BRIEF COMMUNICATIONS

Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial

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In 1997 two independent randomized clinical trials, Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS; 434 patients) and the Stockholm trial (378 patients), were initiated in Sweden to compare menopausal hormone therapy with no menopausal hormone therapy after diagnosis of early-stage breast cancer. Much of the design of both studies was similar; however, a goal of the Stockholm protocol, not shared with the HABITS trial, was to minimize the use of progestogen combined with estrogen. The HABITS trial was prematurely stopped in December 2003, because, at a median follow-up of 2.1 years, the risk for recurrence of breast cancer among patients receiving menopausal hormone therapy was statistically significantly higher (relative hazard [RH] = 3.3, 95% confidence interval [CI] = 1.5 to 7.4) than among those receiving no treatment. In the Stockholm trial, however, at a median follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with menopausal hormone therapy (RH = 0.82, 95% CI = 0.35 to 1.9). Statistically significant heterogeneity in the rate of recurrence was observed (*P* = .02; two-sided likelihood-ratio test) between the two studies, indicating that chance may not be the only explanation. Doses of estrogen and progestogen and treatment regimens for menopausal hormone therapy may be associated with the recurrence of breast cancer. [J Natl Cancer Inst 2005:97:533–5]

In 1997 two independent randomized trials were started in Sweden to assess the effects of menopausal hormone therapy after a diagnosis of breast cancer: the Hormonal Replacement Therapy after Breast Cancer—Is It Safe? (HABITS) trial and the Stockholm randomized trial. Because of slow recruitment in both trials, a joint steering committee for the two studies was formed and agreed to perform a joint safety assessment in 2002 and, eventually, a joint analysis. Although there were differences in study design, including the type of menopausal hormone therapy used, the trials were judged sufficiently similar to permit a joint analysis: both trials compared menopausal hormone therapy with no menopausal hormone therapy in patients with early-stage breast cancer. Each study alone would probably not have achieved sufficient statistical power to detect an increased risk of recurrence exceeding 6% ($1 - \beta = .80$; $\alpha = .05$). An independent data monitoring committee was organized, and a protocol for the joint analyses was selected.

On the recommendation of the data monitoring committee, the HABITS trial was prematurely stopped in December 2003 *(1)*. In that study at a median follow-up of 2.1 years, the risk for breast cancer recurrence associated with menopausal hormone therapy was statistically significantly higher (relative hazard [RH] = 3.3, 95% confidence interval [CI] = 1.5 to 7.4) than that with no menopausal therapy. In contrast in the Stockholm trial at a median follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with menopausal hormone therapy (RH = 0.82, 95% CI = 0.35 to 1.9). There was also statistically significant heterogeneity in the risk of breast cancer recurrence between the two studies (*P* = .02; two-sided likelihood-ratio test). The joint analysis of the two trials showed that the risk of breast cancer recurrence was statistically significantly associated with menopausal hormone therapy (RH = 1.8, 95% CI = 1.03 to 3.10), compared with no menopausal hormone therapy. After extensive discussions between the Stockholm group and the data monitoring committee, the Stockholm trial was stopped in December 2003, despite the lack of an increased risk of breast cancer recurrence among the patients in the menopausal hormone therapy group.

The Stockholm trial was a randomized open study with two parallel groups; postmenopausal patients in the Stockholm region, who had undergone surgery for a primary operable and histologically verified breast cancer, were invited to participate. All patients younger than 70 years were eligible after primary surgery, irrespective of time since surgery, stage of disease, hormone receptor status, and concomitant adjuvant treatment.

After providing informed consent to participate in the trial, patients were randomly assigned to receive menopausal hormone therapy for 5 years (n = 188) or to receive no menopausal hormone therapy (n = 190). Randomization was done by telephone to a central office where patient identifiers were recorded before the treatment allocation was revealed to the responsible physician. The randomization was performed with balanced lists prepared according to a permuted block technique with a block size of six. Stratification was done on the basis of the following three parameters: 1) use of adjuvant endocrine treatment (tamoxifen versus no tamoxifen); 2) type of menopausal hormone therapy that would be used if the patient was allocated to menopausal hormone therapy (cyclic estradiol plus medroxyprogesterone acetate versus "spacing out" estradiol plus medroxyprogesterone acetate versus estradiol valerate alone); and 3) time since primary diagnosis (less than 2 years or 2 years or more).

Cyclic hormonal treatment was recommended for patients younger than 55 years in the menopausal hormone therapy group and consisted of 2 mg of cyclic estradiol for 21 days with the addition of 10 mg of medroxyprogesterone acetate for the last 10 days, followed by 1

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Table 1. Clinical characteristics of patients with available follow-up information in the Stockholm trial

	HT*	No HT
Total No. randomly assigned	188	190
No. with follow-up available	175	184
Median follow-up, y (range)	4.1 (0.2–7)	4.2 (0.3–6)
Time from primary breast cancer diagnosis to randomization, y (range)	1.3 (0.1–16)	1.4 (0.1–20)
Median age, y (range)	56.9 (42–69)	57.5 (44–70)
Lymph node–positive disease, No./No. tested (%)	28/172 (16)	37/183 (20)
Estrogen receptor–positive disease, No./No. tested (%)	113/175 (65)	103/184 (56)
Estrogen receptor status unavailable/unknown, No./No. tested (%)	40/175 (23)	54/184 (29)
Breast-conserving surgery, No./No. tested (%)	123/175 (70)	135/184 (73)
HT before diagnosis, No./No. tested (%)	132/174 (76)	129/177 (73)
Concomitant adjuvant tamoxifen, No./No. tested (%)	91/175 (52)	98/184 (53)

*HT = menopausal hormone therapy.

week with no treatment. The spacing out regimen was recommended for patients 55 years or older and consisted of 2 mg of estradiol for 84 days with the addition of 20 mg of medroxyprogesterone acetate for the last 14 days, followed by 1 week with no treatment. The choice of treatment was typically based on patient age but, in fact, was ultimately decided by the responsible physician. Patients who had had a hysterectomy in the menopausal hormone therapy group were given continuous treatment with 2 mg of estradiol valerate daily.

Patients in the group receiving no menopausal hormone therapy were asked to refrain from use of all types of menopausal hormone therapy. Local vaginal treatment with low-dose estrogen gels or vagitories was allowed.

The study was performed according to World Health Organization Guidelines for Good Clinical Practice and the revised version of the Declaration of Helsinki. The protocol was approved by the Regional Ethics Committee of the Karolinska Institute (on April 22, 1997; registration number 96–153), and all women provided their informed consent to participate.

Follow-up visits were scheduled every 6 months for the first 5 years after the primary diagnosis and, thereafter, every 12 months for the next 5 years, for a total of 10 years of follow-up. Routine visits included a physical examination and an annual mammogram. Chest x-rays, bone scans, blood tests, biopsy examinations, and other tests, as required, were done if clinical signs or symptoms indicated possible relapse. Local recurrence was diagnosed by needle aspiration biopsy examination and mammography. Distant metastases were assessed by skeleton scintigraphy, ultrasound, computed tomography scan, and x-ray and, when possible, by needle aspiration biopsy examination. Clinical records of all patients with a reported recurrence were reviewed centrally.

The primary end point was recurrence-free survival. End points in these calculations were locoregional recurrence, distant metastasis, contralateral breast cancer, or death attributed to breast cancer. Patients were censored if they died from causes other than breast cancer or were lost to follow-up. Secondary end points were type of breast cancer recurrence, cause-specific mortality, and new primary cancers. All analyses were done on an intent-to-treat basis, that is, patients were analyzed according to their allocated treatment.

The Stockholm trial was prematurely closed for patient entry in December 2003; at that time, a total of 378 postmenopausal women had agreed to participate (Table 1). The Stockholm trial steering committee based this decision primarily on considerations related to patient safety and on the fact that it probably would be difficult to achieve sufficient recruitment and statistical power to detect an increased risk of recurrence exceeding 6%, given the HABITS results.

Among the 188 patients who had been randomly assigned to receive menopausal hormone therapy, 42 (22%) started cyclic estradiol and medroxyprogesterone acetate, 94 (50%) started spacing out estradiol and medroxyprogesterone acetate, and 43 (23%) started estradiol valerate alone. Information was incomplete on type of menopausal hormone therapy used for nine (5%) patients.

During follow-up, the following patients were switched to alternative menopausal hormone therapy regimens for various reasons, including subjective side effects or irregular bleeding: eight (19%) patients on cyclic estradiol and medroxyprogesterone acetate, 15 (16%) patients on spacing out estradiol and medroxyprogesterone acetate, and one (2%) patient on estradiol valerate alone. Compliance for 2 years or more of treatment among those patients in the menopausal hormone therapy group who entered the trial before 2002 was assessed by information in medical records and found to be 77%. In the control group, approximately 10% of the patients had taken some form of menopausal hormone therapy after they had entered the trial.

At a median follow-up of 4.1 years (end date for follow-up = January 2004) in the Stockholm trial, there was a total of 24 breast cancer recurrences: 11 in the menopausal hormone therapy group and 13 in the control no-treatment group (Table 2). The total number of deaths in the menopausal hormone therapy group was four (two from breast cancer) and in the control group nine (four from breast cancer).

In contrast to the HABITS trial, the Stockholm trial found that the risk of breast cancer recurrence was not associated with the use of menopausal hormone therapy among patients with early-stage breast cancer *(1)*. The report on the HABITS trial *(1)* suggested that the differential findings in the two trials could be due to chance. However, we found statistically significant heterogeneity between the two studies ($P = .02$), indicating that chance may not be the only explanation. Differences in the design and in clinical characteristics of the patients in the two studies may also have contributed to the differences in their results. For example, the proportion of lymph node–positive patients was higher in the HABITS trial than in the Stockholm trial (26% versus 16%, respectively), and fewer patients received concomitant adjuvant tamoxifen therapy in the HABITS trial than in the Stockholm trial (21% versus 52%, respectively). In addition, the Stockholm protocol attempted to minimize the use of progestogen in combination with estrogen. In contrast to the HABITS trial, the Stockholm trial recommended that patients avoid continuous combined treatment with estrogen and progestogen and use regimens that incorporated 1 week of no treatment every 1 (cyclic regimen) or 3 (spacing out regimen) months.

Table 2. Clinical data on the 24 patients with breast cancer recurrence (median follow-up = 4.1 years)

	HT*	No HT
Total No. with recurrence	11	13
Recurrence-free interval†, No.		
<1 y	3	3
1–2 y	2	6
>2 y	6	4
Type of recurrence, No.		
Locoregional	5	5
Distant	3	5
Contralateral breast	3	3
Axillary lymph node status at primary surgery, No.		
Positive	4	5
Unavailable/unknown	2	2
Concomitant tamoxifen, No.	5	4
Estrogen receptor–positive disease, No.	7	8
Previous HT, No.	8	8

*HT = menopausal hormone therapy.

†From study entry.

These treatment recommendations were based on the following results, available when the trial was initiated, that indicated differential effects on the breast when treatment with estrogen alone was compared with combined treatment with estrogen and progestogen *(2–4)*. First, breast cell proliferation is increased only during the luteal phase of the menstrual cycle when levels of both estrogen and progesterone are high *(2)*. Second, using a relevant prospective monkey model for menopausal hormone therapy, we reported statistically significantly higher proliferation in the breast during continuous combined estrogen and progestogen treatment than during estrogen-only treatment *(3)*. Finally, cyclic discontinuation of hormonal treatment was hypothesized to decrease the expression of local growth factors in breast tissue and to initiate and stimulate apoptosis *(4)*.

Evidence has recently been accumulating to indicate that the combination treatment with estrogen and progestogen may carry a greater risk of breast cancer than treatment with estrogen alone. Several epidemiologic studies have clearly indicated an increased risk for breast cancer in postmenopausal women on combined estrogen and progestogen therapy *(5–7)*. In addition, the prospective data from the Women's Health Initiative, a large randomized trial, indicated an increased risk associated with combined menopausal hormone therapy *(8)*, but the risk, if any, associated with estrogen-only treatment is much more uncertain. In fact, the Women's Health Initiative recently reported *(9)* no increase in the risk of breast cancer associated with an average of 7 years of treatment with estrogen alone but rather a statistically non-significant trend toward a reduced risk (RH = 0.77, 95% CI = 0.59 to 1.01).

In the Stockholm trial, 73% of the women were first assigned to menopausal hormone therapy containing either estrogen alone or the spacing out regimen, in which progestogen was given for only 14 days at 3-month intervals. This protocol could provide one explanation for the lack of difference in breast cancer recurrence between the menopausal hormone therapy group and the no treatment group in the Stockholm trial. However, because of the premature termination of the trial and the limited number of patients included, no firm conclusions are possible.

A greater percentage of women were treated with adjuvant tamoxifen in the Stockholm trial than in the HABITS trial (52% versus 21%, respectively). As shown by the Italian tamoxifen trial, tamoxifen may reduce the increased risk of breast cancer associated with estrogen therapy *(10)*. Thus, the use of adjuvant therapy with tamoxifen may have been associated with the reduced risk of breast cancer recurrence.

In summary, the safety analysis for two independent studies on menopausal hormone therapy in patients with early-stage breast cancer showed statistically significantly different results with respect to its association with the risk of breast cancer recurrence. Although it is tempting to speculate that treatment regimens with estrogen and a minimum of progestogen may be safe, the management of menopausal symptoms and quality of life for patients with breast cancer remains an important unsolved problem. Because doses of estrogen and progestogen and treatment regimens may be associated with the recurrence of breast cancer, there is an urgent need to identify safe and effective strategies to manage menopausal symptoms and improve the quality of life for patients with breast cancer.

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Notes

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