REVIEW ARTICLE

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Therapy for Menopausal Symptoms During and After Treatment for Breast Cancer

Safety Considerations

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Abstract

Breast cancer is the most common newly diagnosed cancer in women. Life-time risk in the US is 1 in 8 (13.2%), in the UK it is 1 in 9 and in Australia it affects 1 in 11 women, of whom approximately 27% will be premenopausal at the time of their diagnosis. Many of these women will experience a sudden menopause as a result of chemotherapy, endocrine therapy or surgical interventions. For these women, the onset of menopausal symptoms is often sudden and severe. The management of such symptoms remains controversial. Women experiencing menopausal symptoms after breast cancer should be encouraged to avoid identifiable triggers for their symptoms and to consider lifestyle modification as a means

of controlling those symptoms. When such measures fail, non-hormonal treatments may also be considered. These include clonidine, gabapentin and some antidepressants. Randomised trials have shown a significant difference in the symptom relief associated with various selective serotonin reuptake inhibitors and selective serotonin and noradrenaline (norepinephrine) reuptake inhibitors compared with placebo. Many women elect to use non-prescription complementary therapies to alleviate their menopausal symptoms. Systematic reviews of phytoestrogens have, however, failed to demonstrate significant relief of menopausal symptoms.

More than 20 clinical trials have been conducted examining the relationship between postmenopausal hormone replacement therapy and breast cancer recurrence. The majority of these have been observational and have shown no increased risk of recurrence. However, the largest randomised trial that has thus far been conducted was recently halted because of a reported increase in the risk of recurrence amongst users of hormone replacement therapy. Tibolone, a selective tissue estrogen activity regulator, is a compound that exerts clinical effects both by receptor-mediated actions and tissue selective enzyme inhibition, and has been shown in preclinical studies to have different effects to estrogen on the breast. Although tibolone may prove safer than estrogen for long-term use in breast cancer survivors, the results of a large randomised trial are awaited to confirm this.

The decision on how best to manage menopausal symptoms must thus be made on an individual basis and after thorough discussion and evaluation of the risks and benefits of each potential intervention.

Breast cancer is the most common newly diagnosed cancer in women. In the US, the annual incidence is 205 000 or 1 per 1326 women. The lifetime risk of breast cancer in the US is 1 in 8 (13.2%),[1] in the UK it is 1 in 9[2] and in Australia it affects 1 in 11 women before the age of 75 years, and it is the most frequent cause of disease and death in middle-aged women. 11 314 new cases of breast cancer were diagnosed in Australia in the year 2000 and breast cancer accounted for 16% of all female cancer deaths in 2002.[3]

In the US 12 600 women aged <40 years are diagnosed with breast cancer each year,[4] and 27% of Australian women with breast cancer are premenopausal at the time of diagnosis.[3]

In premenopausal women, the combination of chemotherapy and endocrine therapy causes premature menopause in >80% of women during the first year after their diagnosis,[5] whilst >90% of those managed with a surgical menopause via bilateral oophorectomy will experience hot flushes, as well as other menopausal symptoms that may be particularly severe and long lasting.[6]

The incidence of hormone therapy (HT) use in western countries such as the US, UK and Australia was, at its peak, 40%. After the release of the Women's Health Initiative (WHI) trial,[7] this declined rapidly.[8] Despite this decline, many women will be receiving HT at the time of breast cancer diagnosis and virtually all of these will immediately stop because of concerns about the effects of the hormone content on the progression of the cancer. Such an immediate cessation will often produce a recurrence of menopausal symptoms.

The menopause and menopausal symptoms are thus closely linked to breast cancer diagnosis and treatment.

The majority of breast cancers are hormone receptor positive and will be treated with anti-estrogen endocrine therapies, most of which will also lead to hot flushes.[9] Up to 20% of breast cancer patients will stop or consider stopping such endocrine therapy because of menopausal symptoms, despite the proven value of such treatment in the prevention of disease recurrence.

It is clear that an induced premature menopause and menopausal symptoms in breast cancer patients will have a significant negative effect on patients' quality of life, body image, sexual function and self esteem;[10,11] hence, it is not surprising that menopausal symptoms are one of the most common and troublesome adverse effects of therapy in breast cancer survivors of all ages.

The management of these symptoms remains a difficult and controversial area of care for these women and their doctors, who need to balance the alleviation of symptoms and quality-of-life issues against the prospect that so-called 'gold standard' treatments such as hormones might increase the risk of recurrence of a life-threatening condition. Manufacturers of HTs consistently list 'hormone sensitive tumours' as an absolute contraindication to their use and many women and their doctors share the belief that to do so will almost inevitably lead to a recurrence of disease.

To test this hypothesis and investigate appropriate treatment modalities we conducted a search of the Cochrane database and MEDLINE from 1960 to June 2005, using the keywords 'hormone therapy', 'hormone replacement therapy', 'estrogen and progestin therapy', 'phytoestrogens' and 'breast cancer'.

1. Menopausal Symptoms

Menopausal symptoms may be divided into several groups: vasomotor symptoms, including hot flushes and night sweats; CNS-related symptoms such as insomnia and changes in memory, concentration and mood; urogenital symptoms including vaginal dryness, dyspareunia urinary tract infections and urinary urgency; and long-term symptoms including osteoporosis.

Of these, it is the vasomotor symptoms, and hot flushes in particular, that are pathognomic of the menopause and that most commonly lead to requests for treatment.[12]

The hot flush is the most characteristic manifestation of the climacteric symptoms and occurs in almost 80% of women,[13,14] of whom approximately 20% will find the symptom intolerable.[14] In most women hot flushes will resolve within 1 year of the menopause but almost one-third will continue to experience symptoms for up to 5 years,[13] and in 10–20% of women, hot flushes will persist for the rest of the woman's life.

Hot flushes are defined subjectively as a sudden feeling of heat in the face, the neck or the chest,[14] and can occur with varying severity or frequency during the day or the night. They may be accompanied by sweating, flushing, palpitations, anxiety or irritability. The average flush lasts for about 4 minutes but may range in duration from a few seconds to up to 10 minutes.

The pathophysiology of flushing is poorly understood, but may be linked to instability of the hypothalamic thermoregulatory centre induced by estrogen withdrawal.[15] There is no clear relationship between low levels of estrogen and hot flushes, but it is hypothesised that estrogen may control thermoregulation via serotonin receptors.[16] Prior exposure to estrogen seems to be an essential prerequisite for the development of hot flushes since they do not occur in women with primary gonadal dysgenesis, which suggests that the flush is related to an incremental decline in estrogen levels in an individual who was previously accustomed to high levels of exposure to that hormone.

Low estrogen levels are also linked to dryness of the skin, hair and vagina, reduced libido, weight gain, fatigue and urinary frequency.[17,18] Sleep disturbances are also linked with the menopause and may occur independently of hot flushes or night sweats.[19] Very little is known about the prevalence of these other menopausal symptoms following breast cancer.

Long-term sequelae of the menopause include a loss of bone density with an increasing risk of osteoporotic fracture.

2. Treatment of Menopausal Symptoms

Estrogen or combined estrogen and progestin therapy have been the cornerstone of the treatment of menopausal symptoms in healthy peri- and postmenopausal women for the past 50 years. Estrogen is generally prescribed with a progestin in order to prevent endometrial hyperplasia in women with intact uteri. Oral estrogen is highly effective, and when used alone or in combination with a progestin, can reduce hot flushes by 70–80%.[20] HT

is also effective in the treatment of urogenital symptoms including vaginal dryness, dyspareunia and urinary tract infections.

HT has long been known to improve bone density,[21] and data from recent randomised trials[22,23] have now demonstrated a reduction in the risk of fractures of both the hip and lumbar spine following the use of estrogen or combined estrogen and progestin therapy in a low-risk population.

Observational studies of symptomatic early menopausal women have also suggested that estrogen or estrogen and progestin therapy may also reduce the risk of cardiovascular disease;[24] however, neither the estrogen nor the estrogen plus progestin arms of the WHI trial showed any protective effect.[22,23] Current opinion thus holds that HT should not be advocated in the treatment of primary or secondary cardiovascular disease.[25]

Despite the benefits of HT with regards to menopausal symptoms and the skeleton, an apparent association between HT use and an increased breast cancer risk observed in recent observational and randomised trials has caused widespread concern amongst the medical profession and women, and has led to an estimated 30–40% reduction in the use of HT worldwide.[7]

3. The Link Between Sex Hormones and Breast Cancer

Ovarian function has a clear relationship to the development of breast cancer, as the risk of this disease increases after puberty and falls by 2.7% per year after the menopause.[26] The Endogenous Hormones in Breast Cancer Collaborative Group reanalysed nine prospective studies and showed a positive correlation between breast cancer risk and elevations in serum estrogen, estrone, estrone sulphate, androstenedione, testosterone and dehydroepiandrosterone levels.[27]

Data from the MORE (Multiple Outcomes for Raloxifene Evaluation) trial[28] has shown that the greatest reduction in estrogen receptor positive breast cancer incidence with raloxifene, a selective estrogen receptor modulator, occurs in women with the highest circulating levels of serum estradiol. A reduction in breast cancer recurrence has been demonstrated with other selective estrogen receptor modulators, including tamoxifen,[29] and with surgical interventions including oophorectomy.[30]

Most *in vivo* studies have shown that maximal proliferation of breast epithelial cells occurs in the luteal phase of the menstrual cycle, an outcome that supports a mitogenic role for progesterone in combination with estrogen.[31]

4. Postmenopausal Hormone Therapy (HT) and Breast Cancer

Until recently, reliable estimation of the risk of breast cancer associated with exposure to HT had been limited because of a lack of randomised controlled trials. Observational studies of differing quality have reported often conflicting results. Bush et al.,[32] in a review of articles on the relationship between HT and breast cancer published between 1975 and 2000, found that 20% of the studies showed a relative risk (RR) for breast cancer amongst patients receiving HT of <0.9, 33% of the studies showed an RR of >1.1 and 47% showed an RR between 0.8 and 1.1. The authors felt that no conclusion could be drawn as to the effects of HT on breast cancer risk.

However, a reanalysis of 51 epidemiological studies based mainly on data from 53 865 postmenopausal women, of whom 17 830 had used HT, revealed that the risk of breast cancer increased with duration of use.[26] Amongst current users (all those whose last use was <5 years prior to diagnosis), the RR of breast cancer was 1.35 (95% CI 1.21, 1.49) for patients with use of ≥5 years' duration compared with no use of HT. The increase in RR per year of use was 2.3%, which is a biologically plausible change given that the authors calculated an increase in RR of 2.8% for every year that a woman's menopause was delayed beyond a mean age of 51 years.[26]

The WHI,[22] a randomised, double-blind, placebo-controlled trial of 16 608 healthy postmenopausal women in North America, reported a RR for breast cancer of 1.26 (95% CI 1.00, 1.59) for patients who had received therapy with conjugated equine estrogen 0.625mg plus medroxyprogesterone 2.5mg daily for a mean duration of 5.2 years compared with those who had received placebo.

In 2002, Beral et al.[33] published an overview of four randomised, placebo-controlled trials of HT that involved >20 000 women who were followed for a mean period of 4.9 years. Overall, there was an excess of 3.2 breast cancers per 1000 women aged 50–59 years and 4 breast cancers per 1000 women aged 60–69 years in patients who received HT compared with those who received placebo, giving an overall hazard ratio of 1.29 (95% CI 1.21, 1.40). This finding was similar to that of the WHI.[22] The risk increased with the duration of HT use, as was seen in the reanalysis of epidemiological studies. Amongst the studies evaluated by Beral et al., only WEST (Women's Estrogen for Stroke Trial),[33] which compared placebo to estrogen alone, failed to show an increased risk of breast cancer.

In April 2004, results from the estrogen-only arm of the WHI trial were published.[23] This trial found no increase in the risk of breast cancer after 6.8 years of use of unopposed estrogen (conjugated equine estrogen 0.625 mg/day) compared with placebo. Amongst 10 739 mostly asymptomatic women with a mean age of 63 years at initiation, the RR for breast cancer diagnosis was 0.77 (95% CI 0.59, 1.01).

A number of other studies have also indicated that combined estrogen and progestin therapy may increase the risk of breast cancer to a significantly greater extent than estrogen alone,[34-38] although the relative effects of continuous and sequential progestins remain unclear.

The WHI trial[39] also reported that the use of combined estrogen and progestin therapy increased the frequency of mammographic abnormalities, including increased mammographic density, and may have led to a delay in the diagnosis of breast cancer.[39] Consistent with this proposition, cancers detected amongst HT users in this trial were slightly larger and more often node positive than those detected amongst the placebo group. This is a finding in contrast to previous data from observational studies, which suggested better prognostic features for cancers detected in HT users.

In late 2003, Beral[40] published the Million Women Study, an observational, questionnaire-based study of 1 084 110 women who had attended routine breast cancer screening throughout the UK. This study found current users of HT were more likely to develop breast cancer than women who were not receiving such treatment and that users of combined estrogen and progestin therapy had the greatest risk compared with both users of estrogen alone or tibolone. The RR reported for patients receiving HT with estrogen alone was 1.30 (95% CI 1.22, 1.38); for patients receiving estrogen and a progestin it was 2.00 (95% CI 1.91, 2.09); and for tibolone recipients it was 1.45 (95% CI 1.25, 1.67).

It is important to note that there were a number of inherent biases in this trial[41] and that the analysis was only preliminary. The magnitude of the effect of HT is greater than that seen in most other randomised or observational studies and it is important that the data from this trial are further verified.

5. HT After Breast Cancer

5.1 Observational Studies

We identified ten observational, uncontrolled and mostly retrospective studies that examined the effects of HT on recurrence rates in breast cancer survivors[42-51] (see table I). Overall, the 728 patients who received either estrogen or combined estrogen and progestin replacement therapy had an overall breast cancer recurrence rate of 7.3%, which was not significantly different to rates seen in patients who were not receiving HT. The stages of disease varied considerably and nodal involvement and receptor status were also variable, thus making comparisons difficult. HT was used by some, but not all, patients

Table I. Observational uncontrolled studies of breast cancer recurrence rates amongst women treated with hormone therapy (HT)

Study (year)	No. of patients on HT	Recurrence (no. [%])
Powles et al.,[42] (1993)	35	2 (5.7)
Wile et al.,[43] (1993)	25	3 (12)
Dhodapkar et al.,[44] (1995)	3	3 (100)
Peters et al.,[45] (1996)	56	0 (0)
Decker et al.,[46] (1996)	61	6 (9.8)
Vassilopoulou-Sellin et al.,[47] (1997)	49	1 (2)
Guidozzi,[48] (1999)	24	0 (0)
Espie et al.,[49] (1999)	120	5 (4.2)
Brewster et al.,[50] (1999)	145	13 (8.9)
Bluming et al.,[51] (2001)	210	20 (9.5)
Total	**728**	**53 (7.3)**

Table II. Retrospective case-control studies of breast cancer recurrence rates amongst women treated with hormone therapy (HT)

Study (year)	Patients on HT		Controls	
	no.	recurrence (no. [%])	no.	recurrence (no. [%])
DiSaia et al.,[52] (1996)	41	6 (14.6)	82	6 (7.3)
Ursic-Vrscaj and Bebar,[53] (1999)	21	4 (19)	42	5 (12)
O'Meara et al.,[54] (2001)	174	16 (9.2)	695	101 (14.5)
Beckmann et al.,[55] (2001)	64	6 (9.3)	121	17 (14)
Durna et al.,[57]a (2002)	286	44 (15.4)	836	247 (29.5)
Dew et al.,[58] (2003)	69	6 (8.7)	1403	330 (22.4)
Total	**655**	**82 (12.5)**	**3179**	**706 (22.2)**

a Data from Eden et al.[56] from the same cohort is not included in this table.

prior to diagnosis. Types of estrogens, their doses, routes of administration and regimens varied between patients and trials, as did modalities of treatment, so that for some women surgery was the only therapy whilst others required additional radiation or chemotherapy.

5.2 Case-Controlled Studies

Seven case-controlled studies were found and are shown in table II.

DiSaia et al.[52] incorporated initial observational data from 1993 into a controlled study by matching 41 of the 77 initially reported participants with 82 women who did not receive HT. Six recurrences occurred in each group, giving recurrence rates of 14.6% in HT users and 7.3% in non-users. These rates were not significantly different.

Ursic-Vrscaj and Bebar[53] reported four and five recurrences amongst 21 women receiving HT and 42 controls, respectively (19 and 12%), and also found that the RR was not affected by the duration of HT.

O'Meara et al.[54] performed a retrospective analysis of 2755 women aged 35–74 years who had a diagnosis of invasive breast cancer. 174 subjects were included in the treatment arm and 695 in the final analysis of the control arm. Each user was matched with four subjects from the control group for age, stage of disease and year of diagnosis. Recurrence rates were 9.2% amongst users and 14.5% amongst the control group. Five users (3%) and 59 non-users (8%) died of the disease, with retrospective mortality rates of 5 and 15 per thousand person years, respectively. Limiting the analysis to estrogen-only therapy made no difference to the outcomes.

Beckmann et al.[55] conducted a retrospective study of 185 women who were diagnosed with breast cancer and followed for 5 years. HT assignment was based on the patients' wishes, rather than randomisation. Sixty-four treated and 121 non-treated women were compared, with six recurrences observed in the treatment group (9.3%) and 17 in the control group (14%).

In a nested case-control study where HT assignment was again based on patient request[56], Eden et al. examined the effects of various HT regimens on the risk of breast cancer occurrence. Interestingly, in this study users of progestin-only therapy, or combined estrogen and progestin therapy received significantly higher doses of progestin than those usually prescribed in HT regimens. 286 women using HT were compared with 836 control women. Overall recurrence rates were 15.4% for the treatment arm and 29.5% for the controls. This study stratified outcomes by different regimens. Numbers in the individual groups were relatively small and recurrence ranges were wide: from 23.5% for estrogen-only users, to 16.7% for combined estrogen and progestin users, 15.4% for progestin-only users and 12.5% for vaginal estrogen users.[57]

Dew et al.[58] published data from the same study, examining the effects of topical estrogens given for vaginal symptoms on the rates of breast cancer recurrence. Sixty-nine women receiving vaginal estrogen therapy were assessed in comparison with the rest of the cohort, some of whom were using various HT regimens (23.2%) Recurrence rates were 8.7% amongst the vaginal estrogen users and 22.4% amongst controls, a difference which was not statistically significant.

5.3 Prospective Case-Controlled Studies

Three such studies were identified (see table III). Vassilopoulou-Sellin et al.[59] enrolled 319 patients with breast cancer. All enrollees had stage 1 or stage 2 disease and were postmenopausal. Thirty-nine women received estrogen therapy without progestin and there were 280 controls not receiving HT. Tumour size, lymph node positivity, estrogen receptor status and menopausal status were comparable. Over 55 months, disease recurred in one patient receiving estrogen therapy (2.6%) and 14 controls (5%). This difference was not statistically significant.

Marsden et al.[60] recruited 100 women who were all at least 1 year postmenopausal and who had stage 1 or 2 breast cancer. After dropouts and randomisation, 42 women remained in the treatment arm and 41 in the control arm for a follow-up of 6 months. Recurrence rates were 4.8% and 2.4%, respectively. The short duration of therapy of this trial makes it difficult to draw any long-term conclusions.

Marttunen et al.[61] conducted a prospective non-randomised trial that offered HT to patients with breast cancer who were experiencing severe menopausal symptoms or who were at risk of cardiovascular disease or osteoporosis. 131 women were recruited, of whom 88 fulfilled the inclusion criteria and completed therapy, having been monitored for an average duration of two and a half years. Forty-three asymptomatic women served as controls. Amongst the treatment group there were five ipsilateral recurrences (5.7%) and two contralateral new breast cancers (2.3%), whilst in the controls there were four ipsilateral recurrences (9.3%) and one contralateral new cancer (2.6%).

5.4 Randomised Controlled Trials

In the 1990s, two randomised clinical trials started in Scandinavia: the Stockholm trial[62] and the HABITS (Hormone replacement therapy After Breast cancer – Is iT Safe?)[8] trial. In the HABITS trial, 434 women had been randomised by September 2003, and 345 had received least one follow-up report. In the treatment arm, 21% of women received estrogen-only therapy, 46% received combined estrogen and progestin therapy and 26% received sequential HT. Eighteen percent of women randomised to the non-HT arm were exposed to HT.

After a median follow-up of 2.1 years, 26 (14.9%) women in the HT group and seven (4.09%) in the placebo group had experienced either a recurrence or new breast cancer (RR 3.3, 95% CI 1.5, 7.4).[8] All women with an event in the HT group, and two of those in the non-HT group, were exposed to HT and most women experienced their recurrence or new cancer whilst receiving treatment. The data and safety monitoring committee decided that these findings represented an unacceptable risk of the recurrence of breast cancer for women exposed to HT and the trial was terminated on 17 December 2003.

In contrast, a preliminary analysis of the Stockholm trial failed to show such an effect, with a RR for HT users of 0.82 (95% CI 0.35, 1.89). This trial was ceased because of anticipated difficulties with recruitment and compliance.[62]

The number of breast cancer events in the HABITS trial was too small for a definitive conclusion to be drawn. The original trial design was to recruit 1300 women, thus giving the power to detect a difference from an expected 20% recurrence rate after 5 years in the control group. The results published so far, therefore, are deficient in both the number of patients and duration of treatment use. Nevertheless a sub-group analysis with very small numbers suggested the risk was confined to women with estrogen receptor positive tumours (RR 4.8, 95% CI 1.1, 21.4) who were not receiving tamoxifen (RR 3.7, 95% CI 1.5, 9.0).[8] This finding was sup-

Table III. Prospective case-control studies of breast cancer recurrence rates amongst women treated with hormone therapy (HT)

Study (year)	Patients on HT		Controls	
	no.	recurrence (no. [%])	no.	recurrence (no. [%])
Vassilopoulou-Sellin et al.,[59] (1999)	39	1 (2.6)	280	14 (5)
Marsden et al.,[60] (2000)	42	2 (4.8)	41	1 (2.4)
Marttunen et al.,[61] (2001)	88	7 (8)	43	5 (11.6)
Total	**169**	**10 (6)**	**364**	**22 (6)**

ported by the Italian Tamoxifen Chemo Prevention trial, in which the breast cancer risk in women exposed to HT was reduced by the concurrent use of tamoxifen.[63] The reason for the disparity in findings in the two Scandinavian trials is unknown and could be due to chance. The Stockholm investigators have, however, postulated that the difference between the two trial results may be due to the greater use of tamoxifen in the Stockholm trial (52% vs 21%) and perhaps because 73% of women in the Stockholm trial used either estrogen-only therapy or long-cycle estrogen and progestin therapy with 3-monthly progestins, whereas in the HABITS study most women used continuous combined estrogen and progestin therapy.[62] Many uncertainties remain, and the HABITS trial, in particular, has demonstrated results at odds with the majority of the observational trials performed. Although cessation of the HABITS and Stockholm trials cannot be taken as definitive evidence of the impact of various HT regimens on breast cancer recurrence, it seems probable that no further randomised controlled trials will be conducted.

6. Other Hormonal Treatments for Menopausal Symptoms

6.1 Progestins

Progesterone has long been recognised as a mitogen for normal breast epithelial tissue. When given alone it binds to progesterone receptors, initiating epithelial cell proliferation and terminal differentiation.[64,65] In the presence of estrogen, however, this response is altered and results in the inhibition of growth and decreased mitosis.[65] In the past, high doses of progestins have been used to treat breast cancer.

Low doses of progestins have been shown to be moderately effective in the alleviation of menopausal symptoms.[66] In an unblinded study, megestrol at dosages of 20–80 mg/day reduced vasomotor symptoms by between 80 and 98%.[67] A prospective randomised trial conducted by Loprinzi et al.[68] enrolled 100 women of whom 97 had a history of breast cancer. This study found an 85% reduction in hot flushes with megestrol 20mg administered twice daily, compared with a 21% reduction in hot flushes with placebo. Importantly, most of the women in this trial were taking tamoxifen. Medroxyprogesterone has also been shown to lessen the frequency of hot flushes.[69-71]

Loprinzi et al.[66] suggested that progestins should be used to relieve vasomotor symptoms in breast cancer survivors. However, the effects of low-dose progestin therapy on normal and malignant breast cells remain uncertain and low-dose megestrol may cause an increase in breast epithelial cell proliferation *in vitro*.[72]

Durna et al.,[73] in an observational case-control study, found that amongst users of progestin-only therapy with a diagnosis of breast cancer, the adjusted RR for recurrence or new cancer was 0.59 (95% CI 0.32, 1.09). The dosage of progestin may be important. Durna et al. used moderate dosages of progestin (on average norethisterone [norethindrone] 5mg or medroxyprogesterone 50 mg/day) and past therapeutic use of progestins as treatment for breast cancer also used high doses that were more likely to arrest the cell cycle.

The WHI trial[22] also suggested that the addition of a low dose of progestin to conjugated equine estrogens will, if anything, increase the risk of breast cancer with long-term exposure to this combination HT.

In contrast to the endometrium, mitotic activity in breast epithelial cells peaks during days 23–25 of the menstrual cycle, shortly after the progesterone peak, suggesting that progesterone, or possibly estrogen and progesterone combined, are responsible for this change.[74,75] Progestins have been implicated in the development of breast cancer in experimental animals[76] and *in vitro*.[77]

Interactions between progestogenic agents and tamoxifen have not been studied in breast cancer survivors.

The safety of progestins in patients who have had breast cancer thus remains uncertain and large randomised trials are required.

6.2 Tibolone

Tibolone is a laboratory derived steroid gonadomimetic with weak estrogenic, androgenic and progestogenic properties. The biological activity of tibolone is derived not only from the parent mole-

cule but also from its 3-α and 3-β hydroxy metabolites and the Δ-4 isomer. Randomised trials have shown that tibolone alleviates menopausal symptoms in a manner similar to HT.[78] Tibolone also increases bone density at both the lumbar spine and the neck of the femur, although fracture prevention data from randomised trials are still awaited. Both these effects are mediated via the estrogen receptor.

In vitro studies of the effects of tibolone on breast tissue have shown that it lowers estrogen levels in normal human breast epithelial cells and also in some cancer cell lines. These effects are thought to be mediated by inhibition of a breast-specific sulphatase enzyme, thus limiting conversion of estrone sulphate to estrone, and also by limiting the conversion of estrone to estradiol by the enzyme 17-β hydroxysteroid dehydrogenase type 1.[79]

In vivo, tibolone has been shown to reduce the growth of dimethylbenzanthracene-induced estrogen receptor-positive (ER+) tumours in rodents.[80]

In women, tibolone does not increase breast density to the same extent as HT and it has also been shown to reduce levels of markers of breast cell proliferation[81] and to increase apoptosis.[82]

Preclinical studies thus suggest that tibolone might have little effect on the breast. Clinical trial data on the effect of tibolone on breast cancer risk is somewhat less consistent. A large observational study, the Million Women Study,[40] reported an increased risk of breast cancer amongst women using tibolone in the UK (RR 1.45, 95% CI 1.25, 1.67) The methodology of this study has been criticised[41] and the reported risks for breast cancer amongst users of estrogen and estrogen plus progestin therapy in this study were greater than those seen in recent randomised trials. Selective prescribing of tibolone may also have led to this finding, which is somewhat unexpected in view of the preclinical data.[83] A second study, published in abstract form only,[84] used data on >7000 cases of breast cancer matched with controls from the General Practice Research Database (GPRD) and showed no increase in the risk of breast cancer associated with use of tibolone or estrogen alone, and a smaller increase with estrogen and progestin therapy than was seen in the Million Women Study; these results were more in line with the randomised trial data.

The Danish Nurses Health Study[85] also reported an increase in breast cancer risk for users of all forms of HT, including tibolone. RRs were 1.96 (95% CI 1.16, 3.35) for estrogen only, 2.70 (95% CI 1.96, 3.73) for combined estrogen and progestin and 4.27 (95% CI 1.74, 10.51) for tibolone.

A double-blind, placebo-controlled study has recently been conducted to assess the effects of tibolone on the frequency of hot flushes in 70 postmenopausal women receiving endocrine therapy (tamoxifen) after breast cancer.[86] After 12 months, hot flush occurrence had reduced by 34% from baseline amongst users of tibolone and had risen by 52% from baseline in the placebo arm. No endometrial abnormalities were reported and no new cases of breast cancer were detected.

Currently, a large randomised trial of tibolone, LIBERATE (Livial Intervention following Breast cancer; Efficacy, Recurrence and Tolerability Endpoints), is ongoing in symptomatic postmenopausal women with a diagnosis of stage 1 or 2 breast cancer.[87]

Meanwhile, it is reasonable to assume that the effects of tibolone on primary breast cancer are unknown and may be equal to that of conventional HT. Similarly, the safety of tibolone following breast cancer cannot be assumed.

7. Non-Hormonal Treatments for Menopausal Symptoms

7.1 Clonidine

Clonidine is an α-adrenoceptor agonist that acts centrally to reduce vasoconstriction. It is primarily indicated for the treatment of hypertension. Pandya et al.[88] performed a randomised double-blind trial in 194 women receiving tamoxifen therapy after breast cancer diagnosis. Patients received either clonidine 100 μg/day or placebo for 8 weeks. There was a 37% reduction in hot flushes in the treatment arm compared with a reduction of 20% in the placebo arm. Several other short-term trials[89-91] have also reported a modest benefit with clonidine in other groups of symptomatic postmenopausal women.

Although statistically significant, the clinical benefit is modest and is achieved at the expense of

an increase in constipation, dryness of mouth and drowsiness.[92] Long-term data on the efficacy and adverse effect profiles of clonidine are lacking.

7.2 Gabapentin

Gabapentin is a γ-aminobutyric acid analogue approved in 1994 for the treatment of seizures. Recent studies have shown that this agent has efficacy in the treatment of neuropathic pain, migraine, essential tremor and panic disorder.[93]

Guttuso,[94] in an open-label trial, reported a reduction in hot flushes amongst four postmenopausal women, one woman receiving tamoxifen and one man with leuprolide-induced hot flushes.

A subsequent randomised, double-blind trial[93] investigated the efficacy of gabapentin 900 mg/day for the reduction of hot flush frequency in 59 postmenopausal women who were experiencing at least seven flushes per day at recruitment. Hot flush frequency was reduced by 45% in the treatment group compared with 29% in the placebo group ($p = 0.02$), while the severity of hot flushes was reduced by 54% compared with 31% ($p = 0.01$). Thirteen percent of patients in the treatment arm withdrew because of treatment-related adverse effects, whilst 50% reported at least one adverse event. The most commonly reported adverse events included somnolence and dizziness.

The exact mode of action of gabapentin is not clear but probably involves modulation of calcium currents and perhaps mitigation of hypothalamic tachykinin activity.

Further large randomised trials are warranted to verify the effects of gabapentin on vasomotor symptoms in postmenopausal women with and without a history of breast cancer.

7.3 Selective Serotonin Reuptake Inhibitors and Serotonin/Noradrenaline (Norepinephrine) Reuptake Inhibitors

An observational study of paroxetine (a selective serotonin reuptake inhibitor [SSRI])[95] reported a mean reduction in hot flushes of 67%; however, 16% of the patients withdrew because of adverse effects. Loprinzi et al.,[96] in a trial of venlafaxine (a serotonin/noradrenaline reuptake inhibitor [SNRI]), reported a 58% reduction in hot flushes, again with significant adverse effects. A subsequent randomised trial of venlafaxine[97] reported a 60% reduction in hot flushes compared with 20% in the placebo group, whilst fluoxetine reduced flushes by 50% compared with 36% for placebo.[98] Paroxetine showed a similar effect in a randomised trial conducted in 2003,[99] but sertraline was no more effective than placebo.[100]

Some of the newer antidepressants increase prolactin levels, which may explain the prevalence of mastalgia and breast enlargement (reported to be as high as 39% in one trial[101]) associated with these agents. This may be of particular concern to those with a history of breast cancer. Another common, significant adverse effect of anti-depressant therapy is sexual dysfunction.[102] As sexual dysfunction is a common sequelae of breast cancer diagnosis and treatment, this is likely to be a major issue when choosing a treatment for vasomotor symptoms.

The relationship between SSRIs/SNRIs and breast cancer has been controversial, but a recent systematic review concluded that there was no evidence that these preparations increase the incidence of breast cancer.[103] The effects of SSRIs/SNRIs on endocrine therapies for breast cancer are unknown. Tamoxifen is converted to 4-hydroxy-tamoxifen and other active metabolites by cytochrome P450 (CYP) enzymes. SSRIs can inhibit CYP enzymes: paroxetine interferes with tamoxifen metabolism in patients with the wildtype CYP2D6 genotype, which is similar to the metabolism observed in those with the CYP2D6 homozygous variant genotype.[104] The clinical implications of this for the actions of tamoxifen are unknown.

7.4 Phytoestrogens

Phytoestrogens are a broad group of plant-derived compounds of a non-steroidal structure that may mimic the effects of estrogens in some individuals.[105] There are two major classes of phytoestrogens: the lignans and the isoflavones. Isoflavones, the most common form of phytoestrogens, are found in all plants but predominantly in legumes and have a diphenolic structure that resembles diethylstilbestrol.

Once ingested, phytoestrogens are converted by intestinal bacteria to hormone-like compounds that

have weak estrogenic activity.[105] However, absorption of phytoestrogens is subject to individual variation and is also affected by factors such as the use of antibacterials. The weak estrogenic effects seen with phytoestrogens appear to be mediated by preferential binding to the β estrogen receptor.[106] The main metabolites of the lignans are enterolactone and enterodiol, whilst the main metabolites of the isoflavones are genistein and daidzein. In the blood and urine of humans, the major detectable phytoestrogens are daidzein, genistein, equol and *O*-desmethylangolensin (*O*-DMA).[107] Importantly, there is considerable individual variation in the metabolism of these compounds, which may explain the inconsistency seen in the results of clinical trials.

Epidemiological studies comparing Asian and Western populations have suggested that phytoestrogens may decrease symptoms of menopause and play a role in breast cancer protection.[108]

In general, clinical trials examining the effects of phytoestrogens on menopausal symptoms in Western women have proven to be inconclusive. Case-control studies measuring overall hot flushes and soy consumption report no dramatic benefit of these agents compared with placebo, although Albertazzi et al.,[109] in a randomised double-blind trial of soy supplementation, did demonstrate a significant reduction in hot flushes for patients receiving this treatment compared with those receiving placebo. Similar results have been reported for isoflavone supplements. van de Weijer et al.,[110] in a double-blind, crossover study of a red clover extract, showed a reduction in hot flushes for red clover compared with placebo recipients. However, a large randomised trial of several doses of red clover isoflavones in menopausal American women failed to show any reduction in symptoms when compared with placebo[111]

A recent systematic review of the use of phytoestrogens for menopausal symptoms found no statistically significant improvement in symptoms in patients receiving these agents compared with those receiving placebo.[112]

The safety of phytoestrogen supplements after breast cancer is uncertain. A study of phytoestrogen excretion in Australian women immediately after breast cancer diagnosis reported lower levels of phytoestrogens amongst breast cancer patients than controls[113] and a double-blind comparison of red clover isoflavones versus placebo amongst women attending breast screening in the UK[114] found no increase in mammographic density, no changes in follicle-stimulating hormone, luteinising hormone or estradiol levels and no change in menopausal symptoms between the active treatment and placebo arms, which suggests a lack of estrogenic or anti-estrogenic effect for the phytoestrogens at the dosage given.

In contrast, studies on breast cancer cell lines *in vitro* show that low concentrations of isoflavones, such as those seen in supplements, cause increased nuclear activity in ER+ cell lines and effected no change in ER− cell lines.[115] Higher doses of genistein have also been reported to antagonise the anti-estrogenic effects of tamoxifen.

There have been no clinical trials investigating the effects of phytoestrogen supplementation on menopausal symptoms in breast cancer survivors. Given the current data, prudent advice would be for women with ER+ tumours to not increase their phytoestrogen intake, given the uncertainty regarding both the efficacy and safety of these compounds.

7.5 Black Cohosh

Black cohosh is a plant native to North America originally used by Native Americans as a remedy for menstrual cramps and menopausal symptoms. Extracts of the root, *Cimicifuga racemosa*, have been used in Europe for more than 50 years. Recently, the German Commission E approved the therapeutic use of black cohosh as a non-prescription treatment for premenstrual discomfort, dysmenorrhoea and climacteric ailments.

A number of clinical trials have been carried out using supplements of black cohosh. Results have been mixed, with either no change or a mild reduction in menopausal symptoms being the usual finding. Huntley and Ernst[116] concluded that despite promise, there was no convincing data to show a benefit of black cohosh on hot flushes that was greater than that with placebo. In a trial of 85 women,[117] most of whom were taking tamoxifen, there was no reduction in menopausal symptoms for women taking one tablet of black cohosh twice daily; however, another trial using double this dos-

age reported a significant reduction in the number and severity of flushes amongst women taking a proprietary preparation of black cohosh together with tamoxifen compared with those taking tamoxifen alone.[118] Osmers et al.,[119] in a randomised controlled trial of 304 postmenopausal women using the same dose, also reported a significant reduction in symptoms compared with placebo, with no adverse effects. Dose, and perhaps gut processing, may thus be important. Black cohosh is not regarded as a phytoestrogen and trials have shown that it does not stimulate the breast. Adverse effects including gastrointestinal disturbances and rash may occasionally occur. A single case report exists that describes a patient who developed acute hepatitis and subsequently required a liver transplant after 1 week of therapy with a preparation containing black cohosh. The histopathological changes were typical of an idiosyncratic autoimmune reaction and it is not known whether this was due to the black cohosh or some other component or contaminant in the preparation.

8. Lifestyle Measures and Non-Pharmacological Approaches

Attempts to alleviate menopausal symptoms should first focus on lifestyle measures.

Regular exercise may reduce hot flushes and improve quality of life, though studies addressing this have reached conflicting conclusions.[120,121]

There are very limited clinical data on non-pharmacological treatments such as behavioural interventions, exercise and acupuncture in the management of menopausal hot flushes, but these appear to show some preliminary positive findings. One small study has indicated that paced respiration may improve symptoms.[122]

One small randomised controlled trial has explored the role of acupuncture in reducing menopausal hot flushes, but the study was not adequately powered to demonstrate statistical significance.[123]

Meanwhile, it is reasonable to advise symptomatic women to try and achieve a normal body mass index, to stop smoking and to maintain a regular exercise regimen since these behavioural changes will all benefit long-term health. For those who can identify 'triggers' to their hot flushes (such as alcohol, hot drinks or spicy food) it is clearly a good idea to avoid such triggers. Anecdotally, the majority of women do not report clear triggers for their hot flushes.

9. Conclusion

Menopausal symptoms are a significant source of distress to women passing through the menopausal transition. For women in whom this transition is premature or in whom it has been preceded by the diagnosis and treatment of a life threatening and emotive illness, such as breast cancer, symptoms often seem worse and also serve as a reminder of what has passed before.

We have reviewed a number of pharmacotherapeutic interventions that may be considered when lifestyle measures prove to be ineffective.

Non-hormonal interventions such as clonidine and gabapentin have, at best, shown a mild alleviation of symptoms with significant unwanted effects. The SSRI and SNRI groups of antidepressants have similarly shown some promise; however, further research is required to determine which of this evolving group of compounds might offer the greatest relief with the most attractive adverse effect profile.

Of the herbal therapies reviewed, with the exception of black cohosh, trial evidence of efficacy is inconsistent. This may be due to the prevalence of small, short-duration trials, variable individual absorption or a lack of effect in the light of severe symptoms. Although no trials have reported an increase in recurrence rates amongst users of herbal remedies there is conflicting *in vitro* data that is sufficient to raise concerns about the long-term safety of some of these preparations amongst women with a personal history of breast cancer.

The use of estrogen and progestin therapy in postmenopausal women has been shown to increase the risk of breast cancer with long-term use. Estrogen therapy alone does not increase risk, at least for 6–7 years. These sex steroids stimulate the breast, increase breast density and may cause breast tenderness.

However, HT still remains the most effective treatment for menopausal symptoms.

More than 20 clinical trials have been conducted to assess the efficacy and safety of HT after breast cancer. HT has been found to be effective in alleviating menopausal symptoms and 19 of these trials have found no increase in breast cancer risk for HT users compared with controls, although fault may be found with the trial designs and durations of follow-up. One randomised trial has recently been stopped because of an increase in breast cancer recurrence amongst the users of HT.[8] Currently, only a letter to *The Lancet* describes the results of this trial and it seems prudent to await further in-depth examination of the data before any conclusions regarding the real effects of HT on risk of recurrence of breast cancer are made.

Of the hormonal interventions, tibolone may offer the greatest hope of a safe effective intervention, but its safety is not yet established. The mode of action of tibolone, the results of preclinical studies and the effects of tibolone on ER+ tumour growth in rodent models all provide encouragement. That tibolone is associated with few unwanted breast effects in recipients, that it does not increase mammographic density to the same degree as HT and that it has been shown to be effective and safe in a short pilot study amongst breast cancer survivors with menopausal symptoms add further reassurance. However, tibolone has been associated with an increase in breast cancer detection in two observational studies of healthy postmenopausal women[40,85] and a final verdict on safety cannot be passed until the results of the ongoing LIBERATE randomised controlled trial investigating the effects of tibolone on menopausal symptoms and breast cancer recurrence are available.

For the moment then, the decision on how best to manage menopausal symptoms remains a difficult one for both patient and clinician that must be made jointly, on an individual basis and after thorough discussion and evaluation of the risks and benefits of each potential intervention.

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Note in Proof

A recently published trial has looked at the efficacy of gabapentin in treating hot flashes in 420 women with breast cancer.[124] In the trial, women were randomised to placebo or gabapentin 300 mg/day or 900 mg/day in three divided doses. Hot flush frequency and severity were reduced in both treatment groups, but there was only a significant reduction between the 900 mg/day and placebo groups.

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