**FERTILITY AND STERILITY®**
*VOL. 73, NO. 2, FEBRUARY 2000*

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

# Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible?

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Received April 13, 1999; revised and accepted October 12, 1999.

Supported by Schering Health Care, Burgess Hill, Sussex, United Kingdom, and Wyeth Laboratories, Taplow, Maidenhead, Berkshire, United Kingdom.

Presented at The British Association of Surgical Oncology, Oxford, England, July 1996; British Oncology Association, St Andrews, Scotland, July 1996 and 1997; The International Menopause Congress, Sydney, Australia, 1996; FIGO, Copenhagen, 1997: Nottingham Breast Meeting, England, 1997.

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0015-0282/00/$20.00
PII S0015-0282(99)00510-5

**Objective:** To evaluate the feasibility of conducting a large randomized trial of HRT in symptomatic women with early-stage breast cancer.

**Design:** Open randomized study.

**Setting:** Outpatient clinics at The Royal Marsden and St. George's Hospitals, London.

**Patient(s):** One hundred postmenopausal women with early-stage breast cancer, experiencing vasomotor symptoms and/or vaginal dryness.

**Intervention(s):** Randomization (1:1) to HRT or no HRT for 6 months.

**Main Outcome Measure(s):** Acceptance, continuance rates, and the reasons eligible women declined study entry.

**Result(s):** Acceptance (38.8%) and continuance rates (>80%) were encouraging. The efficacy of HRT did not appear to be antagonized with concomitant tamoxifen. Seventy-five percent of women continued HRT after the study ended. Three women developed metastatic disease. Two used HRT.

**Conclusion(s):** Despite informed consent, a national UK randomized trial of HRT should be feasible and has now been planned. Successful implementation necessitates the provision of information about HRT and the estrogen deficiency side effects of breast cancer therapy to health professionals and women with breast cancer. (Fertil Steril® 2000;73:292–9. ©2000 by American Society for Reproductive Medicine.)

**Key Words:** Breast cancer survivors, estrogen deficiency symptoms, HRT, randomized trials

Estrogen deficiency symptoms are the most common side effect of adjuvant breast cancer therapy (i.e., ovarian ablation, chemotherapy, and the antiestrogen tamoxifen) and occur in up to 60% of women (1–3). Increasing numbers of symptomatic women with breast cancer are requesting advice on interventions to ameliorate them. At present, HRT is the most effective treatment available, but it is contraindicated for fear of stimulating disease recurrence. Despite this concern, in the absence of effective alternatives to HRT, it is being prescribed to such women on an ad hoc basis. To date, observational studies have not demonstrated whether HRT has an adverse effect on the prognosis of breast cancer survivors (4–10). However, in the absence of controlled, prospective data, definitive conclusions about the safety and efficacy of HRT cannot be made.

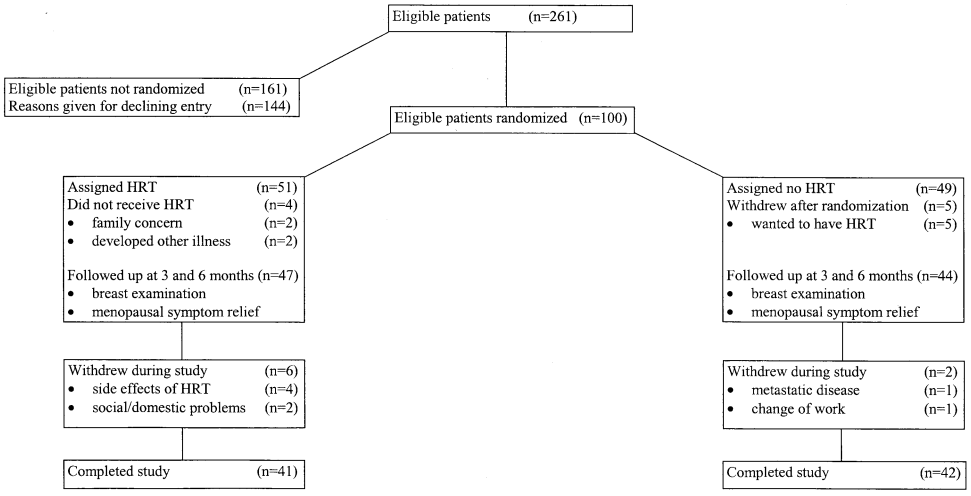
Given the potential benefits of HRT and the lack of any apparent detrimental effect on breast cancer survival, opinion is growing that it is ethical and appropriate to undertake randomized trial of HRT in this clinical context. Although a third of breast cancer patients questioned in surveys would be prepared to use HRT (2, 11), reluctance to take it has adversely influenced patient acceptance of a randomized trial initiated in the United States (12). We conducted a pilot study to determine whether symptomatic women with early-stage breast cancer in the United Kingdom would be willing to be randomized to HRT and, hence, whether a national trial is feasible.

## MATERIALS AND METHODS

The primary end points were to determine [1] the acceptance rate, i.e., the proportion of

**FIGURE 1**

Profile of the pilot HRT study describing the progress of patients from recruitment to study completion.

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eligible patients entering the study, [2] continuance of treatment after randomization, and [3] the effectiveness of HRT in relieving symptoms in patients treated with tamoxifen. We aimed to recruit 100 randomized patients. This study was approved by the respective hospitals' ethics committees before commencement, and all participating women gave their written, informed consent.

## Patients

Postmenopausal women (i.e., >1 year since their last menstrual period), with a previous diagnosis of in situ disease or stage I/II breast carcinoma were identified from preliminary inspection of medical records before their attendance at breast cancer follow-up clinics at The Royal Marsden and St. George's Hospital NHS Trusts, London.

These women completed a self-administered menopausal symptom questionnaire (13) during their clinic appointment to determine whether they were experiencing estrogen deficiency symptoms and, thus, were eligible to participate in the study. In addition, women completed the EORTC-QLC30 quality of life questionnaire (14). Details of their menstrual history and diagnosis and treatment of their breast cancer were obtained. Women were eligible irrespective of their current or previous breast cancer treatment. The questionnaire also documented attitudes to research, and all women were encouraged to comment about factors that influenced their decision whether to participate in the study.

Undiagnosed postmenopausal bleeding, severe liver disease, known drug or alcohol abuse, smoking >20 cigarettes/d, a history of venous thromboembolism without any predisposing factors, or use of an HRT implant within the last 5 years rendered women ineligible. Eligible women were given written and verbal explanations of the study and were contacted within 2 weeks for their decision about participation. The number of eligible women declining study entry was documented, and they were asked to complete a brief, postal questionnaire to determine their reasons.

On recruitment, these women were stratified according to current use of tamoxifen. The TAM − ve group was composed of both those who had never been prescribed tamoxifen and those who had taken the drug in the past. Women currently taking tamoxifen were in the TAM + ve group. The dose of tamoxifen used in this study was 20 mg/d.

Women were randomized (1:1) to HRT or no HRT for the 6-month duration of the study (Fig. 1). The HRT used in this study was either estradiol valerate 2 mg/d (Progynova; Schering Health Care Ltd., Burgess Hill, West Sussex, UK) in hysterectomized women or the same estrogen plus levonorgestrel 75 μg/d for 12 of 28 days (Nuvelle; Schering Health Care Ltd.) in those with an intact uterus. Continuance with HRT was assessed by direct questioning and by measurement of serum estradiol levels. Serum estradiol was measured by enzyme immunoassay using an ES300 immunoassay analyzer (Boehringer Mannheim, Lewes, East Sussex, UK). All patients were seen at 3 and 6 months when breast examination and the menopausal symptom questionnaire were repeated.

Women allocated to HRT who experienced unacceptable side effects or inadequate relief of their symptoms after 3 months had their HRT prescription changed. Reasons for withdrawal from the study were recorded. Documentation

was made of any patients experiencing disease recurrence. At the study end, HRT-treated women were given the option of continuing with it; women allocated to the no HRT arm of the study were given the option of starting HRT.

### Statistical Analysis

A total of 100 women were randomized so that continuance with HRT and no HRT could be estimated in 50 patients, with a 95% confidence interval of at most ±15%. With adequate counseling, short-term HRT continuance rates in healthy women approach 80% (15), and it was our aim to achieve comparable rates.

Nonparametric statistical methods were used throughout for analysis. The $\chi^2$ test or Fisher's exact test was used to look for associations between categorical variables. The Kruskal-Wallis test and Mann-Whitney *U* test were used to compare two or more groups, respectively, if one of the factors was ordinal. $P > .05$ was considered nonsignificant. Changes within patients were assessed with use of the Wilcoxon signed-rank pairs test. The limit of detection of the estradiol assay was 50 pmol/L; values below this were considered to be 50 pmol/L for the purpose of analysis.

## RESULTS

Recruitment into the pilot study started in September 1994 and ended in January 1996. Review of women attending breast follow-up clinics identified 261 who fulfilled all the eligibility criteria. The main reason that women were ineligible was that they were asymptomatic (n = 95). A small number, however, were either already using HRT (n = 24) or the gonadomimetic agent tibolone (Livial; Organon Laboratories Ltd., Cambridge, UK) (n = 2) for symptom control.

The acceptance rate of the pilot study was 38.3% (100 of 261 women). Of the 100 women recruited, 51 were not currently taking tamoxifen (TAM − ve), whereas 49 did take the drug (TAM + ve). Fifty-one women were randomized to receive HRT. This was an open study, and not all women were satisfied with their randomization decision. Seven withdrew from the study at the start: five wanted HRT but were not randomized to this therapy, whereas family concern prompted the withdrawal of two women randomized to HRT. Two women allocated to HRT withdrew before commencing it because of other illness unrelated to their breast cancer. An additional eight women withdrew from the study over the 6 months: three because of work commitments, four because of HRT side effects, and one as a result of the development of metastatic breast cancer (Fig. 1).

The characteristics of women accepting and refusing entry into the study are compared in Table 1. A significantly greater proportion of women accepting study entry had previously had a hysterectomy and had a positive family history of osteoporotic fractures. This group of women was also more likely to be participating in a clinical trial and was less anxious about research. They did, however, experience more frequent and severe hot flashes, and significantly more were affected by night sweats and had more severe vaginal dryness. These women had a worse global quality of life ($P < .001$) with significant reductions in cognitive functioning ($P = .05$), increased sleep disturbance ($P < .001$), and fatigue ($P < .001$).

Comments from women participating in this study demonstrated that the provision of information by clinicians about the estrogen deficiency side effects of their breast cancer therapy was deemed to be inadequate. A survey of estrogen deficiency symptoms was therefore welcomed as some women had previously sought, or were intending to seek, advice about their treatment. Being approached by clinicians in breast follow-up clinics about these symptoms was seen as a positive action. Anxiety about HRT had often been generated by a lack of consensus between hospital specialists, general practitioners, and contradictory media reports about the use of HRT in women with breast cancer and its associated side effects. In addition to the opportunity to obtain relief from estrogen deficiency symptoms, other positive aspects of study participation were the perceived benefit of early detection of recurrent disease with regular follow-up and the lack of any placebo arm. For some, factors unrelated to the specifics of the study, such as the reputation of the hospital and feelings of altruism, were important in their decision to take part.

The response rate to the postal questionnaire administered to women declining study entry was 89.4% (144 of 161). Most of these women did not want to use HRT (87%, 125 of 144) although 9% (13 of 144) did. Four percent (6 of 144) had no preference. Those expressing a treatment preference for no HRT (72%, 91 of 125) were either very or somewhat concerned about disease recurrence; however, there was no statistically significant association between the desire not to have HRT and the perceived fear of risk of recurrence with its use. This treatment preference was not significantly influenced by the severity of estrogen deficiency symptoms experienced.

Most women (87%) declining study entry did not want to use HRT. Fear of disease recurrence was an important factor in this decision, particularly in those women who blamed prior exposure to HRT for causing their breast cancer. However, some stated that concern about the potential side effects of HRT rather than fear of recurrence was an important factor in their decision. In common with women who did participate in this study, inconsistent medical and lay advice about HRT had provoked anxiety about its use.

Estradiol assays confirmed that women were compliant with HRT. At 6 months, three women randomized to receive HRT had serum estradiol levels of <50 pmol/L. At the end of the study, 75.6% (31 of 41) of the women taking HRT wanted to continue its use. The main reason for stopping was that symptom relief did not match with expectations of

**TABLE 1**

Comparison of women refusing and accepting study entry.

| Characteristic | Group: Women who declined (n = 161) | Group: Women who agreed (n = 100) | *P* value |
|---|---|---|---|
| Median age in y (range) | 58 (42–69) | 56 (43–82) | NS |
| Median time (mo) from diagnosis (range) | 34 (2–275) | 37 (2–215) | NS |
| Median time (y) from menopause (range) | 8 (12–30) | 6 (12–30) | NS |
| Hysterectomy ± bilateral salphingo-öophorectomy (%) | 21 | 33 | .05 |
| Previous tamoxifen therapy (%) | 12 | 26 | .005 |
| Family history fractures (%) | 9 | 21 | .01 |
| Participation in clinical trials (%) | | | |
| Currently participating in a trial | 19 | 34 | <.01 |
| Concerned about being in any trial | 62 | 29 | <.001 |
| Concerned used as a "guinea pig" | 73 | 36 | <.007 |
| Research does more harm than good | 32 | 14 | .007 |
| Symptoms* | | | |
| Hot flashes | | | |
| Proportion (%) | 80 | 79 | NS |
| Median frequency (range) | 9 (1–105) | 17.5 (1–168) | .001 |
| Median severity (range) | 3.15 (1–10) | 4.3 (1–10) | .006 |
| Night sweats | | | |
| Proportion (%) | 47 | 66 | .004 |
| Median frequency (range) | 7 (0–4.3) | 9.75 (1–42) | NS |
| Median severity (range) | 3.3 (1–10) | 3.7 (1–10) | NS |
| Vaginal dryness | | | |
| Proportion (%) | 47 | 54 | NS |
| Median severity (range) | 3.5 (0–10) | 5.8 (0–10) | .005 |

*Note:* NS = not significant.

* All scores are derived from the Menopausal Symptom Questionnaire. The greater the value, the more severe the symptoms experienced. Positive values indicate symptom improvement, 0 no change, negative values that symptoms are worse. Proportions were compared using the $\chi^2$ test; frequency and severity scores were compared with the Mann-Whitney *U* test.

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benefit. Three women were concerned about recurrence of their disease with continued use. Continuance in the no HRT arm of the study at 6 months was 85.7% (42 of 49). Fifty percent (21 of 42) of women in the no HRT group wanted to commence HRT, 40.5% (17 of 42) did not, and 9.5% (4 of 42) were undecided.

To date, three women have developed recurrent breast cancer, two of which were taking HRT. One was randomized to receive opposed HRT 38 months after diagnosis and developed recurrence after taking HRT for 2 years. The second patient received unopposed HRT 9 years after diagnosis and developed recurrent disease after only 6 weeks of treatment. The third patient, who never took HRT, developed recurrent disease 6 months after her initial diagnosis.

Comparison of women randomized to receive either HRT or no HRT at baseline did not demonstrate any statistically significant differences in the incidence, frequency, or severity of the estrogen deficiency symptoms experienced (Table 2). These two groups of women were otherwise well matched, with the exception that those allocated to HRT were younger ($P=.03$) and significantly more had grade III tumors. To determine the effect of tamoxifen on estrogen deficiency symptoms, comparison was made between women in the TAM + ve and TAM − ve groups. A greater proportion of women using tamoxifen experienced hot flashes and night sweats and nonsignificant trends toward an increase in their frequency and a decrease in the severity of vaginal dryness were found (Table 3).

After 3 months of treatment with HRT, there was a significant reduction in the proportion of women experiencing vasomotor symptoms, their frequency and the distress associated with them. These significant reductions were sustained at 6 months. Hormone replacement therapy did not significantly affect the proportion of women complaining of vaginal dryness although this was less problematic by 3 months ($P<.05$) (Table 3). Although a significant reduction in the severity of hot flashes ($P=.003$) and night sweats ($P<.05$) was observed after 6 months in women not receiving HRT, symptom improvement was not as pronounced as that reported in women taking HRT. Patient numbers in this study were too small to determine whether there was any variation in the efficacy of opposed or unopposed HRT. The

**TABLE 2**

Comparison of women accepting study entry and the impact of HRT on symptoms.

| Characteristic | No HRT (n = 49) | HRT (n = 51) | *P* value |
|---|---|---|---|
| Median age (y) (range) | 55 (43–66) | 58 (45–82) | .03 |
| Median time (mo) from diagnosis (range) | 36 (4–139) | 40 (2–215) | NS |
| Median time (y) from menopause (range) | 5 (0–23) | 7 (1–25) | NS |
| Median BMI (kg/m$^2$) (range) | 25.8 (19.6–43.4) | 26.2 (19.7–35.5) | NS |
| Current tamoxifen use (%)* | 49 | 49 | NS |
| Symptoms† | | | |
| Hot flashes | | | |
| Baseline | | | |
| Proportion (%) | 82 | 76 | NS |
| Median frequency (range) | 10.5 (0–148.5) | 11.71 (0–168) | NS |
| Median severity (range) | 3.7 (0–10) | 3.0 (0–9.3) | NS |
| 3 Months | | | |
| Proportion (%) | 74 | 45 | .008 |
| Median frequency (range) | 0 (−101–29) | 8.5 (−179–168) | .004 |
| Median severity (range) | 0.3 (−5–4) | 2.0 (−1.4–7.7) | .008 |
| 6 Months | | | |
| Proportion (%) | 67 | 29 | .003 |
| Median frequency (range) | 0.5 (−40–33) | 8.5 (0–168) | .004 |
| Median severity (range) | 0.7 (−2.7–6) | 2.3 (0–7.3) | .006 |
| Night sweats | | | |
| Baseline | | | |
| Proportion (%) | 57 | 75 | NS |
| Median frequency (range) | 1.75 (0–28) | 5 (0–42) | NS |
| Median severity (range) | 1.7 (0–10) | 2.3 (0–9.7) | NS |
| 3 months | | | |
| Proportion (%) | 50 | 26 | .025 |
| Median frequency (range) | 0 (−21–14.5) | 5 (−28–42) | .0002 |
| Median severity (range) | 0 (−4–4) | 2 (−3.7–10) | .0001 |
| 6 Months | | | |
| Proportion (%) | 42 | 18 | .04 |
| Median frequency (range) | 0 (−19–28) | 4.5 (−3.5–28) | .008 |
| Median severity (range) | 0 (−3–4.3) | 3 (0–9.3) | .0001 |
| Vaginal dryness | | | |
| Baseline | | | |
| Proportion (%) | 53 | 55 | NS |
| Median severity (range) | 0.5 (0–10) | 1.25 (3–10) | NS |
| 3 months | | | |
| Proportion (%) | 43 | 36 | NS |
| Median severity (range) | 0 (−7.5–10) | 0 (−3.7–10) | .05 |
| 6 Months | | | |
| Proportion (%) | 41 | 21 | NS |
| Median severity (range) | 0 (−3.5–8.5) | 0 (−4–10) | NS |

*Note:* NS = not significant.

* Median duration of use 24 (5–54) months.

† Scores derived from the Menopausal Symptom Questionnaire. The greater the value, the more severe the symptoms. Positive values indicate symptom improvement, 0 no change, negative values that symptoms are worse. The $\chi^2$ test was used to compare proportions, the Mann-Whitney *U* test to compare frequency and severity scores.

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effectiveness of HRT in controlling symptoms did not appear to be reduced with the concurrent use of tamoxifen.

## DISCUSSION

Despite informed consent, the acceptance of this pilot study (38.3%) among symptomatic women with breast cancer is similar to that predicted by surveys that have shown that between 30% and 50% of women with breast cancer would use HRT for the relief of estrogen deficiency symptoms if it was given under specialist medical supervision (2, 11). Furthermore, clinical decision analysis suggests that women would be prepared to accept a 33% increase in the relative risk of developing breast cancer recurrence with

**TABLE 3**

Comparison of women at baseline according to tamoxifen use.

| Characteristic | TAM − ve (n = 51) | TAM + ve (n = 49) | *P* value |
|---|---|---|---|
| Median age (y) (range) | 55 (43–70) | 55 (45–82) | NS |
| Median time (mo) from diagnosis (range) | 66 (2–215) | 17 (3–121) | <.001 |
| Median time (y) from menopause (range) | 5 (0–23) | 7 (1–25) | NS |
| Hysterectomy ± bilateral salphingo-öophorectomy (%) | 31 | 35 | NS |
| Median duration of tamoxifen in months (range) | 24 (3–84)* | 24 (5–54) | NS |
| Women treated with previous chemotherapy (%) | 11 | 17 | NS |
| Women treated with previous radiotherapy (%) | 26 | 30 | NS |
| Women who had surgery indicated (%) | | | |
| Mastectomy | 8 | 6 | |
| Mastectomy + reconstruction | 7 | 5 | |
| Breast conserving surgery | 36 | 38 | NS |
| Symptoms** | | | |
| Hot flashes | | | |
| Proportion (%) | 71 | 88 | .05 |
| Median frequency (range) | 6 (0–168) | 15 (0–45) | NS (.06) |
| Median severity (range) | 3 (0–10) | 3.7 (0–10) | NS |
| Night sweats | | | |
| Proportion (%) | 53 | 80 | .01 |
| Median frequency (range) | 12 (0–28) | 7 (0–42) | NS (.053) |
| Median severity (range) | 1 (0–10) | 2.3 (0–10) | NS |
| Vaginal dryness | | | |
| Proportion (%) | 63 | 45 | NS |
| Median severity (range) | 2.7 (0–10) | 0 (0–10) | NS (.07) |

*Note:* NS = not significant.

* Ex-users of tamoxifen, n = 25; medium time since stopping tamoxifen 12.5 (4–33) months.

** All scores are derived from the Menopausal Symptom Questionnaire. The greater the value, the more severe the symptoms experienced. Positive values indicate symptom improvement, 0 no change, negative values that symptoms are worse. Proportions were compared with the $\chi^2$ test; frequency and severity scores were compared with the Mann-Whitney *U* test.

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HRT if they could obtain relief from troublesome estrogen deficiency symptoms (16).

The acceptance rate of this pilot study seems to be significantly greater than that observed in a randomized trial of HRT in women with early-stage breast cancer that has been instigated in the United States where an acceptance rate of 17% (72 of 417) has been reported (12). This difference could be explained if women were concerned about recurrence with prolonged HRT exposure because the treatment duration in the pilot study was only 6 months, compared with 5 years in the latter study. However, the fact that most women allocated to HRT in the pilot study wanted to use it beyond 6 months does not necessarily support this.

Continuance rates in this study were high (>80%) in each treatment arm. Most women withdrew within the first 3 months, with over half (10 of 18) doing so immediately after randomization because they or their family were uncomfortable with the treatment allocation. Only a small number of women (5 of 49, 10%) withdrew from the no HRT arm of the study because they wanted to receive HRT. The remaining women who withdrew were predominantly using HRT and experienced side effects attributed to its use. This attrition rate could be considered as unacceptably high for a longer-term randomized controlled trial, but it is anticipated that most women will withdraw within the first few months only; therefore, continuance will be sufficient for the findings of a longer-term trial to be applicable.

Although 60% of eligible women declined entry into the pilot study, this does not necessarily imply that a larger-scale trial cannot be conducted. We have estimated that a total of 2,800 women will need to be recruited into a national, randomized trial to have a 90% chance of excluding a deleterious effect of HRT of >5% (90% power, one-sided 5% significance level). All 100 women participating in the pilot study were recruited in just over 1 year by one dedicated researcher. Thirty breast units recruiting at the same rate would complete recruitment for a national UK trial within 3 years. In conjunction with the observed high continuance rates and desire to continue with HRT after study completion, a larger-scale trial can be implemented successfully.

The quantitative end points of this pilot study suggest that a larger-scale trial is feasible, but they do not indicate issues relevant to women with breast cancer, which could impinge

on their decision to participate in such a trial. Therefore, comments of women accepting and declining entry into this pilot study were documented to gain potential insight into this aspect of trial implementation.

Because of the theoretical risk of promotion of disease recurrence with HRT, the finding that women entering our study experienced vasomotor symptoms to a greater degree than those who refused was not unexpected. Others, however, commented that a personal or family history of cardiovascular disease or osteoporosis was an equally important factor in their decision. Important issues emerging from this patient feedback were the confusion that existed about the cause of estrogen deficiency symptoms, the role that breast cancer therapy played in symptom etiology, and the lack of available, up-to-date information about HRT.

Although some women declining study participation could not accept the theoretical uncertainty of disease recurrence associated with HRT and in this respect mirrors the experience of investigators in the United States (12), this was not exclusively the reason for their decision. A small proportion was very anxious about research and simply unwilling to participate in any trial, regardless of the subject matter. It is unlikely that this well-recognized attitude of some women toward clinical trials can be overcome (17).

Many women expressed altruistic tendencies, agreed with the ethos of clinical trials and thought that it would be a good idea to evaluate HRT in this clinical setting. However, there was reluctance to be exposed to any drug-related side effects; this opinion was reinforced in a significant proportion of women (20%) who commented that side effects of their breast cancer therapy, especially tamoxifen, had been unpleasant and unexpected, and, therefore, they would not participate in further drug trials.

The HRT side effects were perceived to be troublesome, particularly withdrawal bleeding and weight gain. Avoidance of the former may account for the fact that a significantly greater proportion of the women participating in this pilot study previously had had a hysterectomy. The introduction of continuous combined HRT preparations, which were unavailable when the pilot study was initiated, is expected to increase the acceptance and continuance rates of a future trial (15, 18). Demand for accurate information about treatment side effects is not a new finding (19). However, to our knowledge, this is the first demonstration of recruitment into a breast cancer trial being negatively influenced by an inadequate level of information about therapy administered previously in a clinical or trial setting.

Tamoxifen has been shown to significantly increase the incidence and severity of estrogen deficiency symptoms in both premenopausal and postmenopausal women (20, 21). Although women using tamoxifen in this pilot study were found to have an increase in the prevalence and a trend toward an increased frequency of vasomotor symptoms, these changes were not statistically significant. However, the fact that the median duration of tamoxifen treatment was 2 years might account for this finding because prospective randomized data have shown that tamoxifen-induced vasomotor symptoms decline with prolonged use for $>2$ years (22). The efficacy of HRT has been reported to be reduced when prescribed concomitantly with tamoxifen (7).

In this study, however, comparable symptom control was achieved with HRT, irrespective of tamoxifen use, suggesting that in combination, tamoxifen and HRT may not be antagonistic, at least in the control of estrogen deficiency symptoms. Interim analysis of The Royal Marsden Hospital tamoxifen chemoprevention trial has not demonstrated any obvious antagonism for breast cancer incidence in women taking both tamoxifen and HRT (23), but the Italian chemoprevention trial has reported that tamoxifen reduces breast cancer risk in women exposed to HRT (24). These interim analyses should be treated with caution, however, because the evaluation of breast cancer risk in women taking both tamoxifen and HRT was not a primary hypothesis of either of these prevention trials.

Despite conventional wisdom that HRT may promote the outgrowth of distant metastases, endocrine manipulation may have a paradoxical protective effect (25), and promotion of metastases might be compensated for by a reduction in mortality from cardiovascular disease and osteoporosis. We have demonstrated that it is feasible to conduct a large randomized trial of HRT in women with previous breast cancer, and a national UK trial has now been established in which women with early-stage breast cancer will be randomized to HRT for 2 years for the relief of estrogen deficiency symptoms. This will not be a placebo-controlled trial because patient feedback demonstrated that women would not participate in such a trial if it were. Furthermore, because sequential HRT induces regular withdrawal bleeding in 75% of women and 40% of women prescribed continuous combined HRT may experience initial irregular bleeding, it would be both impractical and unethical to administer a placebo, which induces these effects. We have shown that the successful implementation of a national trial will depend on the provision of clear information and continued support to both women and health professionals involved in their care to ensure that common misconceptions about adjuvant breast cancer therapy and HRT side effects are overcome and continuance with or without HRT maintained. This issue has been addressed in the design of the planned UK trial.

*Acknowledgments:* The authors thank Roy Sherwood, M.D., and members of the Department of Clinical Biochemistry, King's College School of Medicine and Dentistry, London, for performing the estradiol assays, Liz Grimsy and Sue Lowndes, the breast care sisters at St. George's Hospital

Trust and all the outpatient nursing staff at The Royal Marsden Hospital Trust, London and Sutton.

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