Endocrine Therapy-related Endocrinopathies—Biology, Prevalence, and Implications for the Management of Breast Cancer

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Nearly 270,000 new breast cancer cases were predicted to be diagnosed in the USA in 2019 with more than 70% being estrogen receptor-positive and treated using endocrine therapy. The suppression of estrogen biosynthesis or action via the use of ovarian suppression, aromatase inhibitors and selective estrogen receptor modulators/degraders, respectively, is effective in approximately 70% of women. The systemic inhibition of estrogen during breast cancer treatment is also associated with side effects due to the important endocrine functions of this steroid hormone, including its role in the maintenance of energy homeostasis and bone health. This article will present perspectives on the impact of endocrine therapy from the point of view of breast medical oncology, endocrinology, and basic science.

Keywords

Endocrine therapy, breast cancer, endocrinopathies, metabolism, bone health

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Breast cancer is one of the most common types of cancers and will affect one in eight women in their lifetime.[1] With the majority of breast cancers being estrogen receptor (ER)-positive, a large proportion of women will receive adjuvant endocrine therapy to prevent recurrence. Endocrine therapy represents a highly effective therapeutic option, with 5-year survival rates over 90%.[2] However, despite being effective at halting the growth of breast tumors, systemic suppression of estrogen biosynthesis/action is also associated with important side effects. Endocrinopathies associated with endocrine therapy use in breast cancer are an issue of significant magnitude and a number of recent studies have highlighted the endocrine and metabolic complications that occur as a result of treatment.[3] More specifically, an association has been observed for risk of diabetes mellitus and osteoporosis, also common in the general population, and especially in postmenopausal and aging women. Treatment may therefore compound the effects of aging and have long-term implications for years after treatment has ended.

What is endocrine therapy?

There are currently three pharmacological classes of endocrine therapy used for the treatment of breast cancer: aromatase inhibitors, selective estrogen receptor modulators (SERMs), and selective estrogen receptor degraders (SERDs). Aromatase inhibitors, steroidal and non-steroidal, bind to the aromatase enzyme and inhibit the conversion of androgens into estrogens. Their use is largely limited to postmenopausal women due to ineffective suppression of ovarian estrogen biosynthesis in premenopausal women.[4] Nevertheless, studies have demonstrated potential benefit of combining aromatase inhibitors with surgical or chemical ovarian ablation in premenopausal women.[4] After menopause, the adipose tissue, including that of the breast, is the main site of estrogen production.[5,6] Estrogens are also synthesized in the bone, joints, and brain.[5] In these women, aromatase inhibitors are effective at suppressing aromatase throughout the body, thus profoundly decreasing estrogen levels both locally and systemically.[7,8] SERMs, e.g., tamoxifen, bind to the ER and block binding of estrogens. SERMs can also act as ER agonists, altering receptor/co-regulators interactions.[8] As such, SERMs have been shown to affect gene expression and cell biology differently in different tissues. For example, despite being effective at stopping the growth of breast cancer cells, tamoxifen can also stimulate the proliferation of endometrial cells, leading to uterine polyps and in some cases, endometrial hyperplasia and cancer.[9] SERDs, e.g., fulvestrant, are pure anti-estrogens and binding to the ER leads to its degradation. Therefore, ligand-independent effects of ER, seen in some cases of endocrine therapy resistance, are not observed with the use of SERDs.[10]

Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers.[11] Approximately 90% of patients with breast cancer are diagnosed at an early stage

and these patients are treated on a curative intent with local therapy and adjuvant systemic therapy based on estimated individual risk for relapse and predicted sensitivity to available systemic therapies.[12–15] Modern endocrine therapy is very effective as treatment for ER-positive breast cancer. In the early stage setting, adjuvant endocrine therapy given for 5 years after primary surgery substantially delays local and distant relapse and prolongs overall survival.[16] Responsiveness to endocrine therapy, for the most part, is dependent on the presence of a functional ER, which is detected in approximately 70–80% of primary breast cancers and regulates endocrine-dependent growth in these tumors. Endocrine manipulation is achieved either at a cellular level by using anti-estrogens, such is tamoxifen, to compete for ER in the breast tumor, or systemically, by lowering estrogen levels in premenopausal women with the use of luteinizing hormone-releasing hormone agonists, and in postmenopausal women by aromatase inhibitors that block estrogen biosynthesis in non-ovarian tissues. Large-scale international trials of adjuvant endocrine therapy over the last three or so decades have investigated and established these treatment approaches.[17] Due to advances in treatment and early detection by screening, death rates in breast cancer have steadily decreased and 5-year survival currently exceeds 80% in most Western countries.[1] However, a significant number of women with HR-positive breast cancer remain at persistent risk of recurrence and death for the rest of their life.

With current standard of care adjuvant therapy, approximately 30% of women with HR-positive breast cancer initially diagnosed with early stage disease, experience distant relapse with metastases.[18] A meta-analysis of the results of 88 trials involving 62,923 women with ER-positive breast cancer reported that after 5 years of adjuvant endocrine therapy, breast-cancer recurrences continued to occur steadily throughout the study period from 5–20 years. The risk of distant recurrence was strongly correlated with the original tumor diameter and nodal (TN) status, with risks ranging from 10–41% depending on TN status and tumor grade. Remarkably, throughout this time, even among women with small, node-negative (T1N0), low-grade tumors, there was a risk of distant recurrence of approximately 10% during years 5–20. TN status was also a strong determinant of loco-regional recurrence, although not of contralateral disease.[19] Despite progress in early detection and therapeutic options, unresectable or metastatic breast cancer remains one of the leading causes of cancer-related suffering and mortality. Although patient survival has improved over the past two decades, metastatic breast cancer is still incurable with the currently established treatment modalities.

Currently available evidence and clinical practice guidelines support endocrine therapy as the primary treatment approach for most patients with HR-positive metastatic breast cancer,[20–23] until more rapidly progressive disease favors a switch to chemotherapy.[24] However, this treatment strategy increasingly requires distinct clinical judgment, as the selection of treatment options continues to expand to include additional endocrine agents, alone or combined with targeted molecular agents; chemotherapy; and other molecularly targeted approaches necessitating clinically useful metrics, alone or in combination, with proven biomarkers to select among the other treatment alternatives.[25] Up to 50% of patients with HR-positive metastatic breast cancer develop resistance to the endocrine therapy.[26] Overcoming *de novo* or secondary resistance in breast cancer remains critical to further enhancing the benefit of existing endocrine therapies.[27] Improving clinical response rates to endocrine therapy and prolonging the duration of those responses while maintaining quality of life has been an important clinical research goal in the ER-positive metastatic breast cancer space. Fundamental to all research approaches has been an understanding of the various biological mechanisms responsible for the development of endocrine resistance together with preclinical evidence that manipulating specific signaling pathways with the use of targeted therapeutics can enhance or restore endocrine sensitivity, and thus improve the efficacy of current endocrine treatment.[28] Co-targeting the ER, together with various key intracellular proliferation and cell survival signaling pathways, has been explored as a strategy.

Why does endocrine therapy lead to metabolic dysfunction and bone loss, and how common is it in women treated for breast cancer?

Estrogens are sex steroids that not only play a key role in reproduction, but are required for the normal functioning of numerous central and peripheral tissues.[5] Early preclinical studies demonstrated that removal of estrogen, by knocking out the aromatase gene or following ovariectomy, or knockout of ER, leads to weight gain, metabolic syndrome, and decreased bone mineral density (BMD).[29–31] This is also common in women who experience a drop in estrogen levels during the menopausal transition.[32,33] The use of endocrine therapy can mimic a state of estrogen deficiency and further exacerbate the endocrine impacts of menopause. Studies have demonstrated that tamoxifen use was associated with a 24% higher risk of diabetes in Canadian breast cancer survivors aged ≥65 years,[34] and a 31% higher risk in Taiwanese women aged >20 years with early breast cancer.[35] Recent observational data in a study of Israeli postmenopausal women with early breast cancer suggested that using an aromatase inhibitor was associated with a fourfold increased risk of diabetes compared with no endocrine treatment. In the same study, tamoxifen use doubled the risk of diabetes compared with no endocrine treatment.[36] Importantly, the women in these studies were followed for 6–12 years. This association was not necessarily evident in limited duration observational studies of <2 years.[37] In light of this evidence, and considering that two-thirds of women with breast cancer in the USA are overweight and obese, with higher rates of insulin resistance and diabetes, there is a risk that endocrine therapy will cause progression to diabetes in pre-diabetics or affect the management of women who have already been diagnosed with diabetes.[38]

There is also strong evidence for a link between endocrine therapy and the risk of skeletal deterioration and fracture. Women with breast cancer are usually post-menopausal and thus have low BMD at baseline, even prior to starting treatment. In the Women's Health Initiative study, breast cancer survivors had a 15% increased risk of fractures compared with women who were cancer-free.[39] In the skeleton, tamoxifen and aromatase inhibitors have quite different effects. The SERM, tamoxifen, is a partial estrogen receptor agonist in the bone, thus it promotes bone loss in premenopausal women, whereas it mitigates bone loss in postmenopausal women.[40,41] In a major breast cancer prevention trial in high-risk postmenopausal women, tamoxifen use after 5 years reduced the risk of osteoporotic fractures by 32% compared with placebo.[42] In contrast, tamoxifen decreases BMD in premenopausal women, even if they maintain regular menstrual cycles.[41] In postmenopausal women, adjuvant aromatase inhibitors are superior to tamoxifen and widely used. In those women, aromatase inhibitors accelerate bone loss and increase fracture risk by at least 10%[43–46] and up to 20% after 5 years of treatment.[47] Longer duration of aromatase-inhibitor therapy is associated with higher increases in the risk of fracture, at 14% versus 9% in those treated for 10 years versus 5 years, respectively.[47]

The incidence of fragility fractures from osteoporosis in women treated with aromatase inhibitors was shown to be 18–20% after 5 years of treatment in the ABCSG-18 clinical trial that used fracture endpoints.[48]

Are there consequences of diabetes and bone loss on risk of recurrence?

Women with diabetes have a 15–20% increased risk of developing breast cancer compared with women without diabetes.[49] The literature is scarce regarding the link of diabetes and specific pathologic characteristics, although reported data suggest that women with diabetes are more likely to be diagnosed with advanced stage and more aggressive breast cancer.[50–54] Studies have also indicated that mortality after breast cancer diagnosis is 30–60% higher among women with diabetes, including after correction for tumor stage;[53,55–58] although it remains unclear whether this is driven by worse breast cancer prognosis or by competing risks such as cardiovascular disease. Self-reported diabetes was associated with more than a two-fold increase in both breast cancer events and all-cause mortality.[59] Research has shown that chronic hyperglycemia is significantly associated with reduced overall survival in survivors of early breast cancer.[56] Clinical studies suggest that the biologic effects of both inflammation and obesity could promote cancer and the hyperinsulinemia associated with these conditions increases cell proliferation and survival.[60–62] Results have been inconsistent from studies investigating the association between breast cancer-specific mortality and diabetes.[63–65]

Experimentally, a number of factors have been shown to have effects on cancer cells that explain, at least in part, the relationship between diabetes and breast cancer. Candidates include insulin and glucose, as well as inflammatory mediators and estrogens produced locally in the breast adipose tissue.[6,66–68] Some tumors rely heavily on glucose as a source of energy and, as a result, display enhanced glucose uptake and metabolism.[69] This is the basis of ^{18}F-fluorodeoxyglucose positron emission tomography, whereby a non-metabolizable glucose tracer is used to image cancer metastases.[70] Hyperinsulinemia has also been shown to be a key driver of the diabetes–breast cancer link via stimulation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling in cancer cells.

The impact of osteoporosis on breast cancer recurrence is not as well defined. A cohort study using electronic medical records of 9,104 patients with breast cancer and 14,020 patients with precancer osteoporosis, showed that cancer osteoporosis was not associated with a risk of bone metastasis, but untreated osteoporosis was associated with accelerated progression of bone metastasis when it occurred.[71] Ultimately, osteoporotic bone loss and bone metastasis share a pathophysiologic pathway that stimulates bone resorption by increasing the formation and activity of osteoclasts.

How are endocrine therapy-related endocrinopathies managed?

There are no data specifically related to the management of diabetes in women with breast cancer on endocrine therapies. The recommendations regarding decreasing the risk of development of diabetes, as well as managing diabetes in order to prevent long term microvascular and macrovascular complications, are currently the same for women with breast cancer on endocrine therapy as in the general population.

In people with prediabetes, lifestyle changes have been shown to reduce the risk of progression to diabetes by almost 70%. Therefore, educating and motivating patients with breast cancer, and survivors, to adopt healthy lifestyle modifications is imperative. Those includes smoking cessation, diet modifications (diet high in vegetables, fruits, whole grains, and legumes, but low in saturated fats and simple carbohydrates), and exercise (at least 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week, including strength training exercises at least 2 days per week). Exercise partially reversed fat mass accumulation and lean mass loss in premenopausal women on tamoxifen plus ovarian suppression.[72]

Pharmacologic treatment of diabetes in women with breast cancer is based on current guidelines for treating the general population of people with diabetes. The first-line agent, and most widely-used agent, in type 2 diabetes is metformin given its strong efficacy in reducing glycated hemoglobin (HbA1c) and maintaining glycemic control; other concurrent beneficial effects include weight loss, reduction of cardiovascular risk, reduction of risk of death, low cost, and good tolerance with minimal adverse events.[73] Beyond metformin, other agents utilized for glycemic control with associated weight loss, cardiovascular risk reduction, and reduction of risk of chronic kidney disease are sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors), or glucagon-like peptide 1 receptor agonists (GLP1), ideally in combination with metformin.[74]

All women receiving treatment for breast cancer should be evaluated for their risk of fracture at the onset of therapy, particularly because osteoporosis may be a pre-existing condition. A thorough history and a dual-energy X-ray absorptiometry (DXA) scan should be performed. Universal lifestyle measures that mitigate the rate of bone loss are highly important and include regular weight-bearing, resistance, muscle-strengthening, and balance exercises; smoking cessation, and a diet rich in calcium, natural antioxidants, protein, without excess red meat, caffeine, colored carbonated beverages or alcohol. Weight-bearing and resistance exercise has been shown to limit bone loss in postmenopausal women with breast cancer, although fracture risk reduction has not been demonstrated.[47] The foundation of maintaining bone health includes intake of adequate calcium (1,000–1,200 mg daily, preferably from food sources; however, supplements may be added) and vitamin D ~800–1,000 units daily for a 25-hydroxy vitamin D level above 30 ng/mL, as is recommended for fall and fracture prevention in the general osteoporosis population.[75] Adequate calcium and vitamin D intake decreases the risk of hypocalcemia and maintains bone mineralization in the setting of antiresorptive therapies.

In 2017, multiple societies issued a combined position statement to address this issue.[47] Medications that reduce bone resorption such as bisphosphonates and denosumab are widely used and indicated in these women as the only effective means to actually reduce fracture risk. Treatment with either a bisphosphonate or denosumab is recommended for the duration of treatment with aromatase inhibitors.[47,76] In postmenopausal women with breast cancer receiving aromatase-inhibitor therapy, oral bisphosphonates (alendronate, ibandronate, and risedronate) when used for up to 5 years are associated with increases in BMD and reduction in fracture risk.[447,76] In women with taking anastrozole, BMD increased by 16% after 3 years of alendronate (compared with 5% loss on placebo in osteoporosis)[77] and by 2% (versus almost 2% loss on placebo) after 2 years of risedronate.[78]

The AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial investigated the addition of zoledronic acid to standard adjuvant treatments

in patients with early breast cancer, over a treatment period of 5 years. The results showed that the addition of zoledronic acid significantly lowered overall fracture rate by 6.2% versus 8.3% in the control group.[79] In Z-FAST (Zometa–Femara Adjuvant Synergy Trial) and ZO-FAST (Zometa–Femara Adjuvant Synergy Trial), postmenopausal women on adjuvant aromatase-inhibitor therapy were randomized to either up-front use of zoledronic acid (4 mg every 6 months) or delayed use of the zoledronic acid regimen.[46,80] Both studies found that those treated with zoledronic acid up-front had increases in BMD, but fracture rates were not statistically different across the treatment arms. Similar data are available from the E-ZO-FAST and ABSCG-12 (Austrian Breast Cancer Study Group) trials.[81,82]

Denosumab is approved for women on aromatase inhibitors at high-risk for osteoporotic fracture. The ABCSG-18 trial of denosumab versus placebo, demonstrated that time to first clinical fracture was decreased in the denosumab-treated group regardless of baseline BMD or age. As expected, denosumab was associated with increasing BMD at all skeletal sites.[48] In postmenopausal women on aromatase inhibitors, denosumab increased bone mass by 6–8% compared with placebo,[45] and reduced the risk of clinical fractures (hazard ratio 0.50), vertebral, and non-vertebral fractures over 3 years of treatment irrespective of baseline T score and age.[41] BMD should also be assessed in premenopausal women with amenorrhea associated with treatment for breast cancer, and treatment should be offered if their BMD is low for their age or they have a rapid rate of bone loss (5–10% annually).[83] There is currently limited evidence to suggest recommendation of bone density measurement in premenopausal women on tamoxifen who are still menstruating and have not had a fragility fracture.

Can the treatment of endocrinopathies reduce recurrence overall?

Metformin and GLP1 analogs may have promising antitumor effects in women with breast cancer either independently, or possibly due to maintenance of glycemic control.[84,85] Metformin, an oral biguanide commonly used to treat type 2 diabetes, has been associated with reduced incidence of breast cancer as well as improved breast cancer outcomes in observational studies largely conducted in individuals with diabetes.[86,87] Preclinical data suggest that metformin might act synergistically with certain chemotherapy;[88,89] however, recent phase II randomized studies failed to provide evidence in support of an anticancer activity of metformin when added to standard chemotherapy in women without diabetes and with metastatic breast cancer.[88,90] *In vivo* evidence from window studies shows an antiproliferative effect of metformin in breast cancer.[91,92] A neoadjuvant "window of opportunity" study of metformin in women without diabetes with operable breast cancer showed that short-term preoperative metformin was well tolerated and resulted in clinical and cellular changes consistent with beneficial anti-cancer effects; evaluation of the clinical relevance of these findings in adequately powered clinical trials using clinical endpoints such as survival is needed.[92,93] Other ongoing studies are investigating the role of metformin in the adjuvant/neoadjuvant early-stage disease setting, including the MA32 large multinational phase III trial (ClinicalTrials.gov identifier. NCT01101438). Meta-analyses have examined the role of metformin in the primary prevention of cancer, demonstrating that it significantly reduces overall cancer incidence, but the findings were inconsistent for tumor types.[94,95]

The mechanism behind the protective effects of metformin has been extensively studied, yet remains incompletely understood. A number of studies have demonstrated effects of metformin on isolated breast cancer cells at micromolar doses.[96] Although there is still debate regarding transport of the drug into/out of cancer cells that would support a direct effect of metformin, these doses exceed those achievable in women, largely due to life-threatening toxicities.[97] Additional studies point towards important effects of lowering systemic glucose and insulin levels, as well as estrogen production in the breast adipose.[93,98,99] Most studies implicate activation of the metabolic sensor AMP-activated protein kinase (AMPK).

Interestingly, a systematic review and meta-analysis involving nearly 1 million women, that included many of the studies mentioned above, demonstrated that the use of bisphosphonates for >1 year was associated with a 12% decreased risk of primary breast cancer.[100] Similar findings were observed for denosumab where use was associated with a 13% decreased risk of developing breast cancer.[101] In women with early breast cancer, bisphosphonates were associated with a 14% reduction in the risk of bone metastases.[102] The role of bone-targeted agents in the adjuvant treatment of early breast cancer has been debated for decades. In 2015, the Early Breast Cancer Trialists Collaborative Group (EBCTCG)[103] conducted a meta-analysis including individual data from 18,766 women from 26 clinical trials including ABCSG-12 and AZURE.[79,82] This meta-analysis provided the strongest evidence to date supporting the use of these agents in postmenopausal women with early-stage breast cancer. The meta-analysis demonstrated specifically in postmenopausal patients that the use of adjuvant bisphosphonates resulted in significant improvements in bone recurrence (6.6% versus 8.8%; p=0.0002), breast cancer mortality (14.7% versus 18.0%; p=0.002), or all-cause mortality (21.1% versus 23.5%; p=0.005) except distant recurrence outside of bone (12.1% versus 13.6%; p=0.10) was not statistically significant. Significantly, subgroup analyses by menopausal status showed a dramatic benefit in postmenopausal women (n=11,767) and there was no benefit in the premenopausal women (n=6,171).[99]

The beneficial effects of bone-targeted agents were reported with each bisphosphonate class, treatment schedule and dose, and were not associated with any particular tumor characteristic (HR status, nodal status, tumor grade); or whether the patient received concomitant chemotherapy.[103] In the EBCTCG analysis, the data examining bisphosphonates in premenopausal women in an induced menopausal through ovarian suppression were provided by the ACCSG-12 phase III randomized trial of zoledronic acid.[104] The mechanism underlying this differential benefit is not clear; however, evidence is accumulating, indicating that reproductive hormones and bisphosphonates can have similar effects on paracrine and cellular components of the bone metastatic niche.

Most studies included in the Oxford meta-analysis were randomized trials examining the use of bisphosphonate for 2–5 years duration.[103] The SUCCESS A trial recently reported no benefit for extending the use of intravenous zoledronic acid from 2–5 years.[105] SWOG S0307 compared the efficacy of three bisphosphonates in early-stage breast cancer and reported no evidence of differences in efficacy by type of bisphosphonate either in the intent to treat analysis or based on age and menopausal status.[106]

As a result of this compelling evidence, bisphosphonates are becoming a part of a standard of care in the adjuvant treatment for early breast cancer. The American Society of Clinical Oncology and

Cancer Care Ontario convened a working group of experts to develop evidence-based recommendations to guide the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer.[76] Results from ABCSG-18, a randomized trial of denosumab, a RANK ligand inhibitor, in postmenopausal women with HR-positive breast cancer, showed that use of denosumab as an adjuvant to aromatase-inhibitor therapy significantly reduced clinical fractures and also improved disease-free survival outcomes (hazard ratio 0.82 [95% confidence interval 0.69–0.98], Cox p=0.0260).[107] Furthermore, the addition of adjuvant denosumab to the regimen did not increase toxic effects—most notably, there were no documented cases of osteonecrosis of the jaw. Shortly after, the D-CARE study challenged the perspective for practice changing, establishing denosumab as an alternative to bisphosphonates since it failed to show benefit in bone metastases-free survival and disease-free survival also in the expense of higher toxicity due to the intense schedule.[108]

Future directions

There is now evidence to support a link between the use of endocrine therapy for the treatment of breast cancer and the development of endocrinopathies. Proper management of these side effects may, in fact, contribute to decreasing the risk of cancer recurrence. Should we therefore consider endocrine consequences of breast cancer therapies and preemptively treat with drugs like metformin or bisphosphonates? Food for thought. ❑

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