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Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial

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Abstract ***Background:*** The management of hormonal deficiency symptoms in breast cancer survivors is an unsolved problem. While hormone replacement therapy (HRT) may increase the risk of breast cancer in healthy women, its effects on recurrence is unclear. Observational studies have suggested decreased recurrence rates from HRT. The few clinical trials in this field have all been closed preterm.

Methods: The Stockholm trial was started in 1997 and designed to minimise the dose of progestogen in the HRT arm. Disease-free women with a history of breast cancer were randomised to HRT ($n = 188$) or no HRT ($n = 190$). The trial was stopped in 2003 when another Swedish study (HABITS, the Hormonal Replacement After Breast Cancer – Is it Safe?) reported increased recurrence. However the Stockholm material showed no excess risk after 4 years of follow-up. A long term follow-up has now been performed.

Findings: After 10.8 years of follow-up, there was no difference in new breast cancer events: 60 in the HRT group versus 48 among controls (hazard ratio (HR) = 1.3; 95% confidence interval (CI) = 0.9–1.9). Among women on HRT, 11 had local recurrence and 12 distant metastases versus 15 and 12 for the controls. There were 14 contra-lateral breast cancers in the HRT

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group and four in the control group (HR = 3.6; 95% CI = 1.2–10.9; $p = 0.013$). No differences in mortality or new primary malignancies were found.

Interpretation: The number of new events did not differ significantly between groups, in contrast to previous reports. The increased recurrence in HABITS has been attributed to higher progestogen exposure. As both trials were prematurely closed, data do not allow firm conclusions. Both studies found no increased mortality from breast cancer or other causes from HRT. Current guidelines typically consider HRT contraindicated in breast cancer survivors. Findings suggest that, in some women symptom relief may outweigh the potential risks of HRT.

1. Introduction

The number of breast cancer survivors is steadily increasing due to an increased incidence, early detection and improved therapy. It is estimated that in Sweden alone, with 7000 new cases of breast cancer a year, more than 120 000 women are living with a previous diagnosis of breast cancer.[1] Many of these women suffer from climacteric symptoms and reduced quality of life as a consequence of adjuvant treatment with e.g. tamoxifen, aromatase inhibitors, gonadotropin-releasing hormone (GnRH) analogues or chemotherapy.

The management of menopausal symptoms and decreased quality of life in women treated for breast cancer are important clinical problems of growing magnitude, which still remain largely unsolved. Hormone replacement therapy (HRT) with oestrogen alone or in combination with progestogen can alleviate these symptoms in healthy women. Women with breast cancer are currently advised against using HRT as it is considered to increase the risk of recurrence. The importance of sex hormones in the pathophysiology of breast cancer is well established and anti-oestrogen therapies are major principles for treatment. There is however limited and to some extent contradictory evidence for strong recommendations due to lack of reliable studies. The therapeutic alternatives to HRT are few and have not been proven to have any substantial effect.[2]

In 1997 two independent randomised trials were started in Sweden to assess the effects of HRT after a diagnosis of breast cancer: the Hormonal Replacement After Breast Cancer – Is it Safe? (HABITS) and the Stockholm trial. In 2002 the organisers agreed to pool safety data and to establish a joint data monitoring committee. Following an interim safety analysis which showed a significant risk of recurrence from HRT for the two trials combined (hazard ratio (HR) = 1.8, 95% confidence interval (CI) = 1.03–3.1) both studies were prematurely stopped in December 2003. However there was significant heterogeneity between the studies ($p = 0.02$). The HR for HABITS at a median follow-up of 2.1 years and 33 breast cancer events was 3.5 (95% CI = 1.5–7.4).[3] In contrast in the Stockholm trial at a median follow-up of 4.1 years and 24 breast cancer events the risk of breast cancer recurrence was not associated with HRT (HR 0.82, 95% CI = 0.35–1.9).[4]

Since then the HABITS study group reported an extended follow-up after 4 years which still showed an increased risk of recurrence for the HRT group (HR = 2.4, 95% CI = 1.3–4.2).[5] Here we report results from the Stockholm trial after a median follow-up time of 10.8 years and a total of 108 events.

2. Materials and methods

The Stockholm trial was a randomised open study with two parallel groups. Postmenopausal women in the Stockholm region who had undergone primary surgery for a histologically verified breast cancer were invited to participate. All patients younger than 70 years were eligible irrespective of time since surgery, stage of disease, hormone receptor status, concomitant adjuvant treatment and irrespective of menopausal symptoms. The participants were required to be free of recurrence, to have no other cancer or serious disease and to have no other contraindications to HRT. The first patient was randomised in June 1997 and the last patient in October 2003.

The trial was performed according to WHO guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the Regional Ethics Committee of the Karolinska Institute (April 22, 1997; reg. no. 96/153). All women gave their informed consent to participate.

After informed consent women were randomised to receive HRT ($n = 188$) or no HRT ($n = 190$) for 5 years. Randomisation was done by telephone to a central office where patient identifiers were recorded before the treatment allocation was reported to the responsible physician. Randomisation was performed with balanced lists using a permuted block technique with a block size of six.

Stratification was done for three parameters: (1) use of tamoxifen versus no tamoxifen; (2) type of menopausal HRT and (3) time since primary diagnosis (less than 2 years versus more than 2 years).

For women randomised to HRT cyclic treatment was prescribed for those younger than 55 years (oestradiol 2 mg for 21 days and addition of medroxyprogesterone acetate (MPA) 10 mg for the last 10 days followed by 7 days with no treatment). A 'spacing out' regimen was used in women 55 years or older (oestradiol 2 mg for

84 days and addition of MPA 20 mg for the last 14 days followed by 7 days with no treatment). Women who had undergone hysterectomy were given continuous treatment with oestradiol valerate 2 mg daily. For women in the non-HRT group only local vaginal treatment with low dose oestrogen gels or vagitories was allowed.

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

The primary end-point was recurrence free survival. This end-point included loco-regional recurrence, distant metastasis, contra-lateral breast cancer or death from breast cancer. Secondary end-points were type of breast cancer recurrence, cause specific mortality and other new primary cancers. All analyses were done on an intention-to-treat basis.

2.1. Follow-up

Patients were recruited to the trial from 13th June 1997 until 10th October 2003. All patients were followed for events until 31st December 2009. The median follow-up time was 10.8 years. The minimum follow-up time for patients still alive at the end of follow-up was 6.2 years, and maximum follow-up was 12.6 years.

2.2. Statistical methods

The median follow-up time was calculated using the reversed Kaplan–Meyer technique.[6] Time to recurrence – any 1st event – was calculated from the date of randomisation to the date of loco-regional recurrence, distant recurrence, contra-lateral breast cancer, other cancer or inter-current death (whichever came first), or in the absence of an event, to the last day of follow-up (December 31, 2009). When using information about all specific events observed during follow-up – not only as a 1st event – time was calculated from the date of randomisation to the date of the studied event, death or to the last day of follow-up. Crude cumulative incidence of a specific event was estimated in the presence of competing risks from other events using Kaplan–Meyer technique generalised to include competing risks.[7] Proportional hazards regression was used to model event specific hazards. In the analysis of 1st events all other events than the studied were treated as censored observations. In the analysis using information about the total number of events, deaths were treated as censored observations. Results from the regression models are presented as hazard ratios together with 95% confidence intervals. Differences in time to specific event distributions were tested using the log-rank test. All analyses were based on the intention-to-treat principle.

3. Results

At a median follow-up time of 10.8 years the 378 women recruited into the trial generated a total of 3601 person-years.

Patient characteristics for the two treatment groups are given in Table 1. There were no apparent differences in patient's age, time since diagnosis, tumour characteristics, type of surgery or adjuvant treatment between the two groups.

Among the 188 women who had been randomly assigned to receive HRT 42 (22%) started cyclic oestradiol/MPA, 94 (50%) started 'spacing out' oestradiol/MPA and 43 (23%) started oestradiol valerate alone. Information was incomplete for nine (5%) patients. Compliance for 2 years or more for women in the HRT group who entered the trial before 2002 was 77% according to a review of the medical records. Among women in the control group 10% had taken some forms of HRT after inclusion. In the treatment group there were eight (19%) women on cyclic oestradiol/MPA, 15 (16%) on 'spacing out' oestradiol/MPA and one (2%) on oestradiol valerate alone who were switched to alternative HRT regimens for various reasons e.g. side-effects or irregular bleeding.

There were a total number of 108 first events i.e. loco-regional recurrence, distant metastases, contra-lateral cancer, other primary cancer and inter-current death (Table 2, Fig. 1). Overall there was no significant difference between treatment groups with 60 events (32%) in the HRT group and 48 events (25%) in the non-HRT group (HR=1.3; 95% CI = 0.9–1.9). Among women treated with HRT there were 11 reports of local recurrence and 12 of distant metastases. The corresponding figures in the non-HRT group were 15 and 12.

In contrast, for the specific first event of contra-lateral breast cancer there were 14 cases reported among women using menopausal hormone therapy versus four in the non-HRT group (Fig. 2). This difference was statistically significant (HR = 3.6; 95% CI = 1.2–10.9; $p = 0.013$).

Among the 18 contra-lateral breast cancers eight were invasive ductal tumours, two ductal cancer in situ and five were of lobular type. Information was missing in three cases. Eleven of the contra-lateral cancers were diagnosed in women on concomitant treatment with tamoxifen. Eight of the contra-lateral cancers were of different histology as compared to the primary tumour

Table 1
Patient characteristics by allocated treatment.

Patient characteristic	Allocated treatment (%)	
	HRT+	HRT−
Age in years at randomisation, mean (SD)	57.0 (5.0)	57.8 (5.7)
Time in years between diagnosis and randomisation, mean (SD)	2.6 (3.1)	2.6 (3.3)
Histopathological nodal involvement		
N0	127 (68)	112 (59)
N1–3	26 (14)	33 (17)
N4+	5 (3)	4 (2)
Unavailable	30 (16)	41 (22)
Histopathological tumour size (mm)		
⩽20	141 (75)	147 (77)
>20	34 (18)	28 (15)
Unavailable	13 (7)	15 (8)
Oestrogen receptor status		
Positive	113 (60)	103 (54)
Negative	22 (12)	29 (15)
Unavailable	53 (28)	58 (31)
Type of surgery		
Mastectomy	53 (28)	51 (27)
Breast conserving surgery	127 (68)	134 (71)
Other type of surgery	7 (4)	1 (1)
Unavailable	1 (1)	4 (2)
Type of axillary surgery		
Axillary clearance performed	155 (83)	149 (78)
Axillary clearance *not* performed	30 (16)	37 (20)
Unavailable	3 (2)	4 (2)
Postoperative treatment (alone or in combination)		
No treatment	11 (6)	15 (8)
Radiotherapy	134 (71)	132 (69)
Chemotherapy	36 (19)	27 (14)
Tamoxifen	98 (52)	99 (52)
Other treatment or data missing	13 (7)	19 (10)
Total number of patients	188	190

treated before inclusion in the trial. The mean duration (±SD) from primary surgery to this first event was 7.4 ± 3.9 years in the HRT group and 2.7 ± 1.2 years in the non-HRT group. The mean duration of hormone use in the HRT group was 2.6 ± 1.2 years. Within the HRT group 4 contra-lateral cancers occurred in women on 'spacing out' oestradiol/MPA and eight cases in women on other regimens. None of the four new cancers in the 'spacing out' group was on concomitant tamoxifen.

At randomisation 123 women were younger than 55 years and 255 women 55 years or older. There were no apparent differences with respect to any of the recorded events between the two age groups. As for the whole material there were in both age groups more contra-lateral breast cancers in the HRT arm compared to the control arm: 5 versus 1, and 9 versus 3, in the younger and older women, respectively. A total of 197 women were on tamoxifen when they were randomised to participate in the HRT trial. Also in these women there were more contra-lateral breast cancers (10 versus 1) in the HRT group than in the non-HRT group.

Among the 378 included in the trial 224 had been diagnosed with breast cancer less than 2 years before randomisation. For these women as in the whole material there was an excess risk of contra-lateral breast cancer (HR 4.8; 95% CI = 1.0–22; $p = 0.046$). There was also a significant increase for risk of any first event 1.7 (95% CI = 1.0–3.0; $p = 0.043$). In contrast, for the women randomised 2 years or more after the primary diagnosis ($n = 154$) there were no differences with respect to any of the first events between those with or without HRT. There were a total of 25 first events in the HRT arm and 26 in the control group (HR 0.9; 95% CI = 0.5–1.6; $p = 0.79$).

There was no difference in overall mortality between the groups (Fig. 1). The total number of deaths in the menopausal hormone therapy group was 19 (10 from breast cancer) and in the control group 18 (11 from breast cancer). Also there was no difference in the occurrence of new primary malignancies other than contra-lateral breast cancer – 21 in the HRT group and 16 in the non-HRT group.

4. Discussion

While hormone replacement therapy has been found to increase the risk of breast cancer in healthy women, its effects on risk of recurrence in breast cancer patients are more uncertain. In fact several observational studies have suggested decreased recurrence rates in breast cancer survivors treated with HRT.[8–11] However, these studies may have potential bias in e.g. patient selection and follow-up.[12] The three randomised trials on HRT after breast cancer diagnosis were all closed prematurely due to concern about the safety of treatment.

In a first preliminary report from the Stockholm randomised trial we found no increased risk of recurrence from HRT.[4]

Also in the present analysis after extensive follow-up for more than 10 years the overall risk for a new breast cancer event did not differ significantly between women in the HRT and the non-HRT group. This finding is at variance with the results of the HABITS trial where a significant excess risk of breast cancer recurrence in the HRT group was recorded after a median follow-up of 4 years.[5] As both trials were prematurely closed, data have limited power and does not allow firm conclusions on the discrepant results. Certainly the different findings

Table 2
Number of events by study arm together with hazards ratios and 95% confidence intervals.

Type of event	First events (%)				Total number of events (%)			
	HRT	No HRT	HR[a,b] (95% CI)	*p*-Value[d]	HRT	No HRT	HR[a,c] (95% CI)	*p*-Value[d]
Loco-regional recurrence	11 (6)	15 (8)	0.8 (0.3–1.7)	0.49	12 (6)	19 (10)	0.6 (0.3–1.3)	0.20
Distant recurrence	12 (6)	12 (6)	1.0 (0.5–2.3)	0.92	16 (9)	16 (8)	1.0 (0.5–2.0)	0.95
Contralateral breast cancer	14 (8)	4 (2)	3.6 (1.2–10.9)	0.016	15 (8)	5 (3)	3.1 (1.1–8.6)	0.020
New primary malignancy	21 (11)	16 (8)	1.4 (0.7–2.6)	0.34	21 (11)	18 (10)	1.2 (0.6–2.3)	0.57
Intercurrent death[e]	2 (1)	1 (1)						
Any event	60 (32)	48 (25)	1.3 (0.9–1.9)	0.18				
Breast cancer death					10 (5)	11 (6)	0.9 (0.4–2.2)	0.85
Other causes of death					9 (4)	7 (4)	1.3 (0.5–3.5)	0.60
Death (all causes)					19 (10)	18 (10)	1.1 (0.6–2.0)	0.83
Number of patients	188	190			188	190		

Abbreviations: HRT, hormonal replacement therapy; HR, hazard ratio; CI, confidence interval.
[a] Estimated using proportional hazards regression with No HRT as the reference category.
[b] Other events than the studied are treated as censored observations.
[c] Ignoring all other events except the studied one and death. Death is treated as censored observations.
[d] *p*-Value from Log-rank test.
[e] HR not estimated.

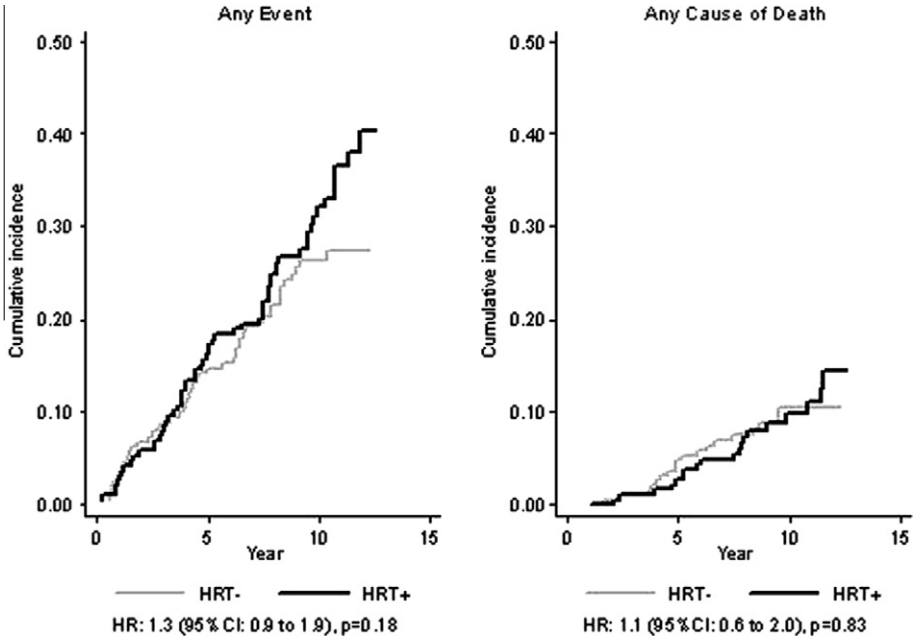

Fig. 1. Cumulative incidence of any breast cancer recurrence and cause of death versus time during follow-up in the Stockholm trial.

in the two trials could be due to chance. However, there was statistically significant heterogeneity between the two studies ($p = 0.02$) indicating that chance may not be the only explanation.

Tibolone is a compound with a mixture of oestrogenic, progestogenic and androgenic properties. This alternative to conventional oestrogen/progestogen treatment was tested in the large randomised, placebo-controlled LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) trial. After a median follow-up of 3.1 years there was an overall increased risk of recurrence also in the tibolone group (HR 1.4; 95% CI = 1.14–1.70).[13]

Recurrences from HRT in the HABITS material were predominantly local and this was not seen in the Stockholm trial. However while there was no overall risk for breast cancer recurrence we found a significant increase of contra-lateral breast cancer, 14 in the HRT group versus 4 in the non-HRT group (HR 3.6; 95% CI = 1.2–10.9; $p = 0.013$). The mean duration from primary surgery to this specific new breast cancer event in the HRT group was 7.4 years and only 2.7 years in the control group. The mean duration of HRT was 2.6 years. It is uncertain whether these contra-lateral tumours should be regarded as a recurrence of the primary cancer or as a new primary malignancy. Half of

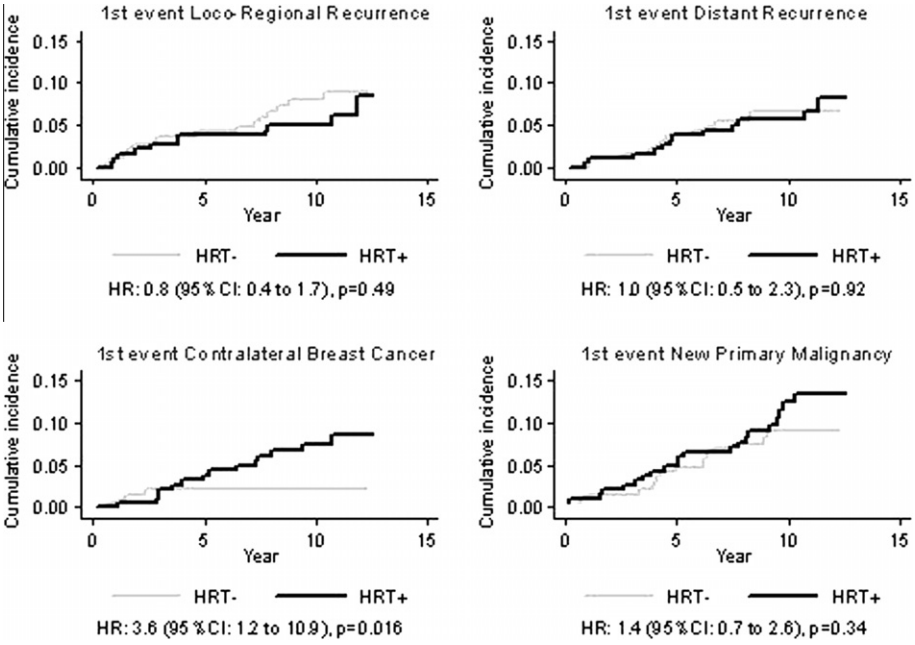

Fig. 2. Cumulative incidence of first events of breast cancer recurrence versus time during follow-up in the Stockholm trial.

the contra-lateral tumours (7/14) in the HRT group were of different histological type compared to the primary cancer.

Recently, timing and onset of HRT in relation to menopause have been suggested to be an important modulator of breast cancer risk in healthy women. In the French E3N cohort and also in the Million Women Study risk from HRT was markedly higher when treatment was initiated in close association to menopause.[14,15] When treatment was started 5 years or more after menopause the risk was low or even absent. One possible explanation for this reduction of breast cancer risk in 'long gap time' patients could be enhanced oestrogen-induced apoptosis developed by cells sensitised after a period of oestrogen deprivation.[16,17] The duration between diagnosis/primary treatment and randomisation was slightly longer in the Stockholm trial (average 2.6 years) than in HABITS (average 2.1/2.2 years). However it seems unlikely that such a small difference would have influenced the apparent discrepancy between the two trials.

Still within the Stockholm trial we found some evidence for an influence of timing. Women randomised to HRT within 2 years after diagnosis had a slightly increased risk of recurrence. On the other hand women who started HRT more than 2 years after diagnosis had no excess risk neither for contra-lateral cancer, nor for any form of recurrence. This finding in a subgroup must be interpreted with caution, but it could be that timing of intervention modulates the risk of HRT not only in healthy women but also in breast cancer survivors.

Both HABITS and the Stockholm trials had a prospective randomised parallel group design but the adverse outcome in HABITS has been attributed to greater progestogen exposure (preferential use of continuous combined HRT versus long cycle 'spacing out' therapy) and less concomitant tamoxifen use than in the Stockholm trial. In healthy women the addition of progestogen during HRT has been found to increase the risk of breast cancer as compared to treatment with oestrogen alone.[18–21] In the Stockholm trial, 73% of the women were first assigned to HRT containing either oestrogen alone or a spacing out regimen where oestrogen were given for only 14 days at 3-months intervals. Also concomitant tamoxifen treatment could prevent a potential risk of HRT as it blocks the oestrogen receptor. A greater percentage of women were treated with adjuvant tamoxifen in the Stockholm trial than in the HABITS trial (52% versus 21%). There is evidence for a breast-protective effect of tamoxifen from chemoprevention trials.[22,23] However this notion was not supported by analyses in the follow-up of the HABITS trial.[5] Also in the present long term follow-up of the Stockholm trial women on tamoxifen at randomisation had an excess risk for contra-lateral breast cancer similar to the risk found for the whole material. On the other hand subgroup analyses of the LIBERATE trial indicated little adverse effect from tibolone among women on concomitant tamoxifen (HR 1.25; 95% CI = 0.98–1.59; $p = 0.076$). The risk of recurrence was markedly higher for those on aromatase inhibitors (HR 2.42; 95% CI = 1.01–5.79; $p = 0.047$).[13]

It has been suggested that HRT in the presence of tamoxifen may be ineffective to relieve symptoms of oestrogen deficiency.[24,25] Nonetheless in a subgroup analysis of the Stockholm material we found improve-

ment in several aspects of quality of life among women with HRT and concomitant tamoxifen.[26] There was also significant symptom relief irrespective of tamoxifen treatment in a feasibility analysis for a randomised trial in the UK.[27] In addition there were significant positive effects from tibolone on vasomotor symptoms and bone mineral density and no difference versus placebo in other safety outcomes such as mortality, cardio-vascular events and gynaecological cancers.[13]

In summary the management of menopausal symptoms and quality of life for patients with breast cancer remain important unsolved clinical problems. Women treated for breast cancer continue to ask for relief of oestrogen deficiency symptoms when non-hormonal alternatives are ineffective. Two prospective randomised trials on HRT were prematurely closed and have yielded somewhat discrepant and inconclusive results. Yet both studies found no increased mortality from breast cancer or any other cause during HRT. Current clinical guidelines suggest that HRT should be considered contraindicated in breast cancer survivors. Still in some women with severe menopausal symptoms an impaired quality of life may outweigh the potential risks from hormone replacement therapy.[12]

Contribution

Mia Fahlén	Follow-up of patients, collection of data from medical records, writing of article, applications for funding of the trial, submitting article for publication
Tommy Fornander	Inclusion of patients in the trial, follow-up of patients, applications for funding of the trial
Hemming Johansson	Statistical analysis, power calculations, writing of statistical part of article
Ulla Johansson	Collection and analysis of statistical data
Lars-Erik Rutqvist	Study design, writing of article, applications for funding of the trial
Nils Wilking	Study design, writing of article, applications for funding of the trial
Eva von Schoultz	Principal trial investigator, study design, inclusion of patients in study, follow-up of patients, applications for funding of the trial, writing of article

Role of the funding source

None.

Conflict of interest statement

None declared.

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