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Managing menopausal symptoms and associated clinical issues in breast cancer survivors

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Objective: Review evidence to guide the management of menopausal signs and symptoms in women after breast cancer and make recommendations accordingly.

Evidence: Randomized controlled clinical trials, observational studies, evidence-based guidelines, and expert opinion from professional societies.

Background: Several symptoms and clinical problems associated with estrogen depletion — sleep disorders, vulvovaginal atrophy (VVA), vasomotor symptoms (VMS), mood changes, depressive symptoms, cardiovascular disease, osteopenia and osteoporosis— confront the estimated 9.3 million breast cancer survivors globally.

Recommendations: Following breast cancer, women should not generally be treated with menopausal hormone therapy or tibolone but should optimize lifestyle. Women with moderate to severe symptoms may benefit from mind-brain-behavior or non-hormone, pharmacologic therapy. The selective serotonin/noradrenaline reuptake inhibitors and gabapentenoids agents exert beneficial effects on VMS and quality of life. For osteoporosis, the panoply of non-hormonal agents is available. Treatment of VVA remains an area of unmet need. Low dose vaginal estrogen is absorbed in small amounts with blood levels remaining within the normal range but could potentially stimulate occult breast cancer cells, and although poorly studied, is not generally advised, particularly for those on aromatase inhibitors. Intravaginal DHEA and oral ospemiphene have been approved to treat dyspareunia, a symptom of VVA but safety after breast cancer has not been established. Vaginal laser therapy is being utilized for VVA but efficacy from sham-controlled studies is lacking. Therapies undergoing development for possible future use include lasofoxifene, neurokinin B inhibitors, stellate ganglion blockade, vaginal testosterone, and estetrol.

Conclusions: A variety of non-hormone options and therapies are available for treatment of estrogen-depletion symptoms and clinical problems after a diagnosis of breast cancer. Individualization of treatment is essential.

The number of breast cancer survivors worldwide is increasing and treatment of estrogen deficiency symptoms in these patients is important and complex as reviewed here.

Introduction:

Early diagnosis and concomitant initiation of more effective cancer treatments have reduced the death rate from breast cancer by 38% from 1989 to 2014 (1;2). The five year survival rate in developed countries is now 99% for patients with localized disease (3). Accordingly, the number of breast cancer survivors is increasing and has now reached 3.1 million in the USA and is
estimated to be approximately 9.3 million worldwide (3;4).* In Western countries, approximately 43% are ≥ age 65 and approximately 25% ≤ age 50 at diagnosis. The numbers of survivors are increasing due to the reduction in disease specific death rates since 1989. Early detection in developed countries has enhanced the number of women free of lymph node metastases; the 5 year survival rate for these women is 99% in comparison with 84% if lymph nodes are positive (3).

A large proportion of women experience menopausal symptoms or clinical manifestations of estrogen deficiency during treatment of their breast cancer or after completion of therapy (5;6). The specific symptoms and clinical challenges differ based on menopausal status prior to initiation of cancer treatment and therapeutic agents used. For example, pre-menopausal women treated with chemotherapy can develop ovarian insufficiency and severe menopausal symptoms as well as infertility resulting from toxic effects of chemotherapeutic agents on the ovary (7). Postmenopausal women treated with aromatase inhibitors (AIs) may experience arthralgia, accelerated bone loss, and an increased incidence of osteoporotic fractures as a result of markedly suppressed estrogen levels (i.e. < 2 pg/ml) (8-10). They may also experience a severe form of vulvovaginal atrophy (VVA) with significantly higher rates of vaginal dryness (16.3%) and dyspareunia (17.8%) compared to women taking tamoxifen (8.4% and 7.5% respectively) (11-13).

The constellation of signs and symptoms related to estrogen deficiency has prompted a variety of studies of menopause management in breast cancer survivors (5;7;14-20). However, the lack of randomized placebo controlled trials (RCTs) in this population has limited the evidence upon which to base therapeutic decisions. Consequently, written guidelines to address menopause management in women during and after treatment of breast cancer have not sufficiently focused on treatment of this subgroup of women. To address this gap, the writing group (C.A.S, S.R.D, AG, M.A.L, J.V.P, and R.J.S) of the Endocrine Society Guidelines on management of menopausal symptoms (13) was prompted to write a review focusing on current and future approaches to management of menopausal symptoms and sequelae in women after breast cancer.

• Footnote The incidence of new breast cancers worldwide in 2008 was 1.38 million with an estimate of approximately 9.3 million survivors. This estimate is based on the ratio of new cases to survivors in the USA (231,000 new cases/3.1 million survivors) reduced by an estimated factor of 0.5 to account for higher mortality outside of North America and Western Europe.(3;4)

The prevalence of estrogen-deficiency symptoms in women after breast cancer ranges from 79% to 95% (6;21-27) and is higher than in women without breast cancer (6;22). Survivors report more sleep disturbance (P<0.01), difficulty concentrating (P<0.01), musculoskeletal pain (P<0.01), crying (P<0.01) and irritability (P<0.01), and vasomotor symptoms (P<0.01) (28). These differences may reflect the rapidity of the menopause transition and the magnitude of estrogen deficiency exacerbated by AI therapy. Illustrative data originate from a follow up study of women with breast cancer no longer on therapy and 6 years on average after diagnosis (6). In the group of women ages 50-59, 72.8% reported vasomotor symptoms, and 80.8% sexual symptoms (6). The prevalence of these symptoms was lower in women younger than age 50 and older than 59 but the symptoms were still frequent (i.e. 50-60%) (6) (19) The authors reported that breast cancer survivors had significantly higher vasomotor domain (P ≤ 0.002) and sexual domain (P ≤ 0.004) scores than community controls (6), indicating more bothersome symptoms. Weight gain is also a common problem associated with breast cancer therapy (29).
Specific components of the problem:
Both pre- and post-menopausal breast cancer survivors often experience moderate to severe VMS and sleep disturbances with related fatigue, mild depressive symptoms, and mood changes (26). Arthralgia, osteopenia, osteoporosis and related fractures occur predominantly in post-menopausal women as does VVA and associated dyspareunia (11;12;28;30;31). Less common problems include weight gain, symptomatic osteoarthritis and intervertebral disk degeneration, degenerative skin changes, radiation and chemotherapy-related cardiovascular disease and reduced quality of life (12) (11).

Strategies for Management:
Key principles are to determine (a) the severity of the signs and symptoms related to estrogen deficiency and (b) the degree of bother to the patient. This allows treatment to be individually tailored based on these assessments. For mild symptomatology or maintenance of health, lifestyle modifications or over the counter options may be sufficient. Moderate or severe signs or symptoms usually require pharmacological management.

Lifestyle modifications:

*Amelioration of symptoms:*
Women with mild VMS frequently do not need pharmacotherapy but do benefit from lifestyle changes (32). Simple behavioral measures such as lowering of room temperature, using portable fans, dressing in layers that can be easily shed, avoiding triggers (such as spicy foods and stressful situations) and likely exercise, may help reduce the number of hot flashes.(32;33) A Cochrane review provided supportive evidence that exercise results in a reduction in hot flashes but suggested that additional randomized trials are needed to resolve existing controversy (34). While a recent RCT provided evidence that exercise training decreases hot flashes, (35) a pooled analysis of 6 studies reported no benefit from aerobic exercise (36). Diet may modify the incidence of vasomotor symptoms (37). Loss of 10% or more of body weight, as part of a healthy dietary intervention may significantly reduce VMS (37). Use of non-pharmacologic agents such as soy, black cohosh , flaxseed, remifemin, equol in equol -producers, and vitamin E have been reported to be beneficial for VMS primarily when mild (13;38;39). However, RCT evidence of efficacy is mostly lacking and safety has not been firmly established in any population, much less in women who have had breast cancer. Of potential concern are products that may have some degree of weak estrogenic actions.

Recent research emphasis has been on the development of non-pharmacologic therapies of VMS. Cognitive behavioral strategies which include stress management, relaxation, deep breathing, and yoga have been tested in clinical trials with varying results (12;13;33).Hypnosis appears to be promising based on recent randomized trials (40). Another approach, stellate ganglion block with a local anesthetic provides improvement in hot flashes, but has more potential risks (41). Acupuncture may be another effective procedure although sham acupuncture is also effective (20;42;43)

*Overall health and survival benefit:*
Increased physical activity, weight reduction and cessation of smoking and alcohol are important for breast cancer survivors based on evidence that these steps may provide objective benefit (44). Specifically, physical activity improves postmenopausal women’s balance, body composition, muscle strength, and bone health; improves mood (45) reduces cardiovascular risk (46;47); and
potentially, reduces falls contributing to osteoporotic fractures (47). As obesity, independent of treatment, is associated with a poorer prognosis after breast cancer, including women with early disease, normalization of body weight is to be encouraged (48). Smoking cessation reduces mortality and improves quality of life (49). These lifestyle improvements may also benefit the metabolic syndrome (50). Adherence to a Mediterranean diet has been shown to decrease the incidence of breast cancer, particularly estrogen receptor negative cancer, and could reduce the incidence of second breast cancers (51).

Another lifestyle modification is to optimize vitamin D levels so as to maintain bone health. (52). A Cochrane meta-analysis (53) concluded that supplementation of vitamin D and calcium in older patients reduces fracture risk (OR 0.89; 95% CI 0.80-0.99). An Institute of Medicine (IOM) report (54) (55) stated that raising low levels to normal are beneficial whereas no benefits accrue from increasing Vitamin D levels above 50 ng/ml. Disagreement exists as to what levels constitute vitamin D deficiency. As defined by the IOM, deficiency represents a level below which rickets or osteomalacia occurs, namely <10-20 ng/ml (25-50 nmol/l) and normal levels are 20 ng/ml and above (56). The Endocrine Society Guidelines consider deficiency to be <20ng/ml, insufficiency 20-29 and normal ≥30 ng/ml (57). The IOM suggests daily supplementation of vitamin D with 600 IU for women <70 years and 800 IU for those older. While vitamin D intoxication is rare unless supplementation exceeds 10,000 IU daily, a recent, detailed IOM report suggests that levels above 50 ng/ml may be associated with cardiac toxicity (56). Selected recent data suggest that levels of vitamin D may correlate with overall survival (58). Calcium supplementation is currently controversial, but postmenopausal women need 1200 mg of calcium, ideally from diet, to maintain bone health during menopausal transition.

**General Advice:**
All breast cancer survivors should be advised to modify their lifestyles to include smoking cessation, weight loss (if indicated), limiting or avoiding alcohol, maintaining adequate levels of vitamin D and calcium, eating a healthy diet and regular physical activity (59).

**Management of moderate or severe signs and symptoms:**

**Vasomotor Symptoms:**
Hot flashes and night sweats have been categorized as mild, moderate or severely bothersome depending on presence of sweating or disruption of usual activity (32). Previous opinion held that hot flashes resolve within 5-10 years after menopause onset in most women. However, recent data suggest that this symptom can continue for 15 years or more in as many as 33% of women with natural menopause (60). Women taking tamoxifen may experience severe flushing which leads to stopping the treatment. While the most effective treatment of moderate to severe VMS is the use of menopausal hormone therapy (MHT) (12;13;13), clinical guidelines consider this approach contraindicated in women with a history of breast cancer based on existing, but limited RCT evidence. Early meta-analyses based on observational data reported this approach to reduce breast cancer recurrence in breast cancer survivors (61). Later, more critical assessments have suggested that selection bias may have confounded this conclusion (62). Specifically women thought to be cured of breast cancer were likely selected to receive MHT, and the women felt to harbor residual tumor were not. Accordingly, the recurrence rate in the women receiving MHT appeared to be reduced compared to the placebo group.

To address the “wellness bias”, three RCTs compared MHT to placebo in breast cancer survivors (63-66). Two, the Habits and Stockholm trials, compared estrogen with or without a
progestogen and were conducted in Stockholm. The trials differed with respect to the progestogen used, primarily norethisterone in Habits trial and medroxyprogesterone acetate in the Stockholm trial. The Habits trial with 898 women, reported an increased hazard ratio (HR) for breast cancer recurrence of 2.2 (CI 1.0-5.1) for those using MHT, whereas the other, the Stockholm trial with 844 women, reported no increased risk (HR 0.82 (CI 0.35-1.9)(63-65). Differences in the trials included continued use of tamoxifen and stage or histology or receptor status of the pre-existing breast cancer. Prior to completion of these studies, the decision was made to combine the data, resulting in an overall hazard ratio of 1.8 (CI 1.03-3.10)(64). The third trial evaluated tibolone, 2.5mg/day, and also reported an increased risk of breast cancer recurrence (HR 1.40 [CI 1.14-1.70]). The results might have been influenced by the inclusion of women taking AIs in the study as tibolone can exert estrogenic effects (66). These three trials, while not definitive, have led the majority of guideline committees to consider MHT to be contraindicated in breast cancer survivors (13) (33;66-68).

Other non-hormonal pharmacological treatments of moderate to severe hot flashes are available which exhibit significant efficacy. RCTs demonstrate the efficacy of the SSRI/SNRI class of agents, transdermal nitroglycerin (69), and of gabapentin and pregabalin (figure 1) (36;70-74). In general, these agents result in an overall 70-80% reduction in hot flash number and severity. However, on average, approximately 30% of the reduction is due to placebo effects (75)(figure 1). From the patient’s point of view, overall efficacy (including both drug and placebo effect) is the most important factor with respect to reduction of hot flash severity, sleep disruption, elevation in mood (76) and improvement in quality of life. Substantial clinical experience has been gained by the numerous trials of Charles Loprinzi and colleagues in breast cancer survivors (15;71;77). The first recommendation from this group is to try low dose antidepressants in women with moderate to severe hot flashes. Women taking tamoxifen should avoid potent CYP2D6 inhibitors as these agents reduce the levels of an active metabolite, endoxifene (73). Higher CYP2D6 inhibitory potency is found with paroxetine and fluoxetine (avoid), weak to moderate with citalopram, and relatively low (better choice) with venlafaxine, desvenlafaxine, escitalopram, gabapentin and pregabalin (78-82).

Nighttime VMS may be associated with a greater risk of minor depression, fatigue, and mood changes than those occurring during the daytime. (83). On this basis, the first step in management is to ascertain whether the symptoms occur predominantly at night as the pattern of hot flash presentation can inform the specific therapy to be chosen. For night time VMS or sleep disruption, a single dose of gabapentin given one hour before sleep is associated with a reduction in night time hot flashes and a soporific effect on initiating sleep. The short half-life of this agent yields fewer side effects upon awakening. Clinical experience has shown that the gabapentin dose must be individually determined and ranges from 100 mg to 1200 mg given as a single dose one hour before bedtime. A formal dose escalation protocol in each patient determines the appropriate dose. For VMS occurring both during the day and night, an additional morning dose of gabapentin can be added.

For women with predominantly daytime hot flashes, the SSRI/SNRI class of agents has been shown to be effective. In the USA, only one agent, paroxetine salt 7.5 mg, is approved by the FDA for treatment of VMS, but others in this class are also effective (figure 1) and have been shown to be successful for symptom relief in breast cancer survivors (15;71;73;84). Another agent, clonidine, is somewhat effective, and can be a second line agent. Because of side effects with oral preparations, the long acting TTS (transdermal therapy system) preparation of clonidine is preferable, with titration of dose depending on symptom relief and effect on blood
pressure. With each of these approaches, approximately half of these women experience at least a 50% decrease in hot flash score (see Table 2 from reference (77)).

In patients refractory to the above agents, intramuscular medroxyprogesterone acetate (MPA), 500 mg at 4-5 month intervals, has been suggested by the Mayo Clinic group to be as effective as estrogen therapy (77). Since this agent has been shown to be an effective therapy for hormone dependent breast cancer (85-87), these investigators consider it safe for breast cancer survivors. However, this conclusion is controversial because of concerns about the proliferative effects of a progestogen on occult breast cancer cells. Until more safety data are available, this agent is generally not recommended. An important side effect of MPA is the weight gain occurring from its glucocorticoid actions. Micronized progesterone 300 mg nightly also significantly decreases VMS and improves sleep when compared with placebo (88). Notably, observational studies in healthy postmenopausal women have suggested a lesser effect of progesterone/estrogen combinations on breast cancer risk compared to synthetic progestogen/estrogen combinations (89-93), but these findings have not been confirmed in RCTs and no data are available in women with breast cancer.

A key question is whether or not MHT might be prescribed to breast cancer survivors refractory to the agents mentioned above. A multidisciplinary conference (94), recommended that MHT can be used in the lowest effective dose but only after obtaining full, written informed consent from the patient with attention to all potential risks and benefits (94). The Endocrine Society 2015 guideline also allows for individual women to accept a degree of risk that might otherwise be considered to outweigh the benefits of MHT (13). The guideline states, “A fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks.” (13).

**Vulvo-vaginal atrophy (VVA):**
This common condition is a consequence of estrogen deficiency. Symptoms of VVA include vaginal dryness, irritation, itching, infection, discomfort and painful sex (dyspareunia). Dyspareunia in turn leads to diminished sexual desire, arousal difficulties, and relationship problems. Up to 25-50% of postmenopausal women, particularly those on AIs, have VVA, and thus many women with breast cancer are profoundly affected in a major way by this problem (25). Dyspareunia interferes with sexual intimacy and disrupts the quality of life and successful partnerships in women with VVA. With the growing awareness of quality of life issues in cancer survivors in general, the issue of VVA has been increasingly emphasized as a major problem. VVA has been recently included under the broader term “Genitourinary Syndrome of Menopause (GSM)” which also includes urinary symptoms (urgency, dysuria, and recurrent urinary tract infections (95).

For mild symptoms, regular use of vaginal moisturizers may be effective in combination with lubricants proximate to intercourse. (Moisturizers are used continuously but not at the time of intercourse, as they may be irritating). Differences between lubricants used acutely prior to intercourse and vaginal moisturizers used chronically to improve vaginal pH and moisture should be emphasized to patients. There are many types of moisturizers and lubricants available, including preservative free if needed. For more severe symptoms, the measures described above are not sufficiently effective. A logical approach is to consider low dose vaginal estrogen therapy. However, high sensitivity mass spectrometry assays have demonstrated that all vaginal estrogen preparations result in a minor degree of systemic absorption but not exceeding normal postmenopausal levels (96). Whether a very small increase in estradiol exposure will stimulate quiescent, occult breast cancer cells or contribute to the development of a breast cancer
is not known. Pre-clinical data have shown that long term estrogen deprivation can result in a state of estradiol hypersensitivity, both to proliferation and apoptosis (97) but it is not clear which effect would predominate.

Low dose vaginal estrogen in women taking the anti-estrogens, tamoxifen or raloxifene, might be theoretically safer than in women not receiving these agents because of blockade of some possible effects of systemic estrogen absorption (98). Three studies (observational and case controlled) have examined the impact of vaginal estrogen administration in breast cancer survivors, and the results are reassuring, at least when vaginal estrogen is administered concurrently with tamoxifen (98-100). These studies, however do not provide robust evidence regarding the safety of vaginal estrogens in breast cancer survivors taking aromatase inhibitors, the efficacy of which is due to markedly suppressed estrogen levels (101). One observational study of breast cancer survivors using tamoxifen or an AI, however, found no increased breast cancer recurrence risk with low dose vaginal estrogen (vaginal ring or 10-mcg tablet) during a 3.5 year mean follow up (98). In general, the use of low dose vaginal estrogen in breast cancer survivors has been discouraged, particularly in those receiving AIs (13:68). If recommended following consultation with the attending oncologist, one should use the lowest effective dose of vaginal estrogen as recommended by ACOG, ASCO, the Endocrine Society (13), and NAMS (33;68;102).

The SERMs, tamoxifen and raloxifene, can exert mildly estrogenic effects on vaginal tissue. In the ATAC (anastrozole, tamoxifen and in combination) trial, 11.4% of women treated with tamoxifen reported vaginal discharge compared with 2.8% treated with an AI (103). In a chemoprevention trial comparing the effects of tamoxifen and raloxifene, vaginal discharge was reported more commonly by women taking tamoxifen than raloxifene (104;105). Ospemiphene, an oral SERM, has been approved in Europe and North America for the treatment of dyspareunia secondary to VVA in healthy postmenopausal women. Comprehensive studies of ospemiphene demonstrated an improvement in vaginal maturation index and relief of most VVA symptoms, as well as improvement in measures of sexual wellbeing (106;107). Safety evaluation showed a negligible estrogen effect on the uterus, and pre-clinical data suggested a predominantly anti-estrogen effect on breast cancer growth (106;107). Current FDA labeling in the US recommends against use of ospemiphene in women with a history of breast cancer which will need to await an adequately powered RCT of its effect on the breast.

A recently FDA approved (i.e. November 2016) therapy for dyspareunia secondary to VVA is intravaginal dehydroepiandrosterone (DHEA). This therapy has not yet been approved beyond the USA. Nightly vaginal application of a 6.5 mg DHEA ovule has been shown to significantly improve vaginal cell maturation indices and the most bothersome symptoms of VVA. As DHEA can be enzymatically converted into both estrogen and androgens locally, this therapy theoretically provides a non-systemic hormonal approach. Carefully conducted studies with highly sensitive and specific mass spectrometry assays suggest a slight but statistically significant increase in plasma estradiol and testosterone (108). Intravaginal DHEA has not been tested in breast cancer survivors; thus there is a warning about its use due to lack of testing.

A small, double blind RCT of women without breast cancer has shown that intravaginal testosterone may be efficacious when compared with a placebo and vaginal estrogen in terms of subjective and objective VVA measures (109). A preliminary, non-controlled trial suggested that intra-vaginal testosterone may provide an effective treatment option for women with breast cancer taking an AI and experiencing symptoms of atrophic vaginitis (110). Further data on safety and efficacy are needed before this approach is recommended.
An additional approach to treatment of VVA includes laser reduction of the vaginal mucosal lining using a fractional carbon dioxide laser (111). Although FDA approved for use on soft tissues, the specific indication for laser treatment of VVA is not included (112). ACOG currently recommends against this procedure due to lack of safety and efficacy data (112). Although results appear promising in a number of observational studies, including one in women with breast cancer (113;114) no RCTs have compared this approach with sham treatment, and its efficacy and safety therefore remain unclear (115).

**Depressive symptoms and mood changes:**
The relationship between menopause, VMS and depressive symptoms and mood changes has been well established (116). Major depression should be identified and treated with specific pharmacologic agents and/or cognitive behavioral therapy. Recent experimental data support the concept that mild depressive symptoms and fatigue may in part result from sleep disruption with frequent awakening at night due to hot flashes (83;117). Further data are needed to confirm this conclusion in women with breast cancer.

**Cognition:**
Menopause appears to be associated with subtle changes in cognitive function, notably delayed verbal memory (118). Sleep disruption may contribute as sleep is important for the encoding and consolidation of memory (119). However evidence that exogenous estrogen therapy improves cognitive function within the first few years after menopause is lacking except for those with early surgical menopause (120;121). Lower testosterone levels, as seen with age, surgical menopause or chemotherapy, have been implicated in cognition (122). As breast cancer survivors experience chemotherapy induced “chemo-brain” and sex-steroid deficiency related effects, further understanding and possible treatments of cognitive problems remain key goals at the present time.

**Osteopenia, Osteoporosis, and Fractures:**
Endocrine therapy for hormone dependent breast cancer impedes either estrogen synthesis or its action. Surgical oophorectomy or chemotherapy induced ovarian insufficiency in premenopausal women reduces estrogen levels and accelerates the rate of bone resorption as does tamoxifen in this population (11). On this mechanistic basis, an increased rate of osteopenia or osteoporosis and fracture has been reported (11). In post-menopausal women with breast cancer, AIs have become first line therapy in preference to tamoxifen. The substantial reduction of estradiol levels to sub-pg concentrations (i.e. 0.05 to 0.6 pg/ml) (8;10) markedly contributes to bone resorption. Quantitative data demonstrate a rapid and substantial increase in markers of bone resorption such as NTX or CTX and a subsequent reduction in bone density with aromatase inhibitors (11;123;124)(Figure 2 below). These effects are not sufficiently counteracted by a reflex rise in bone formation, demonstrated by measurements of osteocalcin and other markers. Accordingly, there is a net decrease in bone density and an increase in fracture rate. As recent data demonstrate the greater efficacy of 10 years vs five years of therapy with the AIs, this problem will become increasingly severe in the future (125). Interestingly, tamoxifen acts as a weak estrogen on bone in postmenopausal women and, as a SERM, increases bone density. On this mechanistic basis, tamoxifen, is associated with fewer fractures than use of AIs (11;126;127).

Minimal trauma fractures are common after a breast cancer diagnosis, with non-pathological rib fracture the most commonly reported fracture (30). In a 6 year follow-up study
of 1683 women after a diagnosis of breast cancer, minimal trauma fracture was not associated with radiotherapy, chemotherapy, treatment with an AI, or bilateral oophorectomy (30).

Several additional approaches have been developed to prevent osteoporosis and fractures in AI treated patients or in women after breast cancer with osteoporosis. Algorithms to guide decisions whether to use pharmacologic agents or life style changes have been developed (figure 3) (11;123). Prophylactic or treatment agents include oral and parenteral bisphosphonates and Denosumab (128). Both are effective but associated with serious, but uncommon (rare) toxicity such as osteonecrosis of the jaw (1 in 10,000 and 1 in 100,000 person years (www.asbmr.org) and atypical femoral fractures 3.2 to 50 cases/100,000 person years (www.asbmr.org). The disproportionate concern about these toxicities by the public has led to a 50% reduction in utilization by patients who are candidates for these agents (https://asbmr.org/call-to-action.aspx).

Published reviews have recommended such agents in all breast cancer survivors with osteoporosis and selective use depending on other risk factors in those with osteopenia (11;123). The algorithm in Figure 3 provides a roadmap for selection of which patients to treat with pharmacologic agents during therapy with tamoxifen, AI, or GnRH agonist. Effects of these agents beyond the bone may also be important in breast cancer survivors. Recent studies have shown that intravenous zoledronic acid and denosumab are associated with a decrease in breast cancer recurrence in postmenopausal but not pre-menopausal women (129). For zoledronic acid, this represented a 34% relative risk reduction of disease recurrence and for denosumab 19% ((130;131) Zoledronic acid also was associated with a 19% relative risk of death (123).

**Cardiovascular disease:**
With aging, the incidence of coronary artery disease, myocardial infarction, and acute coronary syndrome increase as does coronary plaque. Incomplete data address the increased rate of CV disease in premenopausal women < age 45 undergoing chemotherapy-induced premature menopause. Both chemotherapy (anthracycline, trastuzumab, and aromatase inhibitors) and radiation therapy (especially to the left breast and axilla) can contribute to development of ischemic coronary heart disease, valvular injury, pericardial injury, and cardiomyopathy (132;133). Statins are effective therapy in those with increased cardiovascular risk factors and represent a reasonable approach in breast cancer survivors (132). Emphasis on cessation of smoking, maintenance of a healthy body weight, nutritious dietary pattern, regular exercise, and aggressive treatment of traditional risk factors such as hypertension and glucose intolerance also represent appropriate approaches (13;33;68).

**Emerging Approaches for unmet needs in breast cancer survivors:**

**SERMS:**
As VVA and the osteopenia/osteoporosis/fracture complex are common in breast cancer survivors, an approach targeting both conditions would be useful. A major goal of pharmaceutical development has been to create SERMs with three separate actions: (a) prevention of breast cancer (b) decrease of bone resorption and prevention of fractures and (c) improvement in the symptoms of VVA. Most SERMS increase VMS but not enough to cause discontinuation. While tamoxifen and raloxifene prevent breast cancer, these two agents have not been shown to exert sufficient vaginal effects to treat VVA. Ospemiphene objectively improves VVA by increasing vaginal maturation indices and reducing the most bothersome symptoms (106;107) and preclinical studies suggest a neutral effect on breast. No clinical data yet exist to demonstrate breast cancer prevention and reduction of bone resorption. With respect to
Lasofoxifene (an unapproved SERM), the PEARL (Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene) studies indicate prevention of breast cancer and fractures, reduction of bone resorption, and improvement of VVA, suggesting that this agent shows promise for breast cancer survivors. As breast cancer survivors experience a 0.5 to 1.0% rate of contralateral breast cancer per year, an agent blocking growth of these lesions when too small to be detected clinically would be useful. Of note, VTE rates were higher with lasofoxifene than other SERMs, but this agent also significantly reduced both stroke and MI. Lasofoxifene will be starting phase 2 trials for treatment of locally advanced and metastatic breast cancer.

**Tissue selective estrogen complex (TSEC) therapy:**

The concept of combining a SERM with an estrogen to create a TSEC has been studied intensively in the past decade, and one TSEC, pairing oral conjugated equine estrogen, 45 mg, with bazedoxifene, 20 mg, has been approved in the USA, Canada and by the European Union (136-143). In a series of studies (142;143) this combination improves hot flashes, reduces bone resorption, and exerts no stimulatory effects on the uterus while highly effective for VMS and VVA (144). In 2 year clinical trials, the effect on breast tenderness and breast density was the same as placebo (145;146) with no increase in breast cancer cases but further testing is needed. Pre-clinical studies demonstrate that this TSEC blocks the growth of three separate breast tumor models (147-149) (MCF-7 xenografts, NMU induced tumors, and estrogen induced ACI tumors in rats). Confirmation of breast anti-tumor effects in women would support the use of this TSEC in breast cancer survivors.

**Miscellaneous agents:**

Recent data suggest that the KNDy neurons (kisspeptin, neurokinin B and dynorphin) in the arcuate nucleus of the hypothalamus—particularly neurokinin B, mediate hot flashes (150). On this basis, two randomized controlled trials have evaluated the effects of oral neurokinin B receptor antagonists on hot flashes (76;151;152). Both agents (MLE 4901 and fezolinetant) reduced hot flash frequency and severity by 40 to 50% over placebo in postmenopausal women with negligible side effects (151;152). As these inhibitors act on specific hot flash mediating pathways, they show promise as effective, non–hormonal agents to treat hot flashes. The pregnancy-associated natural estrogen, estetrol, is undergoing clinical trials in post-menopausal women as a candidate for hormone therapy. A rationale for use of this agent is that estetrol did not stimulate the hormone dependent DMBA tumors in rats and could potentially be safe for use in breast cancer survivors. (153-159).

**Conclusions:**

Lifestyle optimization may improve estrogen deficiency symptoms, improve quality of life, and possibly improve prognosis. Smoking cessation, weight loss (if indicated), limiting or avoiding alcohol, maintaining adequate levels of vitamin D and calcium, eating a healthy diet and regular physical activity are suggested for all women with prior breast cancer. Non-pharmacologic therapies for VMS such as cognitive behavioral therapy, hypnosis, and acupuncture may be helpful as may vaginal lubricants and moisturizers. For women with more severe symptoms or signs of estrogen deficiency, pharmacologic agents are available to relieve VMS and VVA, and to prevent and treat fractures. Therapy must be individualized based on each woman’s needs and goals for therapy. Several emerging approaches such as SERMs, TSECs, estetrol, and neurokinin...
B inhibitors show promise as useful agents to expand options for symptom relief with less breast cancer risk but not yet tested in women with prior breast cancer.

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Figure 1  Hot flash frequency and composite score with non-hormonal prescription therapies for relief of VMS. Upper panel: Effect on frequency of VMS; lower panel: effect on composite score (severity times frequency; best representation of effect); open bars, placebo, colored bars therapies; length of bars, ranges in studies; horizontal bar, means. The horizontal lines without bars represent studies in which the means but not ranges were reported. Figure reproduced from Stuenkel CA et al “Treatment of Symptoms of the Menopause: an Endocrine Society Clinical Practice Guideline.” JCEM 100:3975-4011, 2015 with permission of the Journal and authors.

Figure 2. Percentage changes from baseline of bone formation (upper panel) and bone resorption markers (lower panel) at the end of 24 month treatment with placebo or exemestane and for 3 to 6 months after treatment discontinuation (i.e. 27 and 30 months). FU, follow-up. Reproduced from reference 124 with the permission of the publisher

Figure 3 Algorithm to aid in decision making regarding patients starting aromatase inhibitors and considering use of agents to prevent bone loss. Reproduced from reference 123 with permission of the publisher
Fig 3

Patient with breast cancer initiating or receiving AI therapy

T-score ≥ -2.0
No additional risk factors

Calcium and vitamin D supplements
Monitor risk status and BMD every 1 to 2 years*

Any 2 of the following risk factors:
• T-score < -1.5
• Age > 65 years
• Low BMI (≤ 20 kg/m²)
• Family history of hip fracture
• Personal history of fragility fracture after age 50
• Oral corticosteroid use of ≥ 6 months
• Smoking (current and history of)

T-score < -2.0

Bisphosphonate therapy, plus calcium and vitamin D supplements (zoledronic acid 4 mg/6 months)

Monitor BMD every 2 years