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The menopause, hormone replacement therapy and breast cancer☆

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Abstract

Concern exists that the reduction in breast cancer risk associated with the onset of the menopause will be negated with exposure to hormone replacement therapy (HRT). Evidence from large-scale randomised HRT trials support observational data that have shown a modest increase in breast cancer risk with long-term use (i.e. >15 years) of combined therapy, although this falls following HRT cessation suggesting a growth-promoting effect. Randomised evidence demonstrates that the efficacy of anti-estrogens, aromatase inhibitors and raloxifene in the treatment and chemoprevention of breast cancer are restricted to women with oestrogen receptor positive (ER +ve) disease; however, HRT has not been associated conclusively with a predominance of hormone sensitive breast cancer. Despite stimulating the breast cancer cell growth, HRT has not been shown to increase breast cancer recurrence or mortality when prescribed to breast cancer survivors experiencing oestrogen deficiency symptoms and randomised trials have been recommended and commenced. In conjunction with controlled breast cancer trials demonstrating a therapeutic benefit of high dose estrogens and interest in the use of additive oestrogen therapy in patients developing resistance to oestrogen deprivation, the dogma that HRT is an absolute contra-indication following diagnosis is challenged.

Keywords: Menopause; Breast cancer; Hormone replacement therapy

1. Introduction

Epidemiological studies provide compelling evidence implicating endogenous oestrogen and ovarian function in the development of most breast cancers. It is a disease that predominates in women and in developed countries is the most common female malignancy, accounting for approximately one quarter of neoplasms diagnosed annually in the United Kingdom (Fig. 1). Breast cancer risk increases after puberty but this rise in disease incidence is less steep in postmenopausal women (Fig. 2). After the onset of the menopause, the relative risk of breast cancer falls by an estimated 2.7% (95% confidence interval 2.1–3.2%) per year. The observations that late age at natural menopause confers an increased breast cancer risk, öophorectomy before the age of 35 years reduces the lifetime breast cancer risk to approximately 40% of that among women who experience a natural menopause and that postmenopausal women have a lower risk of breast cancer than premenopausal women of a similar age, all provide substantial support implicating ovarian function and hence ovarian hormone production, in the etiology of this disease [1]. The assumption that postmenopausal HRT will confer an increase in the incidence of breast cancer has been upheld by observational and randomised data [1,2]. However, a lack of controlled evidence has resulted in continued uncertainty regarding the influence of HRT on breast cancer mortality and recurrence outcomes, including its effect on the biology of this disease. In these circumstances advice about the impact of HRT on the disease burden from breast cancer are by necessity based on extrapolation from observational studies and knowledge of the influence of other hormonally mediated risk factors on disease outcome.

2. HRT prescribing

HRT encompasses a range of regimens, none of which mimic the premenopausal hormonal milieu and this may result in differing effects on breast cancer incidence and prognosis. It is well established that the significant increase in risk of endometrial carcinoma associated with exposure to postmenopausal oestrogen replacement therapy is reduced with the addition of a progestin and therefore any woman requesting HRT who has an intact uterus requires combined oestrogen and progestin replacement rather than unopposed oestrogen replacement, which is only suitable for those who have undergone previous hysterectomy [3]. All HRT regimens consist of a 28-day cycle where either conjugated equine oestrogen or estradiol is administered daily.

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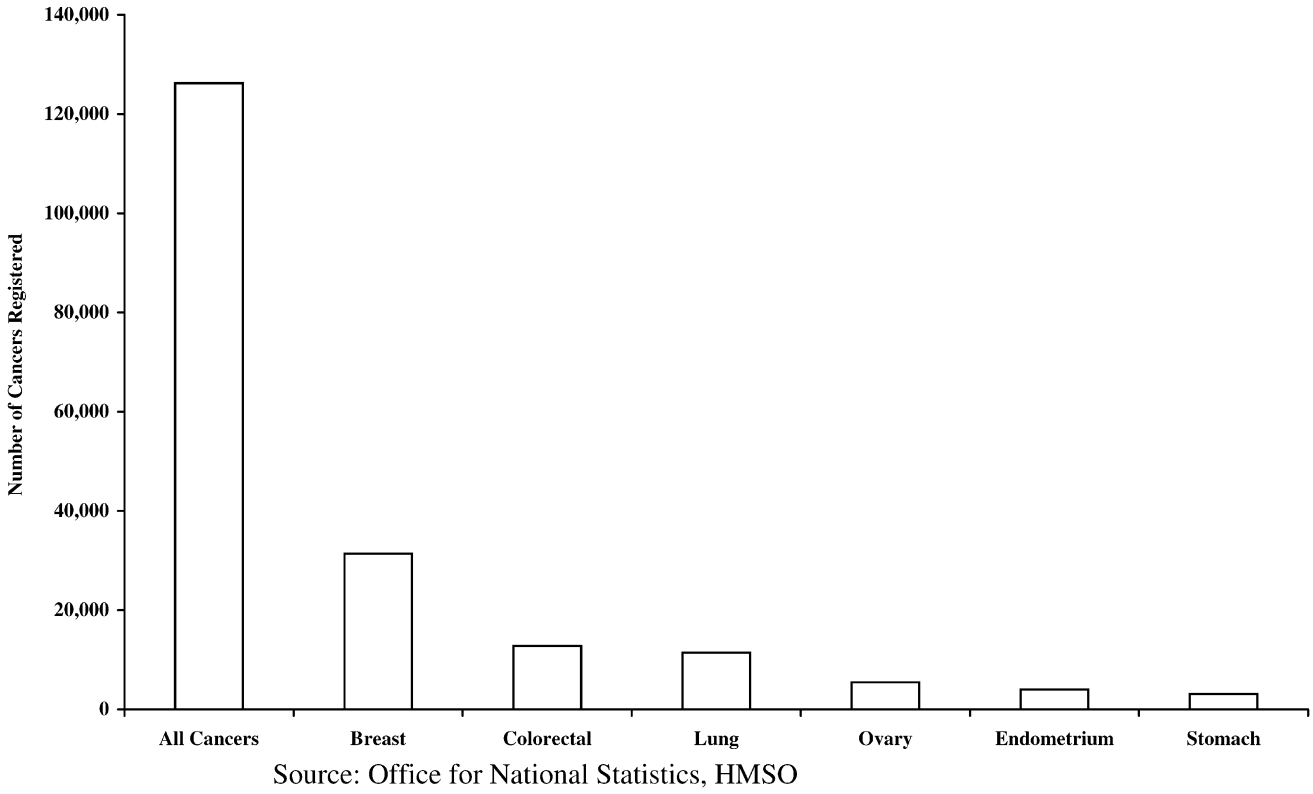

Fig. 1. Registration of newly diagnosed cases of cancer in women in the United Kingdom in 1997.

With oral or transdermal routes of HRT administration, the mean values of serum oestrogen obtained with low and higher dosages are approximately 200 and 360 pmol/l, respectively (Fig. 3) [4]. Oestrogen implants, however, may achieve supra-physiological serum levels [5]. Whilst no epidemiological studies have investigated breast cancer risk in association with implant exposure, data from randomised trials, where high dose estrogens have been shown to be efficacious therapy for breast cancer suggest that implants may not have an adverse effect on incidence [6–9].

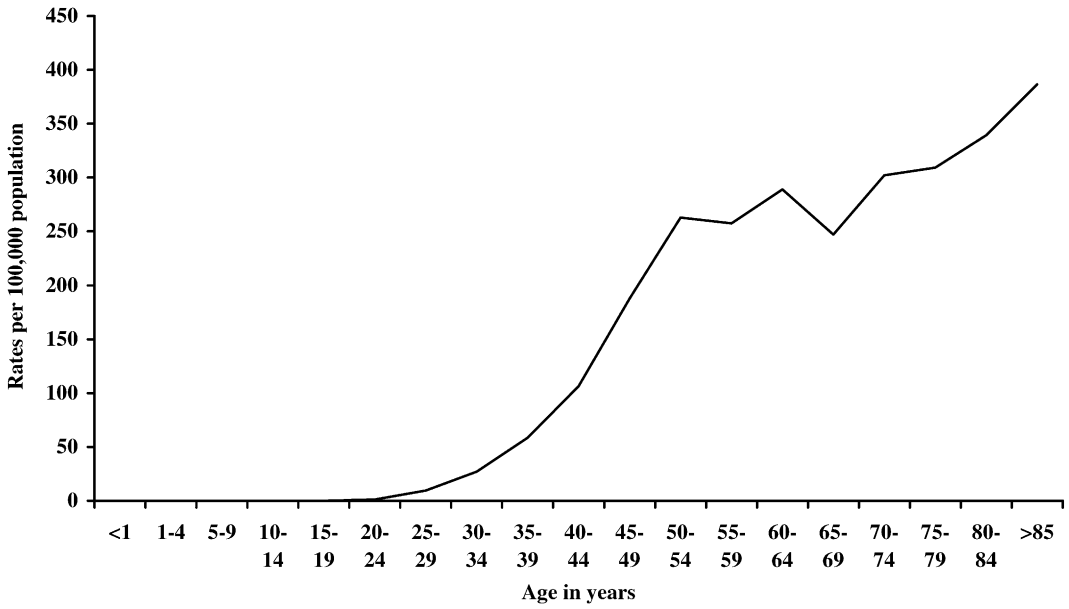

Fig. 2. Age specific incidence rates for breast cancer in the United Kingdom in 1997.

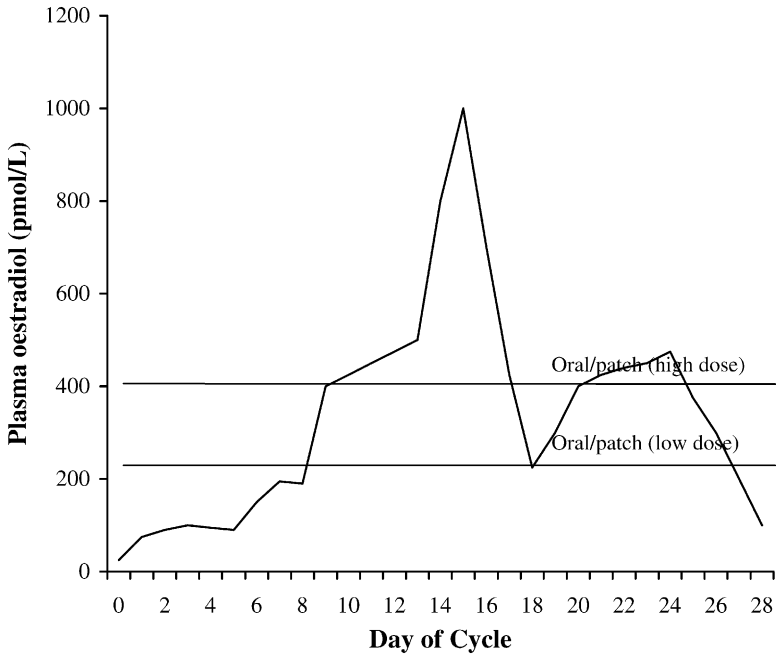

Fig. 3. Plasma oestradiol levels (pmol/l) achieved by conjugated equine oestrogens, 0.625 mg per day or transdermal oestradiol 50 μg per day (oral/patch (low dose)) or by conjugated equine oestrogens 1.25 mg per day or transdermal oestradiol 100 μg (oral/patch (high dose)) as compared to levels during the normal, premenopausal menstrual cycles. Day 1: first day of menstruation. Reproduced with the kind permission of Malcolm Whitehead and Val Godfree.

In combined preparations the progestin component can vary with respect to the pattern of administration (i.e. cyclical or continuous) and the class of progestin prescribed. With cyclical HRT, the progestin is prescribed for 10–14 days of the 28-day cycle, whereas with continuous combined HRT, both oestrogen and a low dose of progestin are taken for all 28 days of the cycle. It has been hypothesised that continuous combined, rather than cyclical HRT, will confer protection against breast cancer development as in vitro data has shown a sustained, inhibitory effect of continuous progestin on oestrogen-driven cell replication [10]. The synthetic progestins used are classified as to whether they are structurally related to testosterone (19 nor-testosterone derivatives) or to progesterone (21 progestogen derivatives). As the 19 nor-testosterone derivatives exhibit relatively greater androgenic and estrogenic activity compared with the C21 progesterone derivatives there is concern that the former may increase breast cancer risk, however, they may also decrease aromatase activity and theoretically have a protective effect [11,12]. Both oestrogen and progestins are subject to large inter- and intra-individual variations, regardless of the route of administration and when prescribed together some progestins may influence the oestrogen metabolism [11].

3. Endogenous serum oestrogen and breast cancer risk

Few prospective studies have investigated the relationship between endogenous sex hormone levels and breast cancer risk and have been too small for reliable risk estimates to be produced but the recent reanalysis of published studies by The Endogenous Hormones and Breast Cancer Collaborative Group (EHBCCG) have confirmed that serum oestrogen levels may be predictive of increased risk [13]. The most consistently evaluated association has been that with elevations in serum estradiol. From a total of nine studies, the relative risk estimate for postmenopausal breast cancer development comparing the highest with the lowest quintile of serum estradiol concentration was 2.0 (95% confidence interval 1.47–2.71). The highest risks were for free estradiol and non sex hormone binding globulin (SHBG)-bound estradiol, which is taken up by cells more readily than SHBG-bound hormone. Similar associations with equivalent estimates of risk were also found for estrone, estrone sulphate, androstenedione, testosterone, dehydroepiandrosterone (DHEA) and DHEA sulphate, although these were based on data from a smaller total of studies. The randomised Multiple Outcomes of Raloxifene Evaluation (MORE) Study also provides evidence that breast cancer risk is increased in women with elevated serum oestrogen levels; the relative risk of breast cancer in women with estradiol levels greater than 10 pmol/l compared with those with undetectable estradiol levels being 6.8 (95% confidence interval 2.2–21.0) [14]. Furthermore, the reduction in the incidence of ER +ve breast cancer observed with the selective estrogen response modulator (SERM), raloxifene was greatest in women with higher circulating estradiol. Collectively these studies suggest that measurement of estradiol in postmenopausal women may identify those

with a higher risk of breast cancer development and that such women may achieve maximal benefit from endocrine chemoprevention, although this requires further evaluation.

4. Endogenous progesterone and breast cancer risk

Most in vivo studies have shown that maximal proliferation of breast epithelium, alveoli and ducts occur in the luteal phase of the menstrual cycle, supporting a mitogenic role for progesterone in combination with oestrogen [15]. However, apoptosis and cell cycle arrest are maximal during the mid to late luteal phase and may occur in response to falling oestrogen and progesterone levels [16]. Induction of apoptosis may explain the paradox observed in premenopausal women, where breast cancer prognosis appears to be improved if surgery is performed during the luteal rather than the follicular phase of the menstrual cycle and that higher circulating levels (i.e. >4 ng/ml) of progesterone may be associated with a decreased breast cancer risk and improved prognosis [17,18]. In postmenopausal women, evidence is accumulating from epidemiological studies that combined therapy may increase risk [19–23]. These studies will be discussed later but it may be inappropriate to extrapolate data obtained from premenopausal women exposed to physiological cyclical fluctuations in serum progesterone to the situation of postmenopausal women using combined HRT.

5. HRT and breast cancer risk—clinical studies

Until recently, only data from observational studies were available upon which risk estimates for breast cancer development with HRT exposure could be based. In summary, the Collaborative Group of Hormonal Risk Factors in Breast Cancer reanalysis of available worldwide studies (1997) and meta-analyses of observational studies (1989–1993) concluded that risk is increased with long-term exposure to HRT (Table 1) [1,24–29]. The main findings of the Collaborative reanalysis were that per year of use, HRT confers a similar degree of risk as that associated with delaying the onset of the menopause (2.3% compared with 2.8% per year, respectively) and that the lifetime risk of developing breast cancer was significantly increased with current long-term use (i.e. the relative risk for more than 5 years use being 1.35, 95% confidence interval 1.21–1.49). Based on the Collaborative reanalysis data, the absolute risk of breast cancer with HRT, which applies the estimated relative risks to underlying population rates and accounts for the duration of use and the duration of elevated risk following the cessation of HRT, appeared to be small, accounting for two extra cancers per 1000 women that use it continuously for 5 years and six additional cancers with 10 years exposure.

Details regarding the type of HRT prescribed were only available for 40% of women reviewed in the Collaborative reanalysis, of these only 5% had been exposed to combined HRT. Despite the relatively small number of incident breast cancer cases, the Collaborative Group provided evidence that the addition of a progestin to oestrogen replacement therapy does not appear to confer protection against the development of breast cancer, in that long-term use of combined HRT was associated with an increase in relative risk of 1.53 (standard error 0.23). Several observational studies published since the reanalysis support this finding but it is not possible to determine how risk may differ according to the pattern of progestin administration (i.e. cyclic versus continuous) or the class of progestin prescribed (i.e. C21 progesterone versus 19 non-testosterone derivatives) due to the small number of incident breast cancer cases and differing outcomes in these individual studies [19–23].

Within the last few years the findings of randomised trials of HRT have been reported [2]. Of those sufficiently powered for reliable assessment of breast cancer risk (i.e. the Heart and Estrogen/Progestin Replacement Study, HERS; the Women's Health Initiative Study, WHI and the Women's International Study of Long-Duration Oestrogen use after Menopause, WISDOM), all evaluated an identical continuous combined HRT regimen (i.e. conjugated equine oestrogen, CEE, 0.625 mg plus medroxyprogesterone acetate, MPA, 2.5 mg) [30–33]. Both the HERS and WHI studies were closed prematurely due to a lack of cardiovascular benefit with the former and a worse global health index due to an excess of cardiovascular, cerebrovascular and breast cancer events in the latter [30,31]. Funding for the WISDOM study, which commenced in 1998 and planned to randomise 22,000 women, has been withdrawn on the basis that it is unlikely

Table 1
Meta-analyses of HRT and breast cancer risk

Reference	No. of studies	Any HRT use (RR, 95% CI)	Duration of use (RR, 95% CI)
Armstrong [24]	Not stated	1.01 (0.95–1.08)	
Dupont and Page [25]	28	1.07 (1.00–1.05)	
Steinberg et al. [26]	16	1.0	>15 years 1.30 (1.20–1.60)
Grady and Ernster [27]	10	1.0	≥10 years 1.23 (1.04–1.51)
Sillero-Arenas et al. [28]	37	1.06 (1.00–1.12)	≥8 years 1.20 (no CI)
Colditz et al. [29]	31	1.40 (1.20–1.63) current use	1.23 (1.08–1.40) >10 years
Collaborative Group on Hormonal Factors in Breast Cancer [1]	51		1.35 (1.21–1.49) >5 years

RR: relative risk; CI: confidence interval; S.E.: standard error.

to add to the information from the HERS and WHI studies although no excess of adverse events has been reported [33]. The combined relative risk estimate of breast cancer with long-term use of HRT from both the HERS and WHI studies is 1.28 (95% confidence interval 1.04–1.58). Interestingly, risk of breast cancer development was only increased significantly in those women participating in the WHI study allocated HRT who have been using it prior to entry into the study. Since the publication of the WHI study, there has been considerable debate as to whether the risk estimates associated with the specific continuous combined preparation used can be extrapolated to all types of combined therapy. Unfortunately, the sample sizes of two randomised trials that have allocated different combined HRT preparations are too small for definitive conclusions to be drawn [34,35]. The unopposed oestrogen arm (i.e. CEE 0.625 mg daily) of the WHI study is continuing, suggesting that risk with oestrogen alone may be less pronounced than with continuous combined HRT. Whilst HRT use has become more widespread in developed countries, most women use it short-term for the relief of oestrogen deficiency symptoms, the median duration being 2 years in the United Kingdom, which on this evidence does not appear to place them at increased risk (unpublished).

6. HRT and other hormonally mediated risk factors for breast cancer—is there a cumulative effect?

It is important to consider whether the magnitude of breast cancer risk associated with HRT is influenced by other known hormonally mediated risk factors as this could be of relevance in counselling women about its use. The only significant association from the Collaborative Group reanalysis was an inverse relationship between body mass index and HRT exposure, no other interaction, positive or negative was found for any other reproductive risk factors or risk factors that may mediate their effect by influencing oestrogen metabolism, including age at menarche, parity, age at first pregnancy, alcohol and smoking [1]. Recently, however, the relationship between lean body mass and risk has been questioned [36] and the WHI failed to show any relationship between HRT, body mass index with breast cancer risk [31].

Mammographic breast density is a further surrogate measure for breast cancer risk but whilst more than 75% breast density on mammography is associated with a four-fold increase in risk (relative risk 4.35, 95% confidence interval 3.1–6.1) both breast stroma and parenchyma are known to contribute towards measured density [37]. As HRT has been shown to increase mammographic density and probably induces proliferation in breast epithelium only, it has been assumed that this may provide a means of identifying women who may be at an increased risk of developing breast cancer with its use but unfortunately, data from randomised controlled trials assessing the impact of HRT on mammography is limited [38]. The placebo-controlled randomised postmenopausal estrogen/progestin interventions (PE/PI) trial has shown that cyclical and continuous combined HRT increase breast density in up to 25% of women who use it (19.4, 95% confidence interval 9.9–28.9 and 23.5, 95% confidence interval 11.9–35.1% in women prescribed CEE plus continuous medroxyprogesterone, or CEE plus cyclic medroxyprogesterone, respectively) whereas unopposed oestrogen replacement has no significant effect [39]. Controlled data evaluating the degree of breast density increase with HRT exposure is minimal. Using digitalised mammography, oestrogen replacement therapy (CEE 0.625 mg) has been reported to increase mean breast density compared with placebo (+1.2% compared with −1.3%, $P < 0.01$) but the mean density increase within the oestrogen treated group of women was not statistically significant [40]. With respect to the effect of combined therapy in the absence of any data, extrapolation of what is known regarding density changes occurring during the menstrual cycle, where an average absolute increase in mammographic density of 1.2% occurs during the luteal compared with the follicular phase, suggests that even with combined therapy, individual change may be small [41]. Preliminary data suggests that HRT may only increase mammographic breast density in women who have already dense breasts but in the absence of any controlled, clinical data it is not possible to determine whether this is an accurate surrogate for additive risk [42].

7. Phenotypic features of cancers arising in women with prior HRT exposure

HRT exposure has been associated with a significant increase in the proportion of women presenting with smaller, better-differentiated, localised breast tumours [1]. In the absence of accurate information about the frequency of mammographic screening and clinical examination in studies comparing HRT users with non-users (the former tending to undergo increased examinations), it is difficult to determine whether this favourable association is due to detection bias or a true biological effect of HRT. Gapstur et al. [43] suggested that the predominance of ‘special type’ cancers in HRT users (i.e. tubular, mucinous and medullary breast tumours rather than invasive ductal or lobular carcinoma) reflected a selective growth-promoting effect although there is no biologically plausible explanation for this and controversy exists as to whether it is correct to categorise medullary cancer with other good prognosis ‘special type’ cancers due to its complex karyotype, which is similar to those described for ductal and lobular carcinoma [44,45].

The Early Breast Cancer Trialists’ Collaborative Group overviews of world-wide randomised adjuvant tamoxifen and ovarian ablation trials in early stage breast cancer and the National Surgical Adjuvant Breast and Bowel Project P-1 tamoxifen chemoprevention study (NSABP P-1) have confirmed that the therapeutic benefit of tamoxifen and ovarian

Table 2
HRT and breast cancer phenotype [36,52,53]

HRT exposure	Invasive ductal carcinoma OR (95% CI)	Invasive lobular carcinoma OR (95% CI)	ER +ve OR (95% CI)	ER −ve OR (95% CI)
Unopposed oestrogen				
Current use	0.70 (0.40–1.10)	0.90 (0.30–3.00)		
	1.08 (0.78–1.50)	1.98 (1.04–3.78)		
Per 5 years use	1.04 (0.95–1.14)	1.09 (0.87–1.36)	1.03 (0.93–1.13)	0.93 (0.77–1.12)
Combined HRT				
Current use	0.70 (0.40–1.10)	2.10 (0.80–5.80)		
	1.25 (0.86–1.81)	3.93 (2.05–7.44)		
Per 5 years use	1.27 (1.08–1.50)	1.34 (0.98–1.83)	1.26 (1.06–1.50)	1.21 (0.90–1.62)

OR: odds ratio; CI: confidence interval; HRT: hormone replacement therapy; ER +ve: oestrogen receptor positive; ER −ve: oestrogen receptor negative.

ablation is confined to women with ER +ve disease [46–48]. Preliminary evidence from the MORE Study has shown a non-significant trend of a predominance of ER +ve invasive breast cancers in women with higher serum levels of endogenous oestrogen (relative risk 1.8, 95% confidence interval 0.7–2.9) [14]. The logical assumption from this evidence is that the any growth-promoting effect of HRT on breast cancer is likely to be restricted to tumours that are hormonally responsive. However, there is little data to support this. The few studies that have assessed the influence of HRT on cellular proliferation according to sex steroid receptor expression imply that its stimulatory effect may be restricted to ER +ve cells but for the most part, patient numbers are small and where presented, confidence intervals are wide [49–51]. Findings of the only three observational studies to have examined the biological characteristics of tumours arising in women using HRT are inconclusive; lobular carcinoma, which often expresses ER does not appear to predominate in women with a history of HRT exposure (Table 2) [33,52,53]. Review of the Italian randomised tamoxifen chemoprevention trial, where the use of unopposed oestrogen was permitted, however, suggests that tamoxifen may reduce breast cancer risk associated with HRT (cumulative frequency of breast cancer in HRT users allocated tamoxifen 0.92%, [95% confidence interval 0.17–1.66] versus 2.58% [95% confidence interval 1.30–3.85] in HRT users allocated placebo) but patient numbers were very small and the combined effect of tamoxifen and HRT on risk was not a primary end point of this trial [54]. This hypothesis is to be tested in a further prevention study. Here, healthy postmenopausal women currently on HRT will be randomised to tamoxifen or placebo for 5 years and the impact on the incidence of invasive and ductal carcinoma in situ assessed as a primary outcome [55].

8. HRT and survival from breast cancer

In the United States and the United Kingdom, breast cancer mortality has fallen by an estimated 25% and has been attributed to the introduction of mammographic breast cancer-screening programs and the more widespread use of adjuvant breast cancer therapy (in particular to the anti-estrogenic effects of tamoxifen and chemotherapy-induced ovarian suppression) [56]. Following the cessation of HRT, irrespective of type, breast cancer risk falls and by 5 years is no greater than that observed in women without a history of HRT exposure [1]. This implies that HRT stimulates the growth of breast epithelial cells that have already undergone malignant transformation and therefore it may adversely affect breast cancer mortality by promoting the growth of occult metastases. In view of this it is important to consider the potential impact that HRT may have if the hypothesis that continued exposure of breast cancer cells to oestrogen will have an adverse effect, is correct. Use of HRT prior to breast cancer diagnosis has not been shown to increase mortality from breast cancer; some studies suggest that mortality may be reduced but two studies imply that this effect attenuates with long-term follow-up [57]. However, inconsistencies in definitions of HRT use and duration of therapy, together with a lack of information about the type of HRT prescribed and a potential ‘healthy user’ effect (i.e. women electing to use HRT generally participate in health-promoting behaviour) all contribute to difficulty in accurate interpretation of these studies.

No randomised controlled trials have been conducted to ascertain the effect of HRT on the accuracy of mammographic breast screening and potential impact on mortality. Reduced mammographic sensitivity is considered to account for most cancers that are diagnosed between screening rounds (i.e. interval cancers). Review of eight observational studies has shown HRT to decrease mammographic sensitivity and increase recall rates but heterogeneity amongst available trials precludes firm conclusions about the effect that HRT may have on the screening program [58]. In the United Kingdom NHS breast screening program, however, invasive cancer detection rates have increased by 36% since 1993, which is in excess of predicted targets and indicates a significant improvement in sensitivity [59]. It would seem unlikely that increased use of HRT during the 1990s has had a major impact on the sensitivity of the national program, although national figures on interval cancer rates, which

are anticipated to have fallen in parallel are not available. Interestingly, HRT-induced breast density increases regress rapidly following its cessation and the specificity and sensitivity of mammography in former HRT users appears to be identical to never users but this should not lead to the recommendation that HRT is stopped prior to screening mammography in the absence of evidence from larger controlled trials as there is a risk of a withdrawal response in a definite carcinoma that could lead to under-treatment [60]. Comparison of the pathological features of screen-detected and symptomatic breast cancers (including interval cancers) diagnosed in women using HRT does not support the contention that inadvertent exposure of tumours to exogenous oestrogen and progestin has an adverse affect on prognosis [61,62]. This further challenges the argument that HRT will reduce the mortality benefit of screening.

Of the known hormonally mediated etiological factors for breast cancer development, only postmenopausal obesity has been shown to be associated with an adverse prognosis with any consistency in clinical studies [63]. A positive association between higher endogenous serum levels of estradiol, estrone and their metabolites and a reduced disease-free survival has been demonstrated for postmenopausal women with early stage breast cancer; the relationship being more pronounced in women with an initial response to first line endocrine therapy [64]. Preliminary data from the large randomised Arimidex, Tamoxifen and Alone or in Combination (ATAC) Trial has shown that the aromatase inhibitor arimidex in postmenopausal breast cancer patients, which results in almost complete suppression of oestrogen production, appears to confer a more significant improvement on disease-free survival compared with tamoxifen [65]. However, in contrast, it has also been reported that postmenopausal patients may have an improved prognosis if circulating oestrogen levels are elevated [66]. High dose estrogens have been shown in randomised trials to be an effective treatment for metastatic breast cancer, recently published long-term survival data has shown a statistically significant superior outcome for women treated with high dose diethylstilbestrol (DES) compared with tamoxifen [6–9]. Further evidence contradicting the assumption that higher serum levels of oestrogen exposure will adversely influence breast cancer prognosis is found from review of observational studies where HRT has been prescribed to postmenopausal breast cancer survivors. The ad hoc prescription of HRT to this group of women has been increasing as a significant proportion experience oestrogen deficiency symptoms such as hot flushes, night sweats and vaginal dryness, as a direct consequence of their endocrine breast cancer therapy [67]. Meta-analysis of observational studies has failed to show any adverse effect of HRT on recurrence rates with a median duration of use of 30 months, irrespective of whether unopposed oestrogen or combined therapy has been taken, or the route of administration [68]. A recent study has not reported an increase in breast cancer mortality either [69]. Unopposed oestrogen replacement therapy (i.e. Premarin 2.5–3.75 mg, or estradiol valerate 2 mg with estriol 1 mg), has been prescribed to women with advanced breast cancer in an attempt to increase the growth fraction of breast cancer cells and thus enhance the clinical response to subsequently administered palliative chemotherapy [70,71]. However, irrespective of tumour ER status, no association

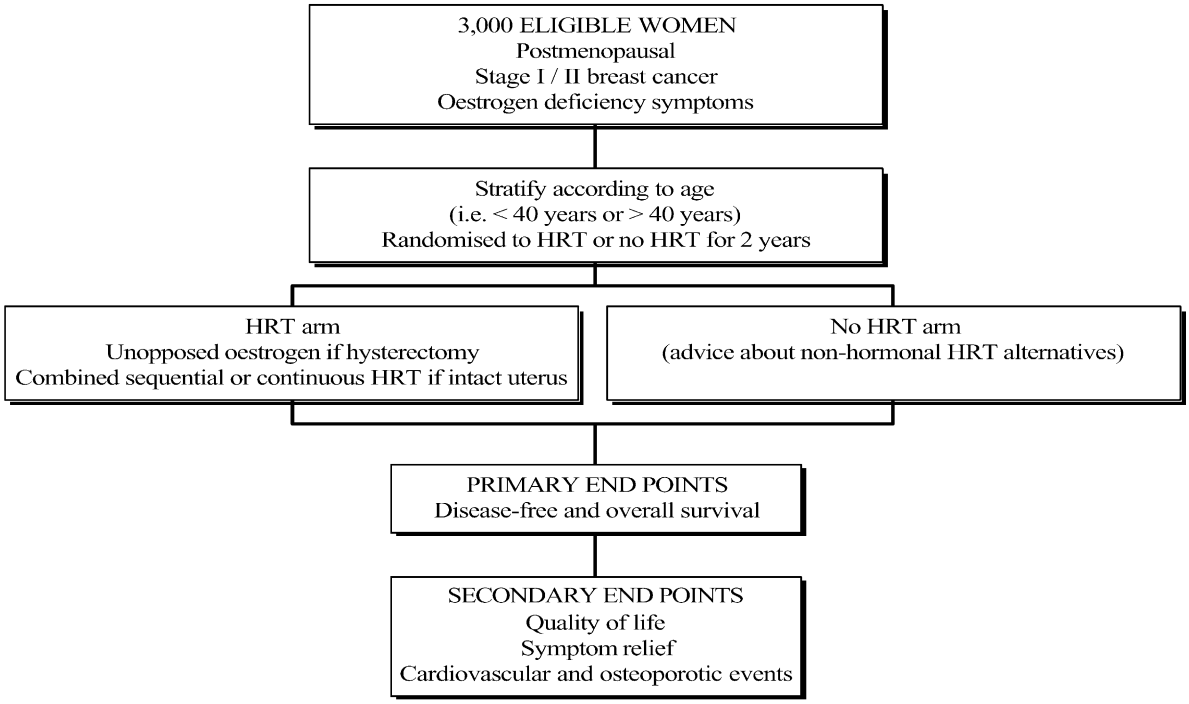

Fig. 4. Plan of the national UK randomised trial of HRT in symptomatic women with a history of early stage breast cancer.

between the time to disease progression and either the percentage change of basal oestrogen level or peak oestrogen levels was detected suggesting a lack of growth stimulation. These studies suggest that whilst plasma oestrogen in the low postmenopausal range may have an adverse effect on the growth of micro-metastatic disease that this may not apply to higher oestrogen concentrations achieved with HRT or high dose estrogens and challenges established dogma that HRT should be contra-indicated in breast cancer survivors. Large randomised trials, however, are warranted to provide more robust evidence before advocating the routine prescription of HRT for symptomatic control in this group of patients and further research is necessary to identify if there are sub-groups of women with particular disease characteristics who may not be suitable for such an intervention. Following the successful implementation of a pilot randomised study in the United Kingdom, larger-scale trials are now underway in the United Kingdom and Scandinavia in symptomatic women with early stage breast cancer, where disease-free survival and overall survival are the primary end points (Fig. 4) [72].

The outcome of these randomised trials is of added importance given the growing interest in exploiting changes in the endocrine environment of hormone sensitive breast cancers that have developed resistance to oestrogen deprivation. It has been demonstrated that human mammary ER +ve cells can adapt their proliferation according to the prevailing oestrogen environment. In oestrogen-deprived conditions, initial inhibition of proliferation is followed after a few weeks by renewed growth, which in turn can be abolished by exposure to oestrogen [73]. The observation that response rates of women with advanced breast cancer to DES appear to be increased with increasing time from the onset of the menopause provides support for enhanced sensitivity of breast cancer cells exposed to oestrogen deprivation [6]. The mechanisms underlying this plasticity of growth response are not fully understood, both enhanced uptake of peripheral oestrogen and increased in situ oestrogen synthesis by breast cancer cells being hypothesised to account for these changes [74]. In vitro, oestrogen deprivation appears to increase aromatase activity in MCF-7 cells, re-exposure resulting in enzyme inhibition and preliminary data suggests that intra-tumoural aromatase activity may be reduced in postmenopausal women who are taking HRT compared with those who have never been exposed [75]. The clinical relevance of this latter observation is unknown but it can be appreciated that further evaluation of the influence of oestrogen and progestins on intra-tumoural hormone concentration regulation may provide a basis for predicting and targeting appropriate therapy in women with breast cancer.

9. Summary

It is without question that oestrogen has an important role in the etiology of most breast cancers and that cessation of ovarian function confers protection against this disease. Randomised evidence does show that combined HRT reduces the benefit in breast cancer risk reduction observed following the onset of the menopause. However, risk only appears to be increased with long-term use (>15 years). There are many further questions related to the impact of HRT on breast cancer that remain unanswered by available randomised data that are essential to understand if women are to be adequately counselled about its use. Breast cancer mortality and recurrence, which arguably are the most important end points paradoxically, may not be adversely affected and if randomised trials of HRT in breast cancer survivors confirm a lack of an adverse effect on prognosis, this will inevitably challenge our understanding of this complex disease further. As most women who use HRT do so for short durations that have not been associated with an increase in breast cancer risk and mammographic breast density is increased by HRT in a minority of women, it is unlikely that this pattern of use has a significant impact on the disease burden from breast cancer.

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