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Postmenopausal hormone therapy before and after breast cancer: clinical experiences

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Abstract

Conventional oestrogen-based hormone therapy (HT) increases the incidence of breast pain and tenderness, mammographic density and the risk of breast cancer. Combined oestrogen plus progestogen therapy (EPT) increases the risk of breast cancer to a greater degree than oestrogen alone (ET). Attention must therefore be focused on identifying women at risk of breast cancer or on producing a HT that has fewer breast side effects. Randomised controlled trials have shown that while EPT induces breast tenderness or pain in up to 50% of women and increases mammographic density in up to 70% during the first year of treatment, only about as many as one-tenth women report breast tenderness or pain with tibolone and increases in mammographic density are rare, occurring with a similar incidence as seen in untreated controls. Many women with breast cancer suffer vasomotor symptoms rather than risk recurrence with conventional HT. However, in a small randomised controlled trial in women with early breast cancer undergoing adjuvant tamoxifen treatment, tibolone reduced hot flushes, night sweats and improved quality of life compared with placebo.

Keywords: Oestrogen; Cancer; Hormone therapy

1. Introduction

Conventional oestrogen-based hormone therapy increases the incidence of breast pain and tenderness, with up to 50% of women reporting such side effects during the first year of treatment. Mammographic density is also increased in up to 70% of women during the same period, an effect that reduces the sensitivity of mammographic screening for breast cancer [1,2]. In a study of interval cancer during the first year after screening, the relative risk (95% confidence interval) amongst women aged 50–64 years old was 1.00 in those who were not receiving HT compared with 2.27 (1.3–3.9) amongst those who were being treated with oestrogen-based HT [3]. With more prolonged HT use or exposure, there is an additional increased risk of breast cell proliferation and breast cancer. Essentially, therefore, oestrogen-based HT increases

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breast tenderness or pain, increases breast density and increases breast cancer risk. The increased mammographic density is a particular problem since it decreases the sensitivity and specificity of mammography [1-3] to detect breast cancer, and a drug that induces breast cancer thus also prevents its detection [1,3].

2. Tibolone and the breast

Tibolone, the first of a class of compounds known as the selective tissue estrogenic activity regulators (STEARs), improves climacteric symptoms and prevents osteoporosis in postmenopausal women. Following oral administration, it is rapidly converted by specific enzymes to three active metabolites: 3α-hydroxy tibolone, 3β-hydroxy tibolone and the Δ^4-isomer of tibolone. These enzymes, together with tibolone, have tissue-selective effects that are the result of several different mechanisms including local metabolism, enzyme regulation and steroid receptor binding and activation [4,5].

Direct activation of the oestrogen receptor by tibolone and its metabolites accounts for the beneficial effects on bone, as well as on climacteric symptoms via the vagina and brain. In contrast, oestrogenic activity is not expressed in the endometrium or breast. In the breast, tibolone and its metabolites inhibit the enzymes sulphatase and 17β-hydroxysteroid dehydrogenase type I and stimulate sulphotransferase and 17β-hydroxysteroid dehydrogenase type II, which prevents their conversion to active oestrogenic compounds. Oestrogenic stimulation does not occur in the endometrium due to the action of the local conversion of tibolone into its highly stable progestogenic Δ^4-isomer of tibolone [6].

Animal models, including rodents and Cynomolgus monkeys, have confirmed that tibolone does not stimulate breast tissue [7–9]. In a nude mouse model, xenografts of normal human breast tissue were implanted at day 0 and the animals were then treated with tibolone (0.1, 0.5 or 2.0 mg/kg) or oestradiol (2 mg/kg via gavage or implant) from days 14 to 28 [10]. The percentage of Ki67/LI-positive cells in the breast tissue did not increase significantly from baseline in animals treated with any dose of tibolone or with oestradiol via gavage. However, animals given an oestradiol implant had a significantly ($P < 0.05$) higher percentage of Ki67/LI-positive cells than those given tibolone after both 7 and 14 days of treatment. The expression of ps2 in breast tissue was also significantly greater with oestradiol than with tibolone. The expression of progesterone and ps2 in breast tissue was significantly greater with oestradiol, given by implant or orally, than with tibolone. In another rodent model, the 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary rat tumour, tibolone exerted a strong inhibitory effect on oestrogen-sensitive tumour development and growth, being at least as effective as tamoxifen [9].

2.1. Clinical experience

Clinical studies have indicated that tibolone has minimal effects on mammographic density (see von Schoultz, this issue) and breast pain, with the incidence of breast tenderness and discontinuation rates for breast-related problems being significantly lower than seen with continuous EPT regimens.

In a 48-week, double-blind study conducted in 423 postmenopausal women, the incidence of breast tenderness was significantly lower with tibolone than with continuous combined 17β-oestradiol plus norethisterone acetate (20% versus 54%; $P < 0.0001$) [11]. None of the women treated with tibolone withdrew due to breast tenderness compared with approximately 2% in the EPT group. In another double-blind comparison with the same EPT regimen, breast tenderness was again reported significantly less often with tibolone (2% versus 33%; $P < 0.001$) in 166 women treated for 6 months [12]. The breast tenderness that did occur was sufficiently severe to cause three of the women receiving EPT to discontinue treatment. Two other studies have confirmed that the incidence of breast tenderness/complaints is approximately 10-times higher with continuous combined 17β-oestradiol plus norethisterone acetate than with tibolone [13,14]. With regard to other continuous combined regimens, a 1-year, double-blind study involving 501 women reported breast tenderness in 2.4% of women given tibolone compared with 17.1% given CEE plus MPA ($P < 0.0001$) [15].

Tibolone has proved to be a useful alternative to conventional HT in women with breast symptoms or a history of benign breast disease. In an 8-year evaluation involving 301 women, a significant proportion

Table 1
Overall analysis of all clinical studies with tibolone vs. continuous combined HT: incidence of most common adverse events

	Tibolone (%, n = 543)	Continuous combined HT (%, n = 545)
Breast tenderness	2.4	24.2*
Vaginal bleeding	5.7	12.8*
Leukorrhoea	5.2	5.7
Weight increase	7.2	6.8
Abdominal pain	1.3	2.0
Hypertrichosis	0.4	0.0

* $P < 0.001$ vs. tibolone.

Table 2
Relative risk of breast cancer by duration of HT use amongst current users or those whose last use was less than 5 years before diagnosis [18]

	Cases/controls	Relative risk
Never users	12467/23568	1.00
HT users		
<1 year	368/860	0.99
1–4 years	891/2037	1.08
5–9 years	588/1279	1.31
10–14 years	04/633	1.24
≥15 years	294/514	1.56

of whom were switched to tibolone due to a history of benign breast disease, breast symptoms were seldom reported (7.5%) and did not occur in any of the women with benign breast disease [16]. Similarly, in a placebo-controlled trial conducted in 64 women who had reported breast symptoms with a range of HT regimens, switching to tibolone or placebo resulted in a significant reduction in a visual analogue scale measuring breast tenderness and mastalgia [17]. There were no significant differences between the placebo and tibolone groups and only one woman reported no improvement in breast symptoms after switching to tibolone.

In an overall analysis of all clinical studies with tibolone versus continuous combined EPT, breast tenderness, as well as vaginal bleeding, was significantly ($P < 0.001$) less common with tibolone (Table 1). Breast tenderness was reported in approximately 10-times more women given oestrogen-based HT than those given tibolone.

2.2. Breast cancer incidence and HT

A reanalysis of 51 epidemiological studies, based mainly on data from 53,865 postmenopausal women of whom 17,830 had used HT at some time, revealed that the risk of breast cancer increased with the increasing duration of HT use [18]. Amongst current users or those whose last use was less than 5 years before diagnosis, the relative risk of breast cancer was 1.35 (1.21–1.49) amongst those who had used HT for 5 years or longer (Table 2). This finding is supported by recent large, randomised, controlled trials, such as the Womens' Health Initiative (WHI) [19], which reported a relative risk for breast cancer of 1.26 (95% confidence interval 1.00–1.59) after a mean follow-up of 5.2 years amongst women receiving continuous combined conjugated equine oestrogens (CEE) plus medroxyprogesterone acetate (MPA) compared with placebo. Although this EPT arm was stopped prematurely, partly because of increased breast cancer risk, the ET arm, when recently stopped, showed no increased breast cancer risk [20]. A further report from the WHI trial indicated that EPT increased the frequency of mammographic abnormalities and led to a delay in the diagnosis of breast cancer. Cancers developing on EPT were larger, more often node positive and had worse prognostic factors.

The WHI study was included in an overview of four randomised, placebo-controlled trials of HT involving more than 20,000 women followed up for a mean of 4.9 years [21]. Overall, there was an excess of 3.2 breast cancers per 1000 women aged 50–59 years and 4.0 breast cancers per 1000 women aged 60–69. Overall, the hazard ratio was 1.29 (95% confidence interval: 1.21–1.40) and the risk increased with the duration of use. Interestingly, only the study that used oestrogen-alone (ET) failed to demonstrate an increased risk of breast cancer (Women's Oestrogen for Stroke Trial: WEST), whilst the three using combined oestrogen plus progestogen therapy (EPT) all supported a significant increase in risk.

A number of other studies have also indicated that combined EPT may increase the risk of breast cancer to a significantly greater degree than ET (Table 3) [22–26], although the relative effects of continuous and sequential progestogen administration remain unclear. This is supported by the higher incidence of increased breast density in women receiving EPT than in those given ET [2,27]. One study involving 46,355 women,

Table 3
Relative risk of breast cancer with ET and EPT

	ET	EPT
Schairer et al. [22]	1.20	1.40
Ross et al. [23]	0.93	1.79
Colditz et al. [24]	1.10	1.58
Magnusson et al. [25]	2.70	2.95
Newcomb et al. [26]	0.81	1.06

of whom 2082 developed breast cancer, showed that the relative risk increased by 0.01 per year of ET use compared with 0.08 per year of EPT use [22]. Similarly, in a report of 2083 women enrolled in the Nurses' Health Study, there was an excess annual risk of developing breast cancer of 3.3% amongst women taking ET compared with 9% amongst those taking EPT [24]. Two case-control studies, each conducted in over 3000 women, both also demonstrated an excess risk with EPT [23,25], although in one of these the effect of HT was significant only in women with a relatively low body mass index (<27 kg/m^2) [25]. These two studies also specifically assessed the influence of sequential or continuous combined preparations on breast cancer risk. One revealed a significantly lower incidence of breast cancer with sequential compared with continuous combined EPT [25], whilst the other showed a non-significant trend towards a greater risk with sequential combinations [23].

These findings with regard to the effect of progestogen addition were strongly supported by the recent UK One Million Women Study [28], which found that current users of HT were more likely to develop breast cancer and EPT users had the greatest risk compared with both ET and tibolone. A total of 1,084,110 women (aged 50–64 years) were recruited into this study over a 5 year period, approximately 50% of whom had used HT at some stage. The overall relative risk of developing breast cancer was 1.66 (95% confidence interval: 1.60–1.72) for current users of HT at baseline. However, the risk differed markedly depending on the type of HT, being significantly ($P < 0.0001$) higher with EPT than with ET or tibolone (Table 4). There was also a high relative risk amongst women taking progestogen only (2.02; 95% confidence interval: 1.05–3.89), but not amongst those given vaginal oestrogen. The relative risk also increased with the duration of use of both ET and EPT (Table 4).

Table 4
Relative risk of incident invasive breast cancer in relation to the type of HT at recruitment and duration of use: results from the Million Women Study [28]

	Cases/Population	Relative risk (95% confidence interval)
All never users	2894/392757	1.00 (0.96–1.04)
All past users	1044/150179	1.01 (0.95–1.08)
Current use of		
ET	991/115383	1.30 (1.22–1.38
EPT	1934/142870	2.00 (1.91–2.09
Tibolone	184/18186	1.45 (1.25–1.67)
Other	93/9548	1.44 (1.17–1.76)
Current use of ET		
<1 year	25/4452	0.81 (0.55–1.20)
1–4 years	251/29582	1.25 (1.10–1.41)
5–9 years	416/47310	1.32 (1.20–1.46)
≥10 years	277/31862	1.37 (1.22–1.54)
Current use of EPT		
<1 year	97/9771	1.45 (1.19–1.78)
1–4 years	582/49240	1.74 (1.60–1.89)
5–9 years	850/56912	2.17 (2.03–2.33)
≥10 years	362/23673	2.31 (2.08–2.56)

Relative to never users, stratified by age, parity and age at first birth, family history of breast cancer, body mass index, region and deprivation index.

It is important to note, however, that there are a large number of inherent biases in this trial and the analysis is only preliminary. The study retrospectively used a questionnaire to assess HT use and patients at recruitment could have been on HT for several years. The magnitude of the effect of HT risk is at variance with previous studies, especially randomised controlled trials, but the concept that combined EPT leads to an increased risk of breast cancer compared with ET or tibolone is undoubtedly correct. However, the data from the One Million Women Study with regard to both ET and tibolone requires verification. A second study published only in abstract form by Allen et al from the General Practice Database in the United Kingdom found an increased risk of breast cancer with more than 5 years' use of HT, but the risk was elevated only for combined EPT preparations and not for ET or tibolone. This is more in keeping with the continuation of the WHI ET trial. The recent Danish Nurse Cohort study reported an increased risk in current users of ET, EPT and tibolone [29]. A number of ongoing clinical trials, together with previous clinical trials that are currently undergoing follow-up,

will clarify the effect of tibolone on the risk of breast cancer. The incidence of breast cancer in the clinical database of all phase III/IV studies conducted with tibolone (excluding women with pre-existing pathology at baseline) does not indicate an increased risk for breast cancer in tibolone-treated women compared with placebo-treated women. Amongst 3343 women given tibolone and 1194 given placebo, the incidence of breast cancer was 1.59 and 3.15 per 1000 woman-years, respectively (relative risk: 0.50; 95% confidence interval: 0.11–2.54) [data on file; NV Organon].

3. Use of HT in women with breast cancer

Although the majority of women with breast cancer will suffer from postmenopausal symptoms, HT is generally considered to be contraindicated due to its effect on breast density, recurrence of breast cancer and risk of contralateral disease. The use of combined HT after breast cancer was explored in the HABITS trial. The trial was stopped partly because of poor recruitment and partly because of an excess of recurrence in the combined HT users. No difference in overall mortality from breast cancer was seen between the groups, mainly because the excess recurrence on combined HT was local and contralateral breast cancer recurrences [30]. This difference was not unexpected given the increased breast cancer risk in the WHI Study results with combined HT and the use of HT whilst affecting local recurrence did not affect mortality. Oestrogen-based HT also increases the chances of developing deep vein thrombosis and pulmonary embolism, conditions that tend to be more common amongst women with breast cancer, as well as increasing the risk of endometrial proliferation and cancer. Many women with breast cancer will be receiving tamoxifen and may therefore already be at increased risk of endometrial cancer. For these reasons, there is currently only a limited amount of data on the use of HT in these women. However, a recent meta-analysis of case-control studies involving more than 3000 women found a relative risk of 0.72 (95% confidence interval: 0.47–1.10) for recurrence in breast cancer survivors using ET compared with non-users [31]. There is also preliminary evidence that concomitant use of tamoxifen can reduce the risk of breast cancer. In the Italian Tamoxifen Prevention Trial [32], which involved a total of 5408 women followed up over 8 years, 18% of the women were treated with ET. Amongst these women, the incidence of breast cancer was significantly (P = 0.0217) lower amongst those who received simultaneous tamoxifen than amongst those given placebo. Tamoxifen had no detrimental effect on climacteric symptoms, whilst the use of ET was beneficial in preventing withdrawal from the study.

Randomised, controlled trials of non-ET that have demonstrated improvements in vasomotor symptoms are shown in Table 5 [33–39]. There is a high placebo response rate in these trials, with improvements in the placebo group reported to be in the range of 25–51%, despite effective blinding [40–42]. Therefore, any trials of such treatments require a placebo-control.

A number of options are available for the management of vasomotor symptoms, including Vitamin E, clonidine, phytoestrogens, tibolone, venlafaxine (a dual serotonin and noradrenaline reuptake inhibitor) [43], fluoxetine (a selective serotonin reuptake inhibitor; SSRI) [44], progestogens (e.g. megestrol acetate) [45], and for women receiving tamoxifen, either a reduction in the dose to 10 mg/day or combination with HT or tibolone. Given its good safety and tolerability profile, the first-line choice would probably be Vitamin E (800 IU/day), although it rarely provides satisfactory or lasting relief of vasomotor symptoms. Failing this, clonidine, venlafaxine, an SSRI or possibly a progestational agent should be prescribed although women should be informed of the potential side effects and the lack of protection against osteoporosis. No long-term safety data exists regarding use of progestogens after breast cancer treatment. Given the Million Women Study data, which indicated that only progesterone HT had an increased relative risk of breast cancer equivalent to that of EPT, the use of such progestogens after breast cancer treatment is contentious. Many oncologists believe that, since pharmacological doses are used after breast cancer treatment compared with standard progesterone only HT (physiological doses), the effects will be different and no increased risk of breast cancer recrudescence will occur, but this is entirely unsubstantiated at present. Prevention of osteoporosis is an important factor, and this can be managed by the use of bisphosphonates [46], tamoxifen [47] or selective-oestrogen receptor modulators (SERMs), such as raloxifene [48]. However, SERMs

are contraindicated in women with a history of venous thromboembolism.

3.1. Antidepressants

The mechanism of action of venlafaxine and SSRIs such as paroxetine and fluoxetine is unclear, although the effects are believed to be central and related to alterations in dopamine, serotonin or noradrenaline pathways. A small dose of venlafaxine (37.5 mg/day) was shown to reduce hot flushes by approximately 40% [36], whilst a higher dose of 75 mg/day had an even greater effect (60% reduction) [35] (Fig. 1). The only evident side effects of venlafaxine were dry mouth, decreased appetite and nausea. In most cases, the nausea resolved after the first week. However, venlafaxine is not licensed for the indication of relief of hot flushes and patients have experienced problems when stopping the drug. In addition, galactorrhoea and sexual dysfunction have been reported on rare occasions during long-term therapy. Paroxetine has been shown to have a similar effect to venlafaxine, with a 75% reduction in hot flushes [49].

3.2. Progestational agents

Many clinicians choose progestational agents, such as megestrol acetate, as a first-line treatment for hot flushes in breast cancer, although data from the Million Women Study will cause us to question their safety. The doses of progestogens used are high, compared with the low doses used in HT, with a usual dose of megestrol acetate of 40 mg/day. A placebo-controlled, double-blind, randomised, crossover trial involving a

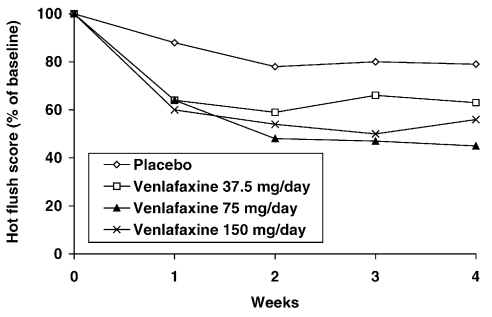

Fig. 1. Effect of venlafaxine (37.5, 75 or 150 mg/day) vs. placebo on hot flush score in postmenopausal women [35,36].

Table 5
Summary of randomised, placebo-controlled studies of treatments for vasomotor symptoms

Reference	Intervention	Type of study	Response	Conclusion
[33]	Vitamin E 800 mg/day	Double-blind, randomised, placebo-controlled, crossover	25% reduction in hot flushes vs. 22% with placebo	One less hot flush than placebo
[34]	Oral clonidine 0.1 mg/day	Double-blind, randomised, placebo-controlled	37% reduction in hot flushes vs. 20% with placebo	Only 1% increase in quality of life
[35,36]	Venlafaxine 37.5 mg/day 75–150 mg/day	Double-blind, randomised, placebo-controlled	40% reduction in hot flushes with 37.5 mg/day, 60% reduction with 75–150 mg/day vs. 27% with placebo	Ongoing clinical trials
[37]	Megestrol acetate 40 mg/day	Double-blind, randomised, placebo-controlled, crossover	75–80% reduction in hot flushes vs. 20–25% with placebo	Long-term risk of breast cancer
[38]	Tibolone 2.5 mg/day	Double-blind, randomised, placebo-controlled, pilot	50–60% reduction in hot flushes vs. 10–20% with placebo	Awaiting results from larger, multinational clinical trials
[39]	Phytoestrogen (soy) 60 g/day	Double-blind, randomised, placebo-controlled	45% reduction in hot flushes vs. 30% with placebo	Similar findings with other phytoestrogen studies

4-week period of oral megestrol acetate (40 mg/day) followed by placebo for 4 weeks [37] showed that women receiving placebo had a 21% reduction in hot flushes whereas those receiving megestrol acetate had an 80% reduction. Once an improvement in hot flushes is seen on progestogens, the dose can be reduced to 20 mg/day or less after a month in order to reduce side effects. It is noticeable that for the first 7–10 days after commencing progestogens a "flare" or increase in hot flushes occurs and women must be encouraged to persevere beyond this period in order to gain the longer term benefits of therapy. Reginster et al. [50] found that progesterone (150 mg depot medroxyprogesterone) given for 25 days/month was better than oestrogen alone over a 3-month period in relieving vasomotor symptoms (18% of women taking oestrogen and 33% taking progesterone had no symptoms). However, long-term side effects of progestogens, including weight gain and carpel-tunnel syndrome [51], limit their use and there is no convincing evidence that progestogens are safe after breast cancer treatment.

3.3. Phytoestrogens

Phytoestrogens are so named because they are plant-derived molecules possessing oestrogen-like activity. Their chemical structure is a based on a steran frame and is structurally similar to 17β-oestradiol and SERMs, although their effects are estimated to be some 1000-fold weaker compared with those of 17β-oestradiol. Potentially, phytoestrogens can act as both oestrogen agonists and antagonists depending on tissue metabolites and processing [52]. The three main types of phytoestrogens are the isoflavones found in soy (the most potent), coumestans and lignans found in flaxseed.

The incidence of menopausal vasomotor symptoms is much lower in Asian countries where consumption of soy phytoestrogens is high. However, evidence from several human studies is controversial. Randomised controlled studies have demonstrated a minimal effect of soy on hot flushes, with a prominent placebo effect. Vincent and Fitzpatrick [53] found a 45% reduction in hot flushes using soy supplements, compared with a 30% reduction on placebo. A similar trend was mirrored by Albertazzi et al. [39] in a randomised, placebo-controlled trial of 104 postmenopausal women. Although these studies had statistically significant results, the clinical significance is unclear. In a trial involving 69 postmenopausal women, Germain et al. [54] found no effect on the severity of hot flushes or night sweats at any point over a 24-week period using isoflavone rich (80 mg/day) protein supplements.

There is even more uncertainty surrounding the use of phytoestrogens for reducing vasomotor symptoms in women treated for breast cancer. Recent studies show no statistical variations between soy and placebo treatments in the reduction of hot flushes. In a trial involving 177 women treated for breast cancer, of whom 66% were receiving tamoxifen, a soy pill equivalent of 150 mg/day was no more effective than placebo in reducing hot flushes [55]. Interestingly, 36% of women who took placebo reported that their hot flush frequency was reduced by 50%, compared with 24% of patients taking the soy pill. In addition, more patients at the conclusion of the study preferred the placebo to the soy supplement (37% versus 33%, respectively).

Two randomised, placebo-controlled trials of red clover tablets showed that doses of both 40 mg/day and 160 mg/day had no effect on hot flushes over a 3-month period [56,57].

Many researchers have argued that concentrated soy isoflavone/high dose plant oestrogen supplements should not be given to women who have been diagnosed with breast cancer as theoretically, and until proven otherwise, it may encourage tumour growth in a potentially low-oestrogen environment.

3.4. Tibolone

A double-blind, placebo-controlled study has recently been conducted to assess the effects of tibolone in 70 postmenopausal women receiving tamoxifen after surgery for breast cancer [38]. The women were randomised to receive 20 mg/day oral tamoxifen plus either 2.5 mg/day oral tibolone or placebo for 12 months. The frequency and intensity of hot flushes and sweats was assessed using the Landgren scale. As shown in Fig. 2, there was a reduction in the occurrence of both hot flushes and sweats in women given tibolone compared with an increase in women given placebo. At the end of the study, the frequency of hot flushes had fallen by 34.8% with tibolone and increased by 52.6% with placebo, compared with baseline. The corresponding percentage changes in the incidence of sweats were –53

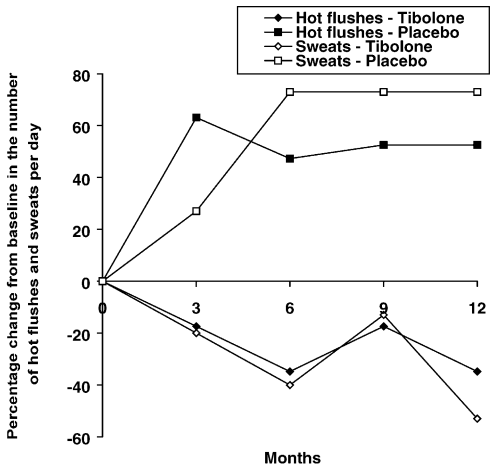

Fig. 2. Percentage change from baseline in the mean number of hot flushes and sweats per day with tibolone or placebo (plus tamoxifen) assessed by the Landgren scale [38].

and +73%, respectively. Comparable findings were reported for the severity of both hot flushes and sweats. Women given additional tibolone also reported an improved quality of life, with 74.3% reporting that hot flushes and sweats did not interfere with their everyday life at the end of the study compared with 51.5% at baseline. No change was seen amongst women given placebo. Tibolone had no unwanted effects on the endometrium; all biopsies were normal and the incidence of vaginal bleeding was low. There were no cases of breast cancer recurrence in either group.

A multinational, double-blind, placebo-controlled study is currently underway (Livial Intervention following Breast cancer; Efficacy, Recurrence And Tolerability Endpoints: LIBERATE) to further investigate the effects of tibolone in women surgically treated for breast cancer in the previous 5 years. A total of 2600 women will be recruited and treated for 4 years. The study aims to investigate the recurrence of breast cancer, as well as overall survival, climacteric symptoms, bone mineral density and thrombosis.

4. Conclusion

There is increasing evidence that HT significantly increases the risk of developing breast cancer, with EPT apparently increasing the risk to a greater extent ET. The risk is also increased with longer duration of use. Oestrogen-based HT is generally considered unsuitable for women with breast cancer and therefore little data is currently available on the associated risks and benefits. A number of other options are, however, available to control menopausal symptoms in breast cancer survivors. Tibolone, for example, appears to have less stimulatory effects on the breast than HT and preliminary evidence indicates that it may be a useful alternative in breast cancer survivors with climacteric symptoms.

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