6% lumbar spine (p &lt; 0.0001) + 4.7% total hip (p &lt; 0.0001) + 3.6% femoral neck (p &lt; 0.0001) + 5.9% trochanter (p &lt; 0.0001)</td>
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**Bisphosphonates (zoledronic acid)**

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<tr>
<th>Study</th>
<th>Patients</th>
<th>Comparison</th>
<th>Endpoint</th>
<th>Results&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>ABCSG-12 bone substudy</td>
<td>Premenopausal stage I or II breast cancer treated with goserelin plus either tamoxifen or anastrozole</td>
<td>Zoledronic acid (4 mg every six months IV), tamoxifen, and goserelin (n = 100) versus tamoxifen and goserelin (n = 103)</td>
<td>Percent change in BMD at five years at lumbar spine</td>
<td>+ 9.7% lumbar spine</td>
</tr>
<tr>
<td>Z-FAST</td>
<td>Postmenopausal stage I, II, or IIIA breast cancer treated with letrozole 2.5 mg daily</td>
<td>Immediate zoledronic acid (4 mg every six months via an IV; n = 301) versus delayed zoledronic acid (4 mg every six months; n = 301), starting when the T score is less than –2 or when fragility fracture occurs</td>
<td>Percent change in BMD at 61 months at lumbar spine and total hip</td>
<td>+ 8.9% lumbar spine (p &lt; 0.0001) + 6.7% total hip (p &lt; 0.0001)</td>
</tr>
<tr>
<td>ZO-FAST</td>
<td>Stage I, II, or IIIA breast cancer, either postmenopausal treated with letrozole or newly menopausal from chemotherapy or GnRH agonist</td>
<td>Immediate zoledronic acid (4 mg every six months via an IV; n = 532) versus delayed zoledronic acid (4 mg every six months; n = 533), starting when the T score is less than –2 or when fragility fracture occurs</td>
<td>Percent change in BMD at 60 months at lumbar spine</td>
<td>+ 9.3% lumbar spine (p &lt; 0.0001)</td>
</tr>
<tr>
<td>E-ZO-FAST</td>
<td>Patients with hormone receptor-positive early-stage breast cancer treated with adjuvant letrozole (2.5 mg daily for five years)</td>
<td>Immediate zoledronic acid (4 mg every six months via an IV; n = 264) versus delayed zoledronic acid (4 mg every six months; n = 264), starting when the T score is less than –2 or when fragility fracture occurs</td>
<td>Percent change in BMD at 12 months at lumbar spine</td>
<td>+ 5.3% lumbar spine (p &lt; 0.0001)</td>
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**Bisphosphonates (risedronate)**

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<th>Study</th>
<th>Patients</th>
<th>Comparison</th>
<th>Endpoint</th>
<th>Results&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Van Poznak et al., 2010</td>
<td>Postmenopausal women treated with anastrozole with established bone loss or osteopenia who were in the moderate-risk group (T score less than –1 to –2 or greater)</td>
<td>Risedronate 35 mg per week (n = 60) versus placebo (n = 51)</td>
<td>Percent change in BMD at two years at lumbar spine and total hip</td>
<td>+ 4% lumbar spine (p &lt; 0.0001) + 2.9% total hip (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Absolute difference between treatment and placebo

ABCSG—Austrian Breast and Colorectal Cancer Study Group; BMD—bone mineral density; CTIBL—cancer treatment–induced bone loss; GnRH—gonadotropin-releasing hormone; SQ—subcutaneous
TABLE 5. Randomized Clinical Trials Evaluating Bisphosphonates and Other Novel Therapies for Prevention of CTIBL in Men With Prostate Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Comparison</th>
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<tr>
<td><strong>Bisphosphonates (alendronate)</strong></td>
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<tr>
<td>Greenspan et al., 2007</td>
<td>Men receiving ADT for nonmetastatic prostate cancer</td>
<td>Alendronate 70 mg once per week orally (n = 56) versus placebo (n = 56)</td>
<td>Percent change in BMD at one year at lumbar spine and femoral neck</td>
<td>+ 5.1% lumbar spine (p &lt; 0.001) + 2.3% femoral neck (p &lt; 0.001)</td>
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| **Bisphosphonates (zoledronic acid)** |                                               |                                                         |                                                                           |                               |
| Israeli et al., 2007        | Men during their first year of ADT for locally advanced prostate cancer | Zoledronic acid 4 mg every three months via IV (n = 106) versus placebo (n = 109) | Percent change in BMD at one year at lumbar spine and total hip | + 6.7% lumbar spine (p < 0.0001) + 3.7% total hip (p < 0.0001) |

| **Denosumab**               |                                               |                                                         |                                                                           |                               |
| Smith et al., 2009          | Nonmetastatic prostate cancer treated with ADT | Denosumab 60 mg every six months subcutaneous (n = 734) versus placebo (n = 734) | Percent change in BMD at two years at lumbar spine Percent change in incidence of new vertebral fractures at 36 months | + 6.7% lumbar spine (p < 0.001) – 2.4% new vertebral fractures (p = 0.006) |

| *Absolute difference between treatment and placebo |
| ADT—androgen-deprivation therapy; BMD—bone mineral density; CTIBL—cancer treatment–induced bone loss |

In addition to advice on dietary and lifestyle modifications, patients who undergo pharmacotherapy for CTIBL also should receive education on the proper administration of medications and potential adverse events. Poor adherence with oral bisphosphonate therapy, which often results from adverse events and improper administration, occurs frequently and has been shown to reduce the efficacy of these treatments (Eastham, 2007; Silverman, Schousboe, & Gold, 2011).

**Monitoring Patients Undergoing Treatment**

Monitoring of serum creatinine prior to each IV bisphosphonate infusion is recommended to detect acute renal toxicity (Eastham, 2007). Although denosumab can be administered to patients with renal impairment without any dose adjustments, it can cause severe hypocalcemia, particularly in patients with severe renal impairment. Therefore, preexisting hypocalcemia should be corrected before denosumab is initiated, calcium levels should be monitored, and calcium and vitamin D supplementation is recommended to prevent or correct hypocalcemia (Amgen Inc., 2013a). In addition, effective daily oral hygiene, routine dental examinations and cleaning, treatment of dental infections, and avoiding invasive dental procedures are important for decreasing the risk of osteonecrosis of the jaw associated with use of bisphosphonate and denosumab therapies (Amgen Inc., 2013a; Eastham, 2007).

**Conclusion**

Early-stage breast and prostate cancers are potentially curable malignancies, and new treatment options have resulted in substantial increases in the prevalence of these survivors. Therefore, managing the adverse events associated with treatment (i.e., decreased bone health) that can have an impact on quality of life is important. Clinical consensus guidelines provide a strong framework for managing CTIBL, including screening, treatment, prevention, patient education, and lifestyle interventions. Oncology nurses are well-situated to implement these recommendations in clinical practice, with the intent of ensuring optimal bone health, functionality, and well-being for patients with breast or prostate cancer.

**References**

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