CLIMACTERIC 2006;9:404–415

Invited Editorial

Is HRT justified for symptom management in women at higher risk of developing breast cancer?

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Key words: HORMONE REPLACEMENT THERAPY, SYMPTOMS, BREAST CANCER, HIGH RISK

ABSTRACT

Hormone replacement therapy (HRT) is the most efficacious intervention for the treatment of estrogen-deficiency symptoms. Prescriptions for HRT have fallen over the last 3 years due to anxiety provoked about breast cancer risk and recurrence that has been generated by recent clinical trials. In women at population risk of breast cancer, these trials have not shown risks greater than estimates from clinical trial evidence that predated them. For women at increased breast cancer risk due to a family history or high-risk benign breast conditions, clinical trial data are limited but suggest a lack of an additive effect of HRT on risk. In symptomatic breast cancer survivors, observational data suggest no increase in recurrence but these data are open to bias. Interim analyses of large, randomized trials have shown contradictory outcomes and, as a result, three large HRT randomized trials have now been closed. The randomized LIBERATE trial evaluating tibolone in breast cancer survivors is fully recruited and continuing. The current clinical climate is 'HRT adverse' but, due to a lack of effective alternatives for symptom relief, women at higher breast cancer risk and breast cancer survivors are still requesting information about HRT. In this situation, discussion of the current clinical uncertainty surrounding the use of HRT must be undertaken to ensure that women are adequately informed.

INTRODUCTION

Breast cancer is the most common female malignancy in developed countries. The overall estimated lifetime risk (up to the age of 85 years) in the United Kingdom is 1 in 9. The incidence pattern of breast cancer implicates endogenous sex hormones in its development, as risk rises rapidly from the thirties until the menopause, after which rates continue to increase but not as steeply. Most breast cancers are diagnosed in women over the age of 50. Despite this high disease incidence, survival rates are improving. Over 70% of women diagnosed with breast cancer in the United Kingdom now survive more than 5 years. This is almost certainly due to the more widespread use of adjuvant endocrine and chemotherapy and the introduction of mammographic breast screening[1].

Epidemiological evidence has consistently shown associations between breast cancer risk and prolonged exposure to endogenous sex

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DOI: 10.1080/13697130601022367

hormones (e.g. early age at menarche, late age of menopause) or exogenous sex hormones (e.g. the oral contraceptive pill and hormone replacement therapy (HRT))[2]. However, the etiology of breast cancer is complex, being attributable to a combination of genetic, lifestyle and reproductive factors. Of the known hormonal risk factors for breast cancer, considerable professional and lay concern exists surrounding the use of HRT. Adverse publicity generated by the Women's Health Initiative (WHI) and the Million Women's Study (MWS) in 2002 and 2003, respectively has fuelled this anxiety[3,4]. As a consequence, women have been denied informed discussion and debate about the risks and benefits of HRT and prescriptions for HRT have fallen[5].

For women placed at a higher than expected age-related breast cancer risk due to a family history of breast cancer or personal history of benign breast change, there is additional uncertainty about the impact of HRT. Debate continues as to whether it is justified to consider HRT in the management of estrogen deficiency, specifically for symptom control where there is a lack of effective alternatives[6]. A further group of women affected are those who have been treated for breast cancer. This has become more controversial following publication of conflicting data from interim analyses of two randomized studies of HRT in breast cancer survivors[7,8]. Symptom control in all these high-risk groups of women is a significant problem in clinical practice. Many seek advice about HRT when alternatives have been tried without success, demonstrating that quality of life may be just as relevant as concerns about breast cancer risk and recurrence. Due to the paucity of evidence about HRT use in these high-risk women, our practice is to discuss all available clinical trial data against the background of our understanding of the development and promotion of this disease. Whilst uncertainty prevails, we consider this essential to ensure informed decision-making.

HRT AND BREAST CANCER RISK IN WOMEN AT POPULATION RISK OF BREAST CANCER

Prior to the publication of the WHI and MWS, the Collaborative Group for Hormonal Risk Factors in Breast Cancer conducted a comprehensive meta-analysis of world-wide observational studies and estimated HRT to confer a similar degree of breast cancer risk as that associated with a late natural menopause (i.e. 2.3% compared with 2.8% per year, respectively). Risk was restricted to women aged 50 years or greater who were current users of HRT for more than 5 years (relative risk 1.35, 95% confidence interval (CI) 1.20–1.49). Combined HRT was associated with a greater risk compared with unopposed estrogen and, irrespective of the type of HRT, risk was shown to fall with cessation of use. In most studies, breast cancer risk with HRT seemed to be limited to lean women (i.e. body mass index < 25 kg/m^2)[8,9].

The placebo-controlled randomized WHI study confirmed breast cancer risk to be increased with current use of combined HRT (i.e. conjugated equine estrogens (CEE) 0.625 mg daily plus medroxyprogesterone acetate (MPA) 2.5 mg) and supported previous evidence that this risk is duration-dependent, beginning to emerge after 3 years' exposure[9,10]. In absolute terms, it has been estimated that combined HRT for 5 years probably accounts for an extra four cancers per 1000 women, an excess risk of 1 in 250[10]. In the unopposed estrogen (i.e. CEE 0.625 mg daily) component of the WHI study, the median duration of use was 4.6 years[11]. This was not associated with an increased breast cancer risk. The absolute risk of invasive breast cancer by age group for both components of the WHI study is summarized in Table 1.

Table 1 Absolute risk of breast cancer incidence by age group in women exposed to hormone replacement therapy (HRT) (per 1000 women, intention to treat for 5 years)*

	Estrogen only		*Continuous combined HRT*	
Age range (years)	*Hazard ratio (95% confidence interval)*	*Difference*	*Hazard ratio (95% confidence interval)*	*Difference*
50–59	0.72 (0.43–1.21)	−4 (−7 to +3)	1.20 (0.80–1.82)	+3 (−3 to +11)
60–69	0.72 (0.49–1.07)	−5 (−9 to +1)	1.22 (0.90–1.66)	+4 (−2 to +12)
70–79	0.94 (0.56–1.60)	−1 (−9 to +12)	1.34 (0.88–2.04)	+7 (−2 to +21)
Overall	0.77 (0.59–1.01)	−4 (−7 to 0)	1.24 (1.01–1.54)	+4 (0 to +9)

*Based on risk estimates from the WHI study[10]

The observational MWS reported an increased risk of breast cancer with all HRT regimens (i.e. combined HRT, unopposed estrogen and tibolone) and routes of administration[4]. In common with previous observational data and the WHI study, risk was greatest with combined regimens. However, in complete contrast to all other evidence, risk became apparent after a very short duration of use (i.e. 1–2 years). Numerous design aspects of this study and the resulting conclusions have been criticized and reviewed elsewhere[12]. Amongst these is the fact that the risks presented were based on HRT use at recruitment only, thereby significantly under-estimating duration of exposure.

In postmenopausal women, mammographic breast density appears to be independent of circulating levels of endogenous sex hormones[13]. Placebo-controlled evidence, however, has shown that combined HRT regimens (both cyclical and continuous combined) increase mammographic breast density in about 25% of women who use them[10,14]. Recent evidence suggests that the impact of combined HRT may be dose-related but this requires confirmation in larger trials[15]. The WHI investigators have concluded that increased density alone may not be the main factor resulting in women being recalled for further evaluation, due to having an abnormal mammogram, if they are using combined HRT, suggesting an effect on both the sensitivity and specificity of screening[16]. Unopposed estrogen (i.e. CEE 0.625 mg) has not been shown to increase breast density compared with placebo in large randomized trials, although current use does appear to result in more women being recalled for further evaluation of abnormal but not suspicious mammographic findings[14,17]. Only one small randomized trial has evaluated the effect of unopposed estradiol valerate on mammographic density[18]. This was not placebo-controlled. Twenty-three women were allocated to receive transdermal 17β-estradiol (50 μg daily) and, after 1 year, four had an increase in mammographic density assessed using the Wolfe classification. This change was significant compared with women allocated to not receive any HRT but was less than that in women who were allocated to receive combined HRT. Obviously, further placebo-controlled studies are required to clarify the effects of all HRT regimens, including opposed and unopposed therapies, on mammographic sensitivity and specificity.

Prospective evidence has shown that withdrawal of HRT for as little as 2 weeks prior to mammography improves screening sensitivity[19]. In the combined HRT component of the WHI study, women who were taking HRT prior to randomization stopped their medication for 3 months before their treatment allocation. There was no difference in the proportion of women with abnormal mammograms who were randomized to receive placebo or combined HRT[20]. Such data completely contradict the MWS that reported impairment of screening accuracy in women using both unopposed estrogen and combined HRT for up to 5 years post-cessation of therapy[21]. This discrepancy is difficult to explain but probably reflects the fact that information of HRT exposure was only recorded at study entry (i.e. when women attended for their first screening mammogram).

There is no evidence to support more frequent mammography in women at population risk of breast cancer who choose to use HRT and are eligible for national screening programs. Likewise, for women at higher risk of developing breast cancer or breast cancer survivors, whilst there is still uncertainty about optimal screening practice, there is no evidence to support deviation from local screening guidance or protocols if HRT is commenced. In breast cancer survivors, the main objective of surveillance mammography is to detect new contralateral breast cancer.

Overall evidence supports that it is the addition of a progestogen to postmenopausal estrogen replacement that incurs the increased breast cancer risk with HRT. It has been suggested that combining the levonorgestrel-releasing intrauterine system (LNG IUS) with unopposed estrogen may confer endometrial protection whilst minimizing breast cancer risk. The only data on breast cancer risk with the use of the LNG IUS have not shown an increase in incidence; however, this is based on post-marketing surveillance[22]. Indirect evidence, implying but by no means definitive, of breast safety is the lack of any increase in mammographic breast density in women using unopposed estrogen combined with the LNG IUS[23]. Further evidence is obviously required before this combination can be recommended as 'breast safe'.

The most important breast cancer end-point is mortality, but no randomized trial will ever be sufficiently large to evaluate this with any reliability. Instead, estimates of the likely impact of HRT on survival are based on observational evidence. With the exception of the MWS, which showed an increased breast cancer mortality (of borderline significance), observational evidence

suggests no overall detrimental effect of HRT on outcome[24]. With all these studies, lack of information about tumor pathology, stage and treatment of cancers diagnosed in HRT users and non-users means that it is very difficult to draw any definitive conclusions.

An alternative to observational data is estimation of survival based on the biological features of tumors diagnosed in women using HRT. Given that endocrine breast cancer therapy is only effective in tumors that express the estrogen receptor (ER), it can be predicted that HRT is only likely to promote tumors that are ER-positive[25]. As over 90% of grade I invasive cancers are ER-positive, it can be hypothesized that HRT will promote better prognostic tumors[26]. Observational studies support this hypothesis but neither the combined HRT nor unopposed estrogen components of the randomized WHI study showed such a relationship[10,17]. It is important to be aware though that, even with 16 000 and 11 000 women recruited, respectively, the number of breast cancer events in the WHI was too small for this association to be evaluated, as most breast cancers (i.e. 75%) are ER-positive[27].

In the WHI study, combined HRT-associated cancers were significantly larger and more likely to be node-positive compared with placebo-associated cancers[10]. The mean difference in tumor size, however, was only 2 mm and the number of events upon which the lymph node data were estimated was small and confidence intervals wide. Tumors diagnosed in women allocated to receive unopposed estrogen were also larger than placebo-associated cancers (mean size difference of 3 mm) but they were less likely to be high-grade[17]. Using data from the WHI study, survival can be predicted with the Nottingham Prognostic Index (this is based on tumor size, grade and number of involved lymph nodes) for women aged 50–59[28]. With a history of exposure to combined HRT for 5 years immediately prior to diagnosis, the estimated 10-year survival difference compared with placebo is 1.5% (HRT 10-year survival 61%, placebo 10-year survival 62.5%)[29]. This probably accounts for an extra 1.4 breast cancer deaths per 1000 women (Table 2). For women allocated to CEE, no survival difference is apparent.

Table 2 Absolute risk of breast cancer death by age group in women exposed to hormone replacement therapy

Age range (years)	*Hazard ratio*	*Absolute difference in number of deaths after 10 years**
50–59	1.25	+1.4
60–69	1.27	+1.5
70–79	1.39	+2.2
Overall	1.32	+1.8

*Based on risk estimates from the WHI study[10]

WOMEN AT ELEVATED BREAST CANCER RISK DUE TO A FAMILY HISTORY

Most breast cancers are sporadic, that is genetic mutations necessary for the malignant transformation of normal breast epithelial cells occur during a woman's lifetime (somatic mutation). These cancers are more likely to occur with increasing age. Only a small proportion of breast cancers (i.e. 5–10%) appear to be attributable to inheritance of a high-risk susceptibility gene. Of these, approximately 75% of families with multiple cases of breast (and ovarian) cancer are probably accounted for by BRCA1 and BRCA2 genetic mutations. A larger proportion of women (i.e. 10–15%) have a family history that places them at a moderately increased risk, but the inherited factors and their interaction with environmental and reproductive factors are poorly understood[30]. Determination of a woman's likely risk of breast cancer requires an accurate assessment of her family history. Women likely to be at risk of an inherited predisposition will have a family history characterized by clustering of breast cancer often with other cancers, a higher incidence of bilateral breast cancer in affected relatives, and a younger age at diagnosis in affected relatives[30]. Identified high-risk susceptibility genes and their degree of associated breast cancer risk are summarized in Table 3.

Studies of HRT in women at moderate or higher risk of breast cancer

Studies of HRT in women with a family history of breast cancer have not shown an additive effect on disease incidence. Many of these studies failed to define family history accurately; hence, it is difficult to determine the baseline risk of women who participated[31]. The unopposed estrogen component of the WHI study showed a non-significant protective effect of CEE in women without a family history (no family history: hazard ratio 0.68, 95% CI 0.50–0.92; ≥ 1 first-degree relative with breast cancer: hazard ratio 1.85, 95% CI 0.95–3.22)[17]. The event rate is small and the

Table 3 Familial breast cancer: high-risk susceptibility genes and NICE referral recommendations

Gene	*Breast cancer risk (%) by age 70 years (95% confidence interval)*	*Other cancers associated with mutations*
High-risk (≥ 4-fold)		
BRCA1	65 (44–78)	ovarian, Fallopian tube, peritoneum, pancreatic, prostate
BRCA2	45 (31–56)	ovarian, Fallopian tube, male breast, pancreatic, prostate, gall bladder
Moderate-risk (2–4-fold)		
CHEK2	11 (9–14)	colorectal
ATM	23 (13–39)	lymphomas and leukemias
TP53	~50–60 by 45 years	Li-Fraumeni syndrome, including sarcomas, brain tumors and leukemia
PTEN	30–50	Cowden's disease (multiple hamartomas, thyroid cancer, mucocutaneous lesions)
	Risk between age 40–50 years	*Lifetime risk*
Near population risk (1st-level care)	< 3% (3 per 100 women)	< 17% (17 per 100 women)
Moderate risk (2nd-level care)	3–8%	17–30%
High risk (3rd-level referral)	>8%	≥ 30%, ≥ 20% chance of finding a faulty high-risk gene

baseline risk, without knowledge of the age or number of affected relatives, unclear. In common with sporadic breast cancer, reproductive factors appear to have a role in the development of breast cancer in BRCA1 and BRCA2 mutation carriers, and prophylactic oophorectomy and tamoxifen have both been associated with a reduction of risk[32–34]. Whilst available evidence suggests that HRT probably increases risk to the same degree as that in women at population risk of breast cancer, the use of add-back HRT in BRCA1 and BRCA2 mutation carriers who have had a surgical premature menopause does not appear to the risk reduction benefit of oophorectomy (combined HRT after oophorectomy ($n = 34$): hazard ratio 0.43, 95% CI 0.07–2.68: unopposed estradiol after oophorectomy ($n = 50$): hazard ratio 0.44, 95% CI 0.12–1.61)[33].

In the United Kingdom, the National Institute of Clinical Excellence (NICE) has issued guidance for the referral of women with a family history that is based on the recommendation for management in primary, secondary or tertiary (i.e. cancer genetics referral) care[31]. This guidance also contains advice about HRT. Overall, this comes down to assessing and balancing individual risk against the indication for HRT. Whilst the use of as low a dose as possible is recommended, there are no data to support lower dosages of HRT to be more 'breast safe'.

BENIGN BREAST CONDITIONS

Benign breast conditions can be defined as any breast problem not symptomatic of breast cancer. They encompass a diverse range of changes, some of which are associated with an increased risk of developing breast cancer. Benign breast conditions are common, constituting a large and increasing part of primary care and breast surgeon practice; the latter is probably due in part to increased breast awareness, screening and media coverage of breast cancer. Most are variations of normal physiological change due to the cyclic changes in ovarian sex hormones during menstruation. Maximal breast epithelial cell proliferation occurs during the luteal phase, when progesterone levels are elevated. From the mid-thirties onwards, the breast begins to undergo involution where epithelial and stromal cells regress and are replaced by fat. After the menopause, symptomatic breast change due to benign breast conditions becomes less common[35].

The most widely recognized classification of benign breast change is histological[36]. Here, benign change is categorized according to the presence of biopsy-proven epithelial proliferation and atypia and hence the likely risk of developing breast cancer (Table 4). Non-proliferative benign lesions do not have an increased risk of breast cancer; risk is approximately doubled

Table 4 Benign breast conditions and breast cancer risk

	Pathology	*Relative risk of breast cancer*	*Absolute risk of breast cancer per 100 women not using HRT over 15 years*
No benign change (normal breast)	normal breast tissue	1.0	5/100
Non-proliferative change	duct ectasia, solitary cysts, fibroadenoma	1.27 (27%)	6/100
Proliferative disease without atypia	multiple cysts, duct papillomata, sclerosing adenosis	1.88 (88%)	10/100
Atypical hyperplasia	atypical ductal or lobular hyperplasia	4.24 (424%)	19/100

with proliferative lesions and elevated five-fold with atypia. This histological classification does not correlate with symptoms. Due to the low associated risk of breast cancer, most benign breast conditions do not require any treatment or follow-up, merely reassurance.

There are two clinical issues to consider in assessing the impact of HRT on benign breast conditions: first, whether it increases their incidence and, second, whether HRT has an additive effect on subsequent breast cancer risk.

HRT and the risk of benign breast conditions

A number of observational studies have consistently shown an association between HRT exposure and an increased risk of benign breast conditions[35]. As these studies have not used the now commonplace histological classification of Dupont and Page, it is not possible to determine whether the impact of HRT is similar across all risk categories described above[36]. Tamoxifen, which acts as an anti-estrogen in the breast, reduces the incidence of both low- and high-risk benign breast conditions compared with placebo[37]. This implies that HRT is likely to increase the incidence of all categories of benign change.

HRT and the risk of breast cancer in women with benign breast conditions

HRT has not been shown to increase breast cancer risk in women with a history of benign breast conditions, but observational evidence upon which this statement is based has almost entirely evaluated unopposed estrogen replacement therapy in women whose baseline risk, according to the presence of proliferative change or atypia, is unknown. In two studies where risk was assessed in women with biopsy-proven benign breast change, current use of either unopposed estrogen or 'any' HRT was not found to increase breast cancer risk in excess of that predicted by the risk conferred by their baseline histological diagnosis, but the number of breast cancer events is very small (Table 5)[38,39].

Placebo-controlled evidence, however, suggests that HRT will have an additive effect on risk (Table 5)[17,40]. The unopposed estrogen component of the WHI study reported a non-significant increase in breast cancer risk in women with a history of a benign breast biopsy (history of one benign biopsy: hazard ratio 1.60, 95% CI 0.82–3.14; history of at least two prior benign breast biopsies: hazard ratio 2.54, 95% CI 0.73–8.86). Again, no information was provided about the histological category of benign change, and the number of breast cancer events upon which these risk estimates have been determined was very small[17]. The National Surgical Adjuvant Breast Cancer Prevention Trial P1 (NSABP-P1) showed a reduction in breast cancer risk in women with biopsy-proven atypia allocated to receive tamoxifen compared with those allocated to receive placebo[40].

It would seem prudent to advise women that, whilst direct observational data have failed to show any additive effect of HRT on breast cancer risk, this cannot be excluded due to potential bias and the small number of breast cancer events. Using risk estimates from the randomized WHI trial, the absolute risk of developing cancer against a background of benign breast change can be estimated. For women with non-proliferative change, the use of combined HRT for 5 years probably accounts for an extra 1.4 cancers per 100 women who use HRT from the age of 50; women with biopsy-proven proliferative change

Table 5 Effect of hormone replacement therapy (HRT) and tamoxifen on breast cancer risk in women with benign breast conditions

	Relative risk (95% CI) of breast cancer (cases/controls) in women with benign breast conditions		
	Non-proliferative change	*Proliferative disease without atypia*	*Atypia*
Observational studies			
Dupont and Page, 1999			
No ERT	1.27 (0.89–1.8)	1.13 (0.69–1.9)	2.53 (1.0–6.3)
	59/1297	21/595	5/54
ERT	1.0	1.37 (0.88–2.1)	2.87 (1.3–6.3)
	65/2266	29/866	7/95
Byrne et al., 2000			
Never HRT	1.0	1.6 (0.8–3.4)	4.0 (1.7–9.5)
	11/91	31/138	19/36
Past HRT	1.2 (0.4–3.1)	2.1 (0.9–4.7)	4.3 (1.4–12.9)
	8/60	18/74	8/15
Current HRT	1.0 (0.4–2.5)	1.9 (0.8–4.3)	2.6 (0.8–8.0)
	10/80	20/88	7/21
Randomized studies			
NSABP P1 Trial* Tamoxifen vs. placebo	–	–	0.14 (0.03–0.47) (tamoxifen $n = 3$, placebo $n = 23$)

*National Surgical Adjuvant Breast Cancer Prevention Trial, P1. Women at an elevated risk of breast cancer (i.e. baseline relative risk > 1.66) were randomized to receive placebo or tamoxifen 20 mg daily for 5 years

an extra 2.4 cancers per 100 women; and those with atypia, an extra 4.6 cancers per 100 women who use it.

WOMEN WITH PREVIOUS BREAST CANCER

Women who have been treated for breast cancer are at risk of developing loco-regional or distant metastatic recurrence. The impact of ipsilateral breast tumor recurrence on survival is controversial. There is uncertainty whether local recurrence is a marker of systemic relapse, and hence worse prognosis, or acts as a nidus for future systemic disease[41]. Prognostic factors predicting an increased risk of distant metastatic disease include ipsilateral axillary lymph node involvement, larger tumor size and high tumor grade. Of these, nodal involvement is the most reliable predictor of metastatic recurrence. Breast cancer survivors also have an increased risk of contralateral breast cancer, estimated to be 0.5–1% per year[42]. In women developing breast cancer that are known or likely to be BRCA1 and BRCA2 mutation carriers, their risk of contralateral breast cancer is significantly higher, being estimated to be up to 40% at 10 years[43].

Use of HRT in women with previous breast cancer

Hot flushes, night sweats and vaginal dryness are common side-effects of breast cancer therapy[44]. Iatrogenic symptoms are more bothersome and persist for longer in postmenopausal breast cancer survivors compared with healthy postmenopausal women and have a significant, negative impact on quality of life[44,45]. In breast cancer survivors, vaginal dryness has been shown to be an important predictor of impaired sexual functioning[46]. In premenopausal women, ovarian suppression with gonadotropin releasing hormone antagonists (e.g. goserelin) or following chemotherapy appears to induce more severe symptoms than estrogen blockade with tamoxifen[9]. Chemotherapy is associated with a high incidence of permanent amenorrhea in women aged over 40 years[47]. In common with tamoxifen, aromatase inhibitors may induce estrogen-deficiency symptoms in approximately one-third of women who use them[48]. Direct head-to-head randomized comparison of tamoxifen with anastrozole and exemestane, using quality-of-life measures validated in breast cancer patients, have shown no significant difference in the incidence of vasomotor symptoms[49,50]. The incidence of hot flushes and night sweats with

letrozole has been reported to be statistically significantly reduced compared with tamoxifen, but, in this adjuvant trial (i.e. the Breast International Group (BIG) 1-98 trial), these finding are based on the incidence of worst-grade adverse events rather than the overall incidence, and no formal quality-of-life data have been reported yet[51]. Based on current evidence, it is counter-intuitive to substitute an aromatase inhibitor in the management of women if they are experiencing tamoxifen-induced symptoms.

The publication of several small observational studies in the 1980s and 1990s that failed to show any adverse effect of HRT on breast cancer survivors, combined with increasing patient demand to use HRT for symptom relief, led to this issue being readdressed. Following the successful implementation of a pilot randomized study of HRT in symptomatic women with early-stage breast cancer, three large-scale randomized trials were commenced: the HABITS (Hormonal Replacement Therapy after Breast Cancer – is it safe?) and Stockholm studies in Scandinavia and a national trial in the UK[7,8,45].

Due to slow accrual into the HABITS and Stockholm studies, agreement was made in 2002 to pool safety data and final analyses (Table 6). The HABITS study planned to recruit 1500 symptomatic women with early-stage breast cancer but was stopped after the first safety analysis (when 345 women had been recruited); it reported an increased breast cancer recurrence (hazard ratio, 3.3, 95% CI 1.5–7.4)[7]. The Stockholm study, which planned to recruit 1000 women with early-stage disease, in contrast failed to show any increase in recurrence rate (hazard ratio 0.82, 95% CI 0.35–1.90)[8]. This safety analysis was performed when 378 women had been recruited and was contemporaneous with that of HABITS. Loco-regional, distant and contralateral breast cancer events were all increased in the HABITS interim analysis, whereas none were affected in the Stockholm analysis. It has been suggested that the lack of an adverse effect of HRT in the Stockholm study can be attributed to the higher concomitant usage of tamoxifen and the prescription of long-cycle rather than continuous combined HRT, thereby minimizing progestogen exposure. However, the number of breast cancer events in both studies is far too small for any definitive conclusions to be made.

The HABITS data generated considerable media publicity, whereas the Stockholm study did not. Despite the contradictory preliminary findings, both Scandinavian studies were closed. HABITS added to the increased anxiety about HRT and breast cancer generated by the Women's Health Initiative (WHI) and Million Women Study (MWS) and, as a result, accrual into the UK trial

Table 6 HABITS and Stockholm studies: interim analyses

	HABITS ($n = 345$)		*Stockholm* ($n = 378$)	
Category				
Lymph node-positive	23.6%		18.3%	
ER-positive	52.1%		60.2%	
Adjuvant tamoxifen	20.9%		52.6%	
Relative hazard of breast cancer events (95% CI)				
		Number of events		
All women	3.50 (1.50–8.10)	33/345	0.82 (0.35–1.90)	
ER-positive	4.80 (1.10–21.4)	14/159		
ER-negative	1.90 (0.40–9.60)	6/72		
Current tamoxifen	2.80 (0.30–27.4)	4/72		
No tamoxifen	3.70 (1.50–9.00)	29/273		
Number (%) of women experiencing recurrence				
	HRT	*No HRT*	*HRT*	*No HRT*
Loco-regional	11 (42%)	2 (25%)	5	5
Distant metastases	10 (39%)	5 (62.5%)	3	3
Contralateral breast primary	5 (19%)	1 (12.5%)	3	3
Mortality				
Breast cancer	3	4	2	4
Non-breast cancer	2	0	2	5

ER, estrogen receptor; HRT, hormone replacement therapy

slowed to such a level that it was unfeasible to continue and this trial closed in January 2005.

Despite editorials arguing that HRT should never be considered in breast cancer survivors, there may be subgroups of patients for whom it is inappropriate to withhold HRT, such as those with receptor-negative (ER-negative, progestogen receptor-negative) disease, or those with receptor-positive cancer who have been cured by their treatment or who are receiving concomitant treatment with tamoxifen, which blocks the estrogen receptor even in the presence of high circulating levels of estrogen. Unfortunately, the current clinical climate is so anti-HRT that further trials cannot be considered in the near future, even though its efficacy in the presence of tamoxifen has been shown[52]. The future generation of HRT trials, if they are ever possible to conduct, should include evaluation of combined HRT as well as unopposed estrogen with intrauterine progestogen in women with an intact uterus, in addition to unopposed estrogen in hysterectomized breast cancer survivors.

A further area of controversy surrounding aromatase inhibitors is whether it is safe to use vaginal estrogen in the management of vaginal dryness. This has been generated by the knowledge that Vagifem® (Novo Nordisk) results in an initial increase in serum estradiol levels that subsequently fall. As aromatase inhibitors result in almost complete suppression of endogenous estrogen production in postmenopausal women, it has been recommended that vaginal estrogen should be contraindicated in women so treated[53]. The absence of any clinical evidence supporting an increase in recurrence with vaginal estrogen, and lack of effective alternatives in the light of such recommendation, yet again places clinicians in a difficult position when advising symptomatic patients and a balancing of survival outcomes with quality of life.

There is considerable interest in the use of tibolone as an alternative to conventional HRT, as it is hypothesized to be 'breast safe'. A large randomized trial (the LIBERATE or Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints trial) is under way to evaluate this. This trial has successfully completed recruitment (3133 women) and is planned to run for 5 years. Preliminary data from this trial are expected to be available in about 3 years. Tibolone is effective for symptom control in healthy women, but the results from a placebo-controlled pilot study in 70 women with early breast cancer are not as significant as anticipated. In this pilot study, where women were allocated to receive tibolone or placebo in addition to tamoxifen, the primary end-point was the frequency and severity of hot flushes at 3 months[54]. Eligibility was not determined by symptoms. Baseline symptom data show that considerably more women allocated to receive tibolone experienced hot flushes (78.6%) compared with those allocated to receive placebo (50%); data on hot flush severity were unavailable for 54.3% (19/35) and 65.7% (23/35) of women allocated to receive tibolone or placebo, respectively. Using patient-completed diary cards, at 3 months there was no significant reduction in the number of hot flushes but the severity of hot flushes was improved ($p = 0.03$). After 12 months, there was a significant reduction in the number of hot flushes in women taking tibolone compared with placebo when symptoms were assessed by an investigator using the Landgren symptom questionnaire. If the LIBERATE trial confirms the lack of an adverse effect on the breast, tibolone will have a role in symptom management and preservation of bone density. Based on the data from the pilot study in women treated with tamoxifen, symptom improvement may not be as significant as hoped and therefore the preliminary report from the LIBERATE trial in 3 years is awaited with anticipation.

CONCLUSIONS

Women at high risk of developing breast cancer or breast cancer recurrence, if seeking advice about HRT, generally do so for the relief of estrogen-deficiency symptoms when alternatives have failed. It can be appreciated that there is a paucity of evidence in these high-risk women but, in counselling them, it is essential to explain our current uncertainty about its safety. Despite this, women may still decide to use HRT to improve their quality of life. If they are fully appraised of potential risk, they should be supported.

Conflict of interest J. M. is the principal investigator of the national UK randomized trial of HRT in symptomatic women with early-stage breast cancer and has been sponsored to attend conferences and received speaker's fees from Organon, Orion, Schering, Servier, Solvay Healthcare Ltd and Wyeth. Consultancy fees have been received from Wyeth and Organon and fees for preparation of educational material from Novartis. She is also on the council of the British Menopause Society and a member of the European Menopause and Andropause Society.

Source of funding Nil.

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