

Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: position statement summary

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Adjuvant endocrine therapy improves oncological outcomes in women with oestrogen receptor-positive early breast cancer, but can accelerate bone loss, which predisposes to increased fracture risk. We summarise recommendations on the assessment and management of bone health in such women. The full position statement is available at <https://onlinelibrary.wiley.com/doi/epdf/10.1111/cen.13735>.¹

In Australia, dual energy x-ray absorptiometry imaging is not currently subsidised for women receiving adjuvant endocrine therapies for oestrogen receptor-positive breast cancer, and the use of anti-resorptive treatment in this population is generally off label.

Adjuvant endocrine therapies for oestrogen receptor-positive breast cancer include aromatase inhibitors (anastrozole, exemestane, letrozole) or selective oestrogen receptor modulators, usually tamoxifen. Aromatase inhibitors block oestradiol production, resulting in > 98% deprivation of circulating oestradiol in post-menopausal women. Aromatase inhibitors inhibit the oestradiol-mediated negative feedback on gonadotropin production and cannot be used as breast cancer treatment in premenopausal women unless ovarian function is suppressed (eg, by gonadotropin-releasing hormone agonists or bilateral oophorectomy). Selective oestrogen receptor modulators act as oestrogen receptor antagonists in the breast but have partial agonistic activity in tissues such as bone and endometrium, and may be used in both pre- and post-menopausal women.

In post-menopausal women, aromatase inhibitors are preferred because of modest improvements in outcomes, including lower 10-year breast cancer mortality compared with tamoxifen (12.1% *v* 14.2%; relative risk, 0.85; 95% CI, 0.75–0.96; *P* < 0.01).² Increasing the duration of endocrine therapy from 5 to 10 years can reduce the risk of breast cancer recurrence,^{3,4} but the absolute benefit is modest, and no survival benefit has been reported to date. In premenopausal women, tamoxifen has traditionally been first line treatment, although, on the background of ovarian suppression, the aromatase inhibitor exemestane improved 5-year disease-free survival compared with tamoxifen (91.1% *v* 87.3%; hazard ratio, 0.72; 95% CI, 0.60–0.85; *P* < 0.001).⁵ These benefits have been confirmed by a recent 8-year follow-up study.⁶ In women < 35 years of age, the 5-year breast cancer-free interval was 67.1% (95% CI, 54.6–76.9%) with tamoxifen alone, 75.9% with tamoxifen plus ovarian suppression (95% CI, 64.0–84.4%), and 83.2% with exemestane plus ovarian suppression (95% CI, 72.7–90.0%).⁷ After 8 years, the rate of freedom from distant recurrence in this age group was 73.8% with tamoxifen alone, 77.5% with

Abstract

Introduction: Representatives appointed by relevant Australian medical societies used a systematic approach for adaptation of guidelines (ADAPTE) to formulate clinical consensus recommendations on assessment and management of bone health in women with oestrogen receptor-positive early breast cancer receiving endocrine therapy. The current evidence suggests that women receiving adjuvant aromatase inhibitors and premenopausal women treated with tamoxifen have accelerated bone loss and that women receiving adjuvant aromatase inhibitors have increased fracture risk. Both bisphosphonates and denosumab prevent bone loss; additionally, denosumab has proven anti-fracture benefit in post-menopausal women receiving aromatase inhibitors for hormone receptor-positive breast cancer.

Main recommendations:

- Women considering endocrine therapy need fracture risk assessment, including clinical risk factors, biochemistry and bone mineral density measurement, with monitoring based on risk factors.
- Weight-bearing exercise and vitamin D and calcium sufficiency are recommended routinely.
- Anti-resorptive treatment is indicated in women with prevalent or incident clinical or morphometric fragility fractures, and should be considered in women with a T score (or Z score in women aged < 50 years) of < -2.0 at any site, or if annual bone loss is ≥ 5%, considering baseline bone mineral density and other fracture risk factors.
- Duration of anti-resorptive treatment can be individualised based on absolute fracture risk.
- Relative to their skeletal benefits, risks of adverse events with anti-resorptive treatments are low.

Changes in management as result of the position statement:

- Skeletal health should be considered in the decision-making process regarding choice and duration of endocrine therapy.
- Before and during endocrine therapy, skeletal health should be assessed regularly, optimised by non-pharmacological intervention and, where indicated, anti-resorptive treatment, in an individualised, multidisciplinary approach.

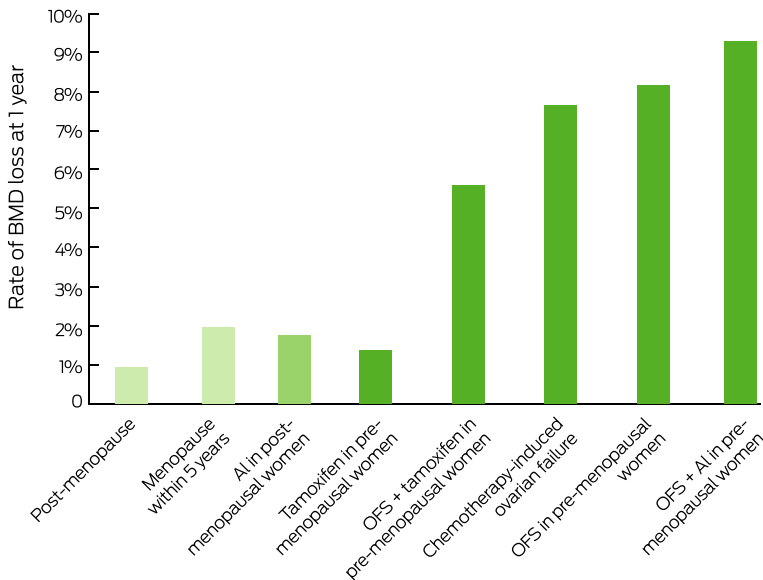
tamoxifen plus ovarian suppression, and 82.4% with exemestane plus ovarian suppression.⁶ These data^{5–7} are expected to increase the number of young, premenopausal women receiving ovarian suppression combined with aromatase inhibitors, which has profound effects on bone health (Box 1).

Due to earlier detection and advances in adjuvant treatment, women with early oestrogen receptor-positive breast cancer now

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1 Annual rates of bone mineral density (BMD) loss at the lumbar spine



AI = aromatase inhibitor; OFS = ovarian function suppression with GnRH analogues. Adapted from Gralow et al.⁸ *Journal of the National Comprehensive Cancer Network*. NCCN Task Force Report: bone health in cancer care. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed 24 March 2018. Available online at <http://www.NCCN.org>. ♦

have a 5-year survival greater than 90%.² Survivorship issues including management of unfavourable treatment effects are of paramount importance and optimally managed by a multidisciplinary team.^{9,10} Here, we focus on bone health.

Methodology

In 2017, the Councils of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia invited authors with expertise in this field to develop a position statement. An endocrinologist with experience leading national and international guidelines (HT) was appointed to advise the working group. A consumer representative (JH) was invited to participate and highlight priorities (Box 2).

Regular communication was accomplished by email before and subsequent to a face-to-face meeting held in October 2017. Conflicts of interests were declared before commencing the manuscript. The position statement was developed using the process proposed by the systematic approach for adaptation of guidelines (ADAPTE) working group.¹¹ Assessment of existing international evidence-based guidelines (Supporting Information, Table 1), identified by a systematic search of medical databases, was conducted using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, and supplemented by

systematic reviews, relevant publications, and the multidisciplinary expertise of the expert working group.

The draft statement was submitted to the society councils who provided feedback. The working group responded to feedback, the final version was approved and, following peer review, was published in *Clinical Endocrinology (Oxford)*.¹

We generated a clinical position statement by evaluating international guidelines through a formal ADAPTE process rather than generating a new evidence-based guideline. We cannot report National Health and Medical Research Council levels of evidence and Grading of Recommendations, Assessment, Development and Evaluation as we did not perform the original data extraction. Therefore, we do not provide evidence levels and refer readers to the original guidelines as needed.

Main recommendations

Assessment and monitoring for fracture risk

Accelerated bone loss and increased fracture risk during endocrine therapy. In post-menopausal women, compared with tamoxifen, aromatase inhibitors are associated with a two-to-threefold acceleration in bone

mineral density (BMD) decline which is most marked within the first 2 years.¹² In a meta-analysis of 30 023 women, aromatase inhibitor use increased fracture risk by 47% compared with tamoxifen (odds ratio, 1.47; 95% CI, 1.34–1.61; $P < 0.001$; number needed to harm to cause one fracture, 46).¹³

Given the beneficial effects of tamoxifen on bone health in post-menopausal women (see below), it is important to note that aromatase inhibitors increase bone loss and fracture rates even when compared with no endocrine treatment. In a randomised controlled trial (RCT) of 1918 post-menopausal women with early breast cancer, 10 years of aromatase inhibitor treatment compared with 5 years of aromatase inhibitor treatment followed by 5 years of placebo led to a higher incidence of osteoporosis (10% *v* 7%; $P = 0.02$) and clinical fractures (133 *v* 86; $P = 0.001$), despite 50% of women in both groups receiving bisphosphonates.⁴ In a meta-analysis, aromatase inhibitor treatment increased fracture risk by 17% (95% CI, 1.07–1.28) compared with no endocrine treatment.¹⁴

The largest magnitude of BMD loss (7–9% at the lumbar spine in the first 12 months) occurs in pre-menopausal women (Box 1).⁸ Use of ovarian suppression and aromatase inhibitor was associated with twice the prevalence of osteoporosis compared with ovarian suppression and tamoxifen (13.2% *v* 6.4% at 68 months).⁵

2 A consumer's perspective (JH)

By the time adjuvant endocrine therapy is suggested as part of a treatment regimen for women with early breast cancer, patients like myself may have been exposed to more than 20 unfamiliar drugs, each with pages of warnings of possible adverse side effects.

When I commenced 5 years of endocrine treatment as part of an 11-year treatment plan, I was given yet another risk sheet, but my clinician did not highlight possible bone loss as a common side effect. As a runner and a gym junkie, I assumed that I was adequately protecting my bone health more than the average woman of my age.

A dual energy x-ray absorptiometry scan at the beginning and later at the end of my treatment showed 10% bone loss.

Had I been counselled about available interventions, such as anti-resorptive agents, to minimise possible adverse effects of my treatment, I would have welcomed the information as providing me with options to protect my bone health.

In contrast to its antagonistic actions in breast, tamoxifen acts as a partial oestrogen receptor agonist in bone and has differential effects on BMD depending on ovarian oestradiol production. In RCTs of post-menopausal women, tamoxifen increased BMD by 1.2% at the lumbar spine at 2 years compared with a 2.0% decrease with placebo,¹⁵ and reduced fracture risk by 32% (relative risk, 0.68; 95% CI, 0.51–0.92).¹⁶ By contrast, in women who continue to menstruate after chemotherapy, tamoxifen (being less potent than native oestradiol) reduced lumbar spine BMD by 4.6% at 3-year follow-up.¹⁷ Therefore, pre-menopausal women have increased bone loss during tamoxifen treatment, with the opposite observed in post-menopausal women.

Prevalence of osteoporosis risk factors in women with breast cancer. Clinical risk factors for osteoporosis and fractures are common in women with breast cancer. Vitamin D insufficiency or deficiency has been reported in 64% of Australian¹⁸ and 76% of American breast cancer survivors.¹⁹ Chemotherapy-induced

neuropathy may increase falls risk. Of 200 Australian women with breast cancer > 50 years of age, 37% were current or previous smokers, 21% had elevated parathyroid hormone levels (3% primary hyperparathyroidism), 5.5% had a history of hyperthyroidism, and 11.5% were taking oral or inhaled glucocorticoids.¹⁸

How and when can fracture risk be assessed and monitored?

Clinical risk factors should be ascertained in all women commencing endocrine therapy. In addition, basic laboratory testing and dual energy x-ray absorptiometry imaging, repeated 12 months after commencement of endocrine therapy, with subsequent individualised monitoring frequency, are advised in all women (Box 3; Supporting Information, Table 1). If reduced bone mass (Z score < -1.0) is present, individualised assessment is needed to identify and exclude other causes of secondary osteoporosis. Lateral radiographs of the thoraco-lumbar spine can be used to assess for vertebral fractures (Box 3).

3 Management algorithm*

Women with early receptor-positive breast cancer treated with AI ± OFS

Initial bone health evaluation in all women

History	Blood and urine tests	Imaging
<ul style="list-style-type: none"> • Prior fragility fracture/s > 50 years of age • Parental history of hip fracture • Pre-existing metabolic bone conditions • Age at menopause • Smoking status • Alcohol consumption > 3 standard drinks/day • Assessment of falls risk • Chronic glucocorticoid use ≥ 5mg for ≥ 3 months • Diabetes (type 1 or 2) • Malabsorptive conditions • Rheumatoid arthritis • Low BMI < 20 kg/m² 	<p>UEC, LFT, 25-OHD, TSH, calcium, magnesium, phosphate</p> <p>If reduced bone mass is present, also consider the following:</p> <ul style="list-style-type: none"> • serum PTH, coeliac serology • serum and urine electrophoresis if age > 60 years or presence of risk factors for myeloma • urinary fractional calcium excretion rate (to assess for hypercalcaemia) 	<p>1. Baseline BMD by DXA <i>Repeat 1 year after commencement of AI and then every 2 years or every 1 year if:</i></p> <ul style="list-style-type: none"> • annual bone loss > 5% at any site • T score[†] < -1.5 at any site • commencing/changing anti-resorptive therapy <p>2. Thoraco-lumbar x-ray or VFA by DXA <i>Baseline: post-menopausal women only or pre-menopausal women if Z score < -1.5. Subsequent analysis if T score[†] < -1.5, back pain or loss of height ≥ 4 cm</i></p> <p>Note: VFA may miss vertebral fractures associated with mild height loss; lateral radiographs would therefore be preferential in individuals with a history of back pain or height loss</p>

Management

<p>Weight-bearing exercise <i>At least 30 minutes/day most days of the week</i></p> <p>Calcium <i>1000–1200 mg daily</i> <i>Dietary sources[‡] are optimal but if unable to achieve the recommended target through diet alone, consider supplemental elemental calcium</i></p> <p>25-OHD <i>Target level 75 nmol/L (do not exceed 150 nmol/L)</i></p>	<p>Anti-resorptive therapy</p> <p>We recommend anti-resorptive therapy if any of the following criteria are met:</p> <ul style="list-style-type: none"> • Prevalent or incident fragility or morphometric fracture/s • T score[†] < -2.0 at any site • Annual bone loss ≥ 5% and/or ≥ 0.05 g/cm² considering baseline BMD and other fracture risk factors • FRAX 10-year risk for major fracture > 20% or hip fracture > 3% (for post-menopausal women only)[‡]
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25-OHD = 25-hydroxyvitamin D; AI = aromatase inhibitor; BMD = bone mineral density; BMI = body mass index; DXA = dual energy x-ray absorptiometry; FRAX = fracture risk assessment tool; LFT = liver function test; OFS = ovarian function suppression (either bilateral oophorectomy or use of GnRH analogues); PTH = parathyroid hormone; TSH = thyroid-stimulating hormone; UEC = urea, electrolytes, creatinine; VFA = vertebral fracture analysis. * The recommendations do not apply to women who are receiving adjuvant bisphosphonates to improve breast cancer outcomes, or to women with natural menopause receiving endocrine treatment with tamoxifen alone. However, some elements of evaluation and management (eg, certain blood tests and non-pharmacological management) may still be relevant for such women in an individualised clinical context. † For women aged < 50 years, Z score should be used instead of T score. ‡ <https://www.osteoporosis.org.au/sites/default/files/files/OA%20Calcium%20Ed4.pdf>. § FRAX not validated for women aged < 40 years. FRAX may also underestimate fracture risk in women being treated with AI as this is not included in the algorithm. ♦

Given insufficient evidence regarding the clinical usefulness of bone remodelling markers, routine measurements are not recommended. The utility of bone imaging other than dual energy x-ray absorptiometry, such as high resolution peripheral quantitative computed tomography,²⁰ also requires further evaluation.

The Fracture Risk Assessment Tool or the Garvan Fracture Risk Calculator do not take aromatase inhibitor treatment or chemotherapy into consideration and are not validated for use in women aged < 40 years. Therefore, these tools may underestimate fracture risk in women receiving these treatments.

Management of fracture risk

Efficacy of non-pharmacological measures and pharmacotherapy in reducing the risk of adverse bone outcomes during endocrine therapy. The evidence regarding benefits of non-pharmacological measures specific to breast cancer survivors is limited. A systematic review and meta-analysis including 1199 women with breast cancer did not demonstrate a benefit of various exercise programs on bone density in post-menopausal women.²¹ However, a large RCT ($n = 498$)²² reported that combined step aerobic and circuit training modestly reduced bone loss in pre-menopausal women at the femoral neck (mean BMD difference, 1.2%; 95% CI, 0.2–2.2; $P = 0.02$). Exercise leads to multiple benefits in women with breast cancer, including improved quality of life, reduced aromatase inhibitor-associated arthralgia, and possible improved breast cancer outcomes.^{23,24} Evidence regarding vitamin D and calcium supplementation specific to breast cancer survivors is not available.

In RCTs of post-menopausal women with early breast cancer, bisphosphonates consistently prevented endocrine therapy-induced bone loss. The data were strongest for zoledronic acid (Supporting Information, Table 2). However, fracture outcome data, as an adjudicated primary endpoint, for bisphosphonates are lacking. By contrast, denosumab (60 mg given 6-monthly for 3 years) reduced clinical fractures by 50% compared with placebo (hazard ratio, 0.50; 95% CI, 0.39–0.65; $P < 0.0001$) in post-menopausal women receiving aromatase inhibitors, irrespective of baseline BMD.²⁵ In this dedicated fracture endpoint RCT, 10% of placebo-treated patients had a new clinical fracture within 3 years of aromatase inhibitor treatment,²⁵ comparable to rates seen in placebo groups of trials in established post-menopausal osteoporosis.^{26,27} This was despite participants in the aromatase inhibitor study²⁵ being 5–10 years younger than the osteoporosis trial participants^{26,27} and having bone density in the normal to osteopenic ranges rather than osteoporosis.

In pre-menopausal women receiving concurrent aromatase inhibitors and ovarian suppression, the marked bone loss observed in women not receiving anti-resorptive treatment (13.6% at the lumbar spine over 3 years) was prevented by 6-monthly administration of zoledronic acid.²⁸

When should non-pharmacological measures and pharmacotherapy with anti-resorptive treatment be considered, which agent could be used, and for how long can it be used? Despite the lack of rigorous evidence specific to breast cancer survivors, general measures to prevent bone loss including exercise, ensuring calcium and vitamin D sufficiency, smoking cessation and minimising alcohol consumption are recommended for all women starting endocrine therapy (Box 3; Supporting Information, Table 3).

In line with recommendations for the general population,²⁹ women with a fragility fracture (including subclinical vertebral fracture) or women aged ≥ 70 years with a BMD T score ≤ -2.5 could commence anti-resorptive therapy unless contraindicated. There is limited evidence specific to women receiving endocrine therapy to guide recommendations outside these criteria. Although recommendations differ slightly between guidelines (Supporting Information, Table 3), anti-resorptive therapy can be considered in aromatase inhibitor-treated women not fulfilling general population criteria if the BMD T score is < -2.0 at any site; two or more fracture risk factors are present; there is a $\geq 5\%$ and/or ≥ 0.05 g/cm² decrease in BMD in one year, considering baseline BMD and other fracture risk factors; or the Fracture Risk Assessment Tool 10-year risk is $> 20\%$ for major fracture or $> 3\%$ for hip fracture (Box 3).

In pre-menopausal women, accelerated bone loss occurs predominantly through treatment-induced suppression or failure of ovarian function and through the inhibition of oestradiol effects on bone (Box 1). Some recovery of BMD occurs in those who subsequently resume menses, but whether the deterioration in bone structure is reversible is unknown.²⁰ All pre-menopausal women should be informed about the potential for bone loss during anti-cancer therapy. Decisions regarding anti-resorptive treatment should be carefully discussed. If the Z score is < -2.0 , or if it is < -1.0 and there has been an annual decrease in BMD of $\geq 5\%$, anti-resorptive therapy may be considered.³⁰ Zoledronic acid is the only agent shown to prevent bone loss associated with concurrent ovarian suppression and tamoxifen/anastrozole therapy³¹ or with chemotherapy-induced ovarian failure.³² The uncertainties regarding optimal fracture risk assessment and management in pre-menopausal women treated for breast cancer is an area deserving of further research.

The duration of anti-resorptive treatment should be individualised based on absolute fracture risk. Most guidelines (Supporting Information, Table 3) comment on the uncertainty regarding the duration of anti-resorptive treatment during endocrine therapy. In women with high fracture risk, anti-resorptive treatment may need to be continued until the adjuvant breast cancer treatment is complete or even longer.

Zoledronic acid trials in this population have used 4 mg every 6 months (Supporting Information, Table 2). Alternative dosing schedules using 5 mg yearly with anti-fracture efficacy in other populations³³ may be relevant here but are yet to be trialled in this population.

Bisphosphonates persist in the bone matrix for years after therapy is discontinued. In contrast, there is loss of benefit with denosumab soon after cessation of therapy and, uncommonly, an increased risk of multiple vertebral fractures,³⁴ including case reports of women treated with aromatase inhibitors.³⁵ Pre-clinical evidence suggests that accelerated bone remodelling may promote the development of skeletal metastasis.³⁶ Denosumab should be given strictly 6-monthly. Based on currently available data, denosumab should not be stopped without considering bisphosphonate treatment to decrease rebound BMD loss and vertebral fracture risk. Optimal timing of initiation, mode and duration of bisphosphonate administration following denosumab cessation is unclear.

Currently, the use of anti-resorptive treatment in this population is generally off label. However, off label use is supported by evidence in this and the general population and is allowed in Australia. Health professionals should inform women and

discuss the evidence, possible concerns and side effects of treatment.

Anti-resorptive therapies are generally well tolerated, especially if dosing regimens used in osteoporosis studies are prescribed. However, discussion regarding potential side effects (reviewed in the full position statement) is necessary, with particular caveats for women who desire future pregnancy.¹ Briefly, oral bisphosphonates can cause gastrointestinal toxicity and should be avoided in patients with active upper gastrointestinal disease. Zoledronic acid is associated with a self-limiting acute phase reaction in 30% of patients, which is less severe with subsequent infusions.²⁶ Antiresorptive treatment-associated hypocalcaemia is uncommon in the absence of renal dysfunction and/or vitamin D deficiency. Rare but serious adverse effects of long term anti-resorptive use include atypical femoral fractures and osteonecrosis of the jaw.¹

Of note, in RCTs among post-menopausal women with early breast cancer, zoledronic acid and clodronate have not only demonstrated prevention of cancer treatment-induced bone loss but also modest reductions in the risk of disease recurrence and metastasis.³⁷ Current practice guidelines in the United States and Europe^{38,39} recommend that adjuvant zoledronic acid or clodronate should be considered in post-menopausal women to improve breast cancer outcomes, especially in high risk women. For women not receiving adjuvant bisphosphonates, the use of anti-resorptive agents for prevention of bone loss will be the primary reason for their use.

Conclusions

Before commencement of adjuvant endocrine therapy, women should be counselled about associated side effects. Adverse effects on skeletal health should be considered in the decision-making process, especially in women at high risk of fracture.

Treating clinicians should ascertain treatment-related adverse effects and pursue interventions known to mitigate these effects and enhance treatment adherence. Management is best individualised, using a multidisciplinary approach. Key research priorities include the conduct of clinical trials to better delineate the long term fracture risks of adjuvant endocrine therapy and to determine the efficacy of interventions designed to mitigate these risks. Availability of robust data on fracture rates and their prevention is important to generate health economic data to inform health policy.

Acknowledgements: We thank the Endocrine Society of Australia Council (chair Warrick Inder); the Australian and New Zealand Bone and Mineral Society (ANZBMS) Council (president Emma Duncan during the writing and reviewing of this statement); the ANZBMS Therapeutics Committee (chair Richard Prince); the ANZBMS Densitometry Committee (chair Nicholas Pocock); Australasian Menopause Society board members, executive director and past presidents Jane Elliott and Anna Fenton; and the Clinical Oncology Society of Australia Council (chair Phyllis Butow) for their support, expert reviews and valuable contributions to this statement.

Competing interests: Mathis Grossmann has received speaker honoraria and conference support from Besins and Amgen Australia, has been an advisory board member for Otsuka, and has received research support from Bayer, Novartis, Weight Watchers and Eli Lilly. Sabashini Ramchand has received speaker honoraria from Counterpart (breast cancer). Frances Milat has received speaker honoraria and conference support from Novo Nordisk. Amanda Vincent has received speaker honoraria, conference support and research support from Amgen Australia, and has been a Cancer Australia working party member on management of menopause in women with breast cancer (honorary position). Elgene Lim has received speaker honoraria and conference support from Roche, Novartis and Amgen Australia, has been an advisory board member for TEVA, Novartis, Roche, Pfizer Oncology and Bayer, and has received research support from Bayer and Novartis. Mark Kotowicz has received speaker honoraria and conference support from Amgen Australia and Eli Lilly, has been an advisory board member for Amgen Australia and Eli Lilly, and has received research support from Amgen Australia. Helena Teede has received speaker honoraria and conference support from Novo Nordisk, has been an advisory board member for Diabetes Australia Victoria (honorary position), has received research support from Janssen Cilag, and is director of the Epworth Sleep Centre, Melbourne.

Provenance: Not commissioned; externally peer reviewed. ■

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Supporting Information

Additional Supporting Information is included with the online version of this article.