

## Research letters

## 📄 HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped

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**In the 1990s, two randomised clinical trials started in Scandinavia addressing whether hormone replacement therapy (HRT) is safe for women with previous breast cancer. We report the findings of the safety analysis in HABITS (hormonal replacement therapy after breast cancer—is it safe?), an open randomised clinical trial with allocation to either HRT or best treatment without hormones. The main endpoint was any new breast cancer event. All analyses were done according to intention-to-treat. Until September, 2003, 434 women were randomised; 345 had at least one follow-up report. After a median follow-up of 2.1 years, 26 women in the HRT group and seven in the non-HRT group had a new breast-cancer event. All women with an event in the HRT group and two of those in the non-HRT group were exposed to HRT and most women had their event when on treatment. We decided that these findings indicated an unacceptable risk for women exposed to HRT in the HABITS trial, and the trial was terminated on Dec 17, 2003.**

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Treatment of menopausal symptoms in breast-cancer survivors is a highly relevant clinical problem for several reasons. Due to increased incidence and improved survival, the number of premenopausal women who survive breast cancer and experience climacteric symptoms has increased. Modern hormonal and cytotoxic treatments may induce early menopause. There has been an increasing focus on quality of life both in cancer treatments and around the menopause in general. Observational findings suggest that the risk of impairing prognosis by giving hormone replacement therapy (HRT) to breast cancer survivors is low.<sup>1,2</sup> However, the increased risk of breast cancer—and possibly also mortality—in healthy women taking HRT and the hormonal dependence of a large proportion of breast cancers call for caution.<sup>3–5</sup>

Several trials investigating the safety of recommending HRT for menopausal symptoms in survivors of breast cancer started in the 1990s. On Dec 17, 2003, the steering committee of the HABITS study (Hormonal replacement therapy after breast cancer diagnosis—is it safe?) decided to stop the trial and recommend that all patients on HRT stop treatment. The decision was based on information from the data monitoring committee (DMC) and analyses from the trial secretariat prompted by the report from the DMC. We report the findings of the safety analyses and the reasons for the early termination of the trial.

The HABITS trial started to recruit women in May, 1997, to investigate whether a 2-year HRT treatment for menopausal symptoms was safe in women with a previously treated breast cancer. The main endpoint was any new breast cancer event. The trial was designed as a non-inferiority study<sup>6</sup>

and was dimensioned to exclude a relative hazard (RH) equal to or greater than 1.36 comparing HRT with no HRT. With a median follow-up of 5 years and a 5-year relapse rate equal to 20% in the control group, a total sample size of 1300 women was needed for a one-sided test with significance level 5% (at RH=1.36) and power 80% when there was no increased risk (RH=1.00).

Women were eligible if they had previously completed treatment for Tis up to stage II breast cancer (less than four positive nodes), were free of recurrence, had no other cancer or serious disease, had no contraindication for HRT (active cardiovascular disease was added as a contraindication in 2001), and had menopausal symptoms deemed by the patient and the doctor to need treatment. Treatment with adjuvant tamoxifen was allowed.

Local networks of oncologists, surgeons, and gynaecologists recruited, randomised, and followed up the participants. Centres in Scandinavia from the International Breast Cancer Group and from the European Organisation for Research and Treatment of Cancer joined the study. The trial protocol is available at <http://www.roc.se>. Randomisation was done by telephone, post, or fax to central secretariat. Random allocation was computer-generated and stratified by participating centre, HRT before diagnosis, and treatment with tamoxifen; block size was unknown to the trialists. Interventions were either HRT or best symptomatic treatment without hormones. Blinding was not applied. Choice of the specific type of HRT was directed by local practice (tibolone was not allowed in the trial). In the absence of a specific preferred therapy, women with an intact uterus and last bleeding within 2 years were recommended a cyclic oestrogen-progestagen combination and those with last bleeding more than 2 years ago a continuous combined oestrogen-progestagen combination. Women who had been hysterectomised were recommended a medium potency oestrogen only.

	HRT (219 randomised)	No HRT (215 randomised)
Number with follow-up	174	171
Median follow-up in years (range)	2.1 (0.1–5.3)	2.1 (0.1–5.6)
Median time in years between primary treatment and randomisation (range)	2.6 (0.1–23.3)	2.7 (0.2–26.5)
Median number of follow-up reports (range)	3 (1–15)	3 (1–12)
Mean age in years (range)	55.5 (42–75)	55.0 (40–74)
Node-positive*	38 of 147 (26%)	31 of 145 (21%)
Hormone-receptor positive*	86 of 154 (56%)	73 of 151 (48%)
Hormone receptor status unknown*	41 of 154 (27%)	33 of 151 (22%)
Breast preserved*	100 of 162 (62%)	96 of 167 (57%)
On HRT before diagnosis*	86 of 165 (52%)	91 of 163 (56%)
On adjuvant tamoxifen*	36 of 174 (21%)	36 of 171 (21%)

\*Data are number (%).

Table 1: **Baseline characteristics in women with follow-up data**

	RH (95% CI)	Number of events (number of women in subset)
All women	3.5 (1.5–8.1)	33 (345)
All women, adjusted	3.5 (1.5–8.1)	33 (345)
Hormone-receptor positive	4.8 (1.1–21.4)	14 (159)
Hormone-receptor negative	1.9 (0.4–9.6)	6 (72)
Tamoxifen	2.8 (0.3–27.4)	4 (72)
No tamoxifen	3.7 (1.5–9.0)	29 (273)
HRT before diagnosis	6.9 (1.6–31.1)	14 (177)
No HRT before diagnosis	2.1 (0.8–5.9)	19 (168)

Analyses done by subgroups defined by stratification variables and by hormone receptor status. Adjusted model incorporates HRT before diagnosis (yes vs no), use of tamoxifen (yes vs no), and hormone receptor status (positive vs negative or unknown).

Table 2: Relative hazards (RH) for risk of new breast-cancer event in HRT group versus non-HRT group

HRT was given for 2 years in the HRT arm. Participants were followed up by a breast cancer specialist at least twice yearly for the first 3 years, and had at least 5 years of follow-up in total. Clinical mammograms every 12–24 months or participation in screening was recommended, and participants were seen by a gynaecologist once every year. Compliance was reported at every clinical visit. The trial secretariat asked patients to complete quality of life questionnaires at 1 and 3 years after randomisation.

Due to slow recruitment, in 2002, HABITS and a similar trial in Stockholm, Sweden, agreed to pool safety and final analyses in the future. At the same time, the DMCs of the trials formed a joint DMC. The DMC did three interim analyses of HABITS, first with HABITS alone and the next two pooled with the Stockholm trial. All analyses were according to intention-to-treat and Cox proportional hazards model was used. The interim analyses were designed to detect an increased risk, and such repeated analyses do not increase the significance level of the one-sided test of the non-inferiority hypothesis for the final analysis stipulated in the protocol. However, the relative risk estimates will be somewhat biased upwards after stopping for safety.

The protocol agreement between the Stockholm trial and HABITS stipulated that the DMC should discuss the findings with the steering committee when the combined estimate of the relative hazard of HRT compared with no HRT was statistically significantly larger than 1.00. This result was reached in the recent third safety analysis (RH=1.8, 95% CI 1.03–3.1). However, there was a statistically significant ( $p=0.02$ ) heterogeneity between the studies; in HABITS the RH was 3.3 (95% CI 1.5–7.4) and in the Stockholm trial it was 0.82 (95% CI 0.35–1.9). The DMC recommended that the HABITS trial should stop, and that the investigators of the Stockholm trial should consider the consequences for their trial.

The results we report here are based on data from the HABITS trial only and on 345 women with at least one follow-up of 434 women randomised and followed up until September, 2003. The baseline characteristics were similar, with the possible exception of hormonal receptor status, in the two trial groups and there were no signs of a differential follow-up (table 1). 37 (21%) of the 174 women in the HRT group were exposed to oestrogens only, 80 (46%) to continuously combined regimens, 46 (26%) to sequential combinations, and 11 (6%) were exposed to non-protocol treatments (eg, tibolone) or never exposed to HRT. In the non-HRT group, 39 (18%) of 171 women were exposed to HRT.

26 women in the HRT group and eight in the non-HRT group were reported to have experienced new breast cancer events. In the HRT group, 11 of these events were local recurrences, five were contralateral cancers, and ten were distant metastases; the corresponding figures in the control group were two, one, and five, respectively.

To double-check data quality and the pattern of compliance to recommended treatment, the original case record forms were studied for all women with an event and for two controls for each case, matched for time at risk and randomisation arm. No major coding errors were found, with the exception for one event in the control group that could not be verified; this woman was not further counted as having had an event in the analyses. However, an analysis in which she was included as having had an event showed that the results were not sensitive to whether she was included or not. In the HRT group all women who had events had been exposed to HRT and all but five women experienced the event while on treatment. In the non-HRT group two of the seven women with new breast cancer events were exposed to HRT. Six out of 52 controls in the HRT group were never exposed to HRT. 13 of 16 controls in the non-HRT group were never exposed to HRT, two were reported as non-compliant, and one woman was lost to follow-up.

Further analyses were done by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis, to elucidate whether the risk seemed isolated to any one subset or if any of these factors strongly modified the effect (table 2). In all subsets, RH was above unity, but the CIs were wide due to the small number of events. An analysis adjusting for the stratification variables and hormone receptor status gave the same overall result as the basic safety analysis (table 2). We compared the risk by specific type of HRT and compared continuously combined, sequential, and other preparations to oestrogens only; the differences were both nominally small and far from statistically significant (data not shown).

Five women died in the HRT group (three due to breast cancer, one due to other reason, and one due to unknown reason) and four (all due to breast cancer) in the non-HRT group.

Eight serious adverse events were reported in the HRT group. Of these, two were rapidly progressing recurrences of breast cancer, one was lung cancer, one pulmonary embolism, one deep venous thrombosis, one endometrial cancer, one suicide, and one thrombophlebitis (which was not on the list of serious adverse events). In the non-HRT group, two instances of breast-cancer progression, one deep venous thrombosis, and one diagnosis with pulmonary embolism were reported as serious adverse events.

The results were based on reporting and a safety analysis during a trial and the results might change after the complete assessment of all patients' original records. However, for several reasons, the steering committee of the HABITS trial judged the data to be mature enough to strongly indicate that exposure to HRT conveys an unacceptable risk in the HABITS trial. The relative risk estimate was high and the lower limit of the 95% CI even exceeded the stipulated non-inferiority limit 1.36. All women with events in the HRT group were exposed to HRT and most of them had the new breast cancer event while under treatment. The data are biologically plausible in view of the patterns of compliance and our knowledge about breast-cancer risk in previously healthy women. We noted no clear sign of a differential follow-up suggesting a detection bias. Coding errors were small in the database.

We found no clear evidence of an effect modification by the factors mentioned in table 2, with the possible exception of hormone receptor status. At this stage, all interpretations of the subgroup analyses should be made with caution, since the precision is very low. It is difficult to judge whether the different proportions of hormone-receptor-positive women in the study groups have affected the results. The proportion of women with unknown hormone receptor status was fairly large and also differed between the study arms. In reality, the

prevalence of hormone-sensitive tumours may be well balanced. A model including hormone receptor status did not change the results

There are not yet enough data to explain why the findings of the HABITS and Stockholm trials might differ. It can be a chance finding. The steering committee of HABITS decided that the apparent discrepancy between the studies should not stop us from terminating the trial early due to concerns about patient safety. The steering committee of the Stockholm trial has decided to stop their trial due to anticipated difficulties in recruitment and compliance.

The HABITS trial was terminated because women with a history of breast cancer allocated to receive HRT for menopausal symptoms experienced an unacceptably high risk of breast cancer compared with breast-cancer survivors allocated to best symptomatic treatment without hormones. Women on active treatment have been advised to discontinue. However, the women in the trial will be followed up for at least 5 years after randomisation and the steering committee of the HABITS trial will continue to collaborate with other studies in the same clinical domain.

#### Steering committee and DMC of HABITS

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