AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

# Endocrine Consequences of Breast Cancer Therapy and Survivorship

**KEY POINTS**

- Approximately 1 in 8 women will be diagnosed with invasive breast cancer in their lifetime, with the incidence rising due to improved screening
- The majority of breast cancers express oestrogen and/or progesterone receptors, in which case endocrine therapies such as tamoxifen and aromatase inhibitors reduce the risk of breast cancer recurrence and improve survival
- Many breast cancer treatments, especially for hormone-positive breast cancer, reduce oestrogen production or effect
- This can cause early menopause, menopausal symptoms, bone health implications, increased cardiovascular risks, and fertility and pregnancy considerations
- With 5-year survival rates of breast cancer in Australia of 92%, clinicians should ensure they are well informed about survivorship care of these women

## Introduction

Menopause/menopausal symptoms in women with breast cancer have a significant negative impact on quality of life, and thereby have the potential to reduce adherence to life-saving breast cancer treatments (1). These symptoms may occur due to:

- Natural menopause occurring spontaneously and simultaneously to the breast cancer diagnosis
- Recurrence of menopausal symptoms upon cessation of menopausal hormone therapy (MHT) following a diagnosis of breast cancer
- Treatments for breast cancer, including bilateral oophorectomy, chemotherapy or ovarian function suppression (OFS) with gonadotrophin releasing hormone agonists (GnRH agonists), or with endocrine therapies such as tamoxifen or aromatase inhibitors (AIs).

Management of menopause in women with breast cancer is directed towards alleviating symptoms and improving quality of life, as well as assessing and managing bone health and cardiovascular health impacts. In women who haven't completed their families, fertility and pregnancy implications may also need to be considered.

## Diagnosis of menopause

The diagnosis of menopause is clear in women who have undergone a bilateral oophorectomy. In women receiving chemotherapy with or without GnRH agonists for OFS, assessing resumption of menses following completion of chemotherapy and OFS is required. Age, type of chemotherapy, and duration of chemotherapy are factors associated with risk of premature ovarian insufficiency (POI), with older women and alkylating agents carrying a higher risk (2). In premenopausal women receiving tamoxifen, gonadotrophins are stimulated, while in postmenopausal women, there may be a partial suppression of gonadotrophins (3). Assessment of anti mullerian hormone (AMH) prior to chemotherapy may be of assistance in predicting resumption of menses post chemotherapy, but a reliable cut-off across assays has not been established (4).

## Management

### Vasomotor Symptoms

Vasomotor symptoms (VMS) due to menopause can be severe in women with breast cancer, particularly those at a younger age and where the onset of menopause was very rapid.
Systemic MHT is usually completely contraindicated in women with breast cancer, irrespective of the hormone receptor status of the cancer.

Non hormonal therapies for vasomotor symptoms are generally less effective than MHT. See the AMS information sheet on Non-Hormonal Treatments for Menopausal Symptoms for more information.

NK3 +/- NK1 inhibitors are emerging as an effective treatment option in women with breast cancer, by targeting the KNDy neurons in the hypothalamus which are important in the control of both reproduction and thermoregulation. A phase 3 multicentre placebo controlled trial in women taking endocrine therapy for hormone receptor positive breast cancer showed elizanetant (an NK-1 and NK-3 inhibitor) led to a significantly lower frequency of VMS than placebo (5), with trials in similar populations being undertaken with Fezolinetant, an NK-3 antagonist.

### Genitourinary Syndrome of Menopause

Genitourinary symptoms are reported by up to 69% of breast cancer survivors (6), with symptoms including vaginal dryness, itching, burning, pain and irritation, dyspareunia,

dysuria, urinary urgency or incontinence, and recurrent urinary tract infections. Unlike other symptoms of menopause, these symptoms are usually chronic and progressive. They are often particularly severe in women on AIs.

The vaginal administration of oestrogen is very effective for the relief of the genitourinary syndrome of menopause (GSM), however the safety of its use in women with breast cancer has been a controversial topic.

Initial treatment with non-hormonal vaginal lubricants and moisturisers is recommended, however where this is ineffective, it may be possible for vaginal oestrogens to be offered to women with persistent symptoms on discussion with the treating oncologist.

The available evidence is reassuring for women on tamoxifen, as any systemic absorption of vaginally administered oestrogen would be expected to be blocked at the breast. Vaginal oestrogen administration would also be deemed safe in women with a history of breast cancer who have completed or stopped adjuvant endocrine therapy (usually 5-10 years after diagnosis), or those with hormone receptor negative breast cancer (7).

There are fewer data available for women with breast cancer taking AIs, and shared decision making with the treating oncologist is recommended. A switch to tamoxifen may be considered in this context (7).

Prasterone shows good efficacy for treating GSM with minimal effect on oestradiol levels but longer follow up to assess breast cancer outcomes is needed (8).

## Skeletal Health

Most treatments for breast cancer reduce oestrogen and cause bone loss.

AIs are associated with an increased incidence of osteoporosis and fractures. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) study showed five years of anastrozole treatment caused a median 6.1% loss of BMD at the lumbar spine and 7.2% at the total hip (9). Two years after completion there was partial recovery at the spine but not the hip (10).

In premenopausal women, since AIs induce ovulation, they can only be used with concurrent OFS. Combined use of AIs and OFS in premenopausal women results in the most profound suppression of oestrogen production and the most pronounced bone loss among all types of endocrine therapies for breast cancer. Pre-menopausal women on anastrozole and goserelin had a reduction in BMD of 13.6% at the lumbar spine after three years, which partly recovers but doesn't return to baseline two years after treatment is completed (11).

Tamoxifen has variable effects in women depending on their menopausal status. In pre-menopausal women, tamoxifen acts as a partial antagonist in bone and prevents the more potent activity of endogenous oestrogen, thereby causing detrimental effects on bone density. In post-menopausal women with low circulating oestrogen concentrations, tamoxifen has a partial agonist effect and prevents bone loss, thereby having a mild beneficial effect on bone.

In women with iatrogenic menopause due to bilateral oophorectomy or chemotherapy-induced POI, detrimental impacts on bone health are well recognised.

There are a number of guidelines on the management of bone health in women with breast cancer receiving endocrine therapy. All of these women should be assessed for general osteoporosis risk factors, and a baseline bone density scan should be undertaken. Standard advice regarding adequate calcium intake, vitamin D sufficiency, smoking cessation, avoiding excessive alcohol intake, and partaking in regular weight bearing exercise should be given.

Most guidelines recommend that when the t-score is ≤2.0 and risk factors are present, pharmacological treatment of osteoporosis should be commenced (12). Bisphosphonates and denosumab both increase bone mineral density.

Reduced fracture risk is reported with denosumab in women treated with aromatase inhibitors, whilst adjuvant bisphosphonate therapy (especially IV zoledronic acid given at a dose of 4 mg every 6 months) may have survival benefits and confer a reduced risk of skeletal metastases (12).

The optimal duration of bone protective treatment is uncertain, particularly in the context of extended use of endocrine therapies beyond five years. Currently 3-5 years of bisphosphonates is recommended, with extension of therapy beyond five years possibly not being of additional benefit and carrying higher risks of side effects.

Concerns about discontinuation of denosumab exist in this population as in others, and therefore consideration should be given to the likely duration of treatment in an individual at the time of initiation of denosumab.

Regarding osteoanabolic therapies, teriparatide is contraindicated in women with a prior history of radiotherapy due to potential osteosarcoma risk. There is a theoretical concern that stimulating bone resorption could stimulate skeletal micro-metastases. There are no data available on romosozumab in this population.

Bone mineral density should be monitored every 1-2 years in women on endocrine therapy for breast cancer and no bone-targeted therapy, or two yearly for women on antiresorptive treatment (12).

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## Cardiovascular Health

With the improvement of breast cancer treatments, a greater number of breast cancer survivors will die from non-cancer diseases, including cardiovascular disease.

A systematic review and meta-analysis showed that breast cancer survivors had an increased risk of cardiovascular disease, heart failure and atrial fibrillation (13). This can be due to:

- Treatment effects, including cardiotoxic chemotherapy agents or radiation therapy.
- Shared risk factors for breast cancer and cardiovascular disease, including obesity, smoking and physical inactivity; and
- Hormonal factors, such as women having iatrogenic POI, or being on endocrine therapies which adversely affect their lipid profile and blood pressure.

Primary care physicians caring for breast cancer patients are involved across the continuum of care and usually beyond the duration of the treating oncologist (14). They have expertise in screening for and managing cardiovascular risk factors including blood pressure, lipids, glucose and other lifestyle factors, as well as other conditions which can adversely affect cardiovascular health such as depression, anxiety and sleep disturbance.

No lipid targets or guidelines specific to breast cancer survivors exist.

## Fertility and Pregnancy Considerations

Fertility in women with breast cancer is of increasingly common importance, due to the high incidence of breast cancer in young women and the later age of childbearing in western countries, meaning many women have not completed their families at the time of diagnosis.

Given that many breast cancer treatments affect ovarian function, fertility preservation is of paramount importance in many of these women.

Oocyte or embryo cryopreservation is standard of care prior to initiation of breast cancer therapy in women desiring future conception, but unfortunately the access to assisted reproductive technology is not always available, or a delay in commencement of anti-cancer therapy is not desirable.

GnRH analogues may be used to preserve ovarian function during chemotherapy but the outcomes on fertility preservation are inconsistent and long-term safety results are not available (15).

Tamoxifen carries some unique ovarian, fertility and pregnancy considerations (16). It acts as an antagonist at the pituitary similar to clomiphene, leading to ovarian hyperstimulation in premenopausal women with the potential for high serum levels of 17beta oestradiol, increased incidence of ovarian cysts, and induction of ovulation (17), putting women at risk for on-treatment pregnancy. Tamoxifen is teratogenic and careful counselling of the pregnancy risk in pre-menopausal women taking tamoxifen is required. Reliable contraception is very important; however, options are limited. Hormonal contraceptives are generally contraindicated. Reversible mechanical methods of contraception e.g. male condoms are most commonly used but are recognised to be less effective. Reversible long-acting non-hormonal options e.g. the copper IUD can also be considered.

## MHT in women with a history of breast cancer

A consensus statement published in 2026 acknowledged that in some women with a history of breast cancer, a blanket ban on MHT may not be appropriate (18). Some women have significant struggles with quality of life and find non-hormonal treatments for menopausal symptoms to be ineffective. In such women, the use of MHT may be considered in a shared decision-making model involving the patient, their oncologist, and their physician (primary care or specialist). This would take into account factors such as the individual's menopausal symptoms and impact on quality of life, the potential increased risk of relapse with MHT, and the patient's preference.

## Summary

Breast cancer survivorship is increasing, due to increased screening and better treatments. Consequently, survivorship issues are increasing in prevalence and improved awareness among treating clinicians is important. Holistic management is key and primary care physicians are well placed to support women along the continuum of their cancer journey and beyond. Quality of life factors are very important and if poorly managed, could lead to discontinuation of breast cancer therapies with a potential worsening of breast cancer outcomes. Shared decision-making with other members of the care team including the patient's oncologist may be necessary. More research to guide the safe use of MHT in breast cancer survivors would be helpful.

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February 2026.