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ORIGINAL ARTICLE

Family history influences the tumor characteristics and prognosis of breast cancers developing during postmenopausal hormone therapy

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Abstract Long term use of postmenopausal hormone therapy (HT) has been reported to increase breast cancer risk. On the other hand, observational studies suggest that breast cancers diagnosed during HT may have a more favorable prognosis. While family history is a risk factor for breast cancer, and genetic factors also influence prognosis, the role of family history in combination with HT use has been little studied. We investigated the relationship between HT, family history, and prognosis in 584 (267 exposed) familial and 952 (460 exposed) non-familial breast cancer cases, using three survival end points: death from breast cancer (BCS), distant disease free survival (DDFS), and local recurrence free survival (LRFS). Among non-familial cases, HT was associated with better BCS (HR 0.63, 95% CI 0.41–0.94; $p = 0.025$), and DDFS (HR 0.58, 95% CI 0.40–0.85; $p = 0.005$), with a consistent but not statistically significant effect in LRFS. This effect was not seen in familial cases (HR > 1.0), and family history was found to interact with HT in BCS ($p_{(interaction)} = 0.0067$) (BC-death) and DDFS ($p_{(interaction)} = 0.0070$). There was phenotypic heterogeneity between HT-associated tumors in familial and non-familial cases, particularly on estrogen receptor (ER) status, although the interaction between HT and family history appears to be at least partially independent of these markers ($p = 0.0370$ after adjustment for standard prognostic factors). If confirmed by further studies, our results suggest that family history should be taken into consideration in clinical counseling before beginning a HT regimen.

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Introduction

Breast cancer is the most common cancer for women worldwide and one of the leading causes of death. In Finland there were on an average 4564 new cases of female breast cancer diagnosed between 2010 and 2014 (age standardised incidence 90.1 per 100,000) and the incidence of breast cancer is increasing [1], although the age-standardized mortality rate has slightly decreased in recent years.

Hormonal factors play a significant role in the occurrence and prognosis of breast cancer. Exposure to ovarian hormones throughout life affects the risk of developing breast cancer. Early menarche, delayed menopause, high endogenous levels of estrogens, nulliparity, a late age of giving birth to the first child, alcohol consumption, and high body-mass index in postmenopausal women all increase the risk of breast cancer [2].

Menopausal symptoms affect more than 50% of women. Hormone therapy (HT) with estrogen or combining estrogen with progestin has been used by postmenopausal women for symptom relief [3]. The associations between risk of breast cancer and use of HT have been investigated intensely, the overall consensus being that the use of HT regimens increased the risk of breast cancer. A large meta-analysis comprising 51 individuals studies indicated that breast cancer risk was proportional to the duration of HT use with no significant differences between different regimens, however information of used regimens were available for only a proportion of the participants (39%) [4]. In contrast a study by Olsson et al. indicated a significantly elevated risk of developing breast cancer after combined estrogen and progestore use, while estrogen use only did not increase the risk [5]. More recently the large placebo-controlled trial by the 2002 Women's Health Initiative (WHI) indicated that the breast cancer risk may be different with estrogen only and estrogen combined with progesterone: breast cancer risk was significantly increased during the intervention in the combined treatment arm, but on the contrary decreased in the estrogen only arm [6–8].

Most observational studies show that the breast cancers diagnosed during HT are less aggressive and have a more favorable prognosis. Breast cancers associated with HT have been associated to lobular or tubular histology, small size, low grade, and estrogen receptor positivity and diagnosed at an earlier stage [4, 9–19]. In general, prognosis seems to be more favorable among patients with HT-related breast cancer [18, 20–23]. Again, however, the WHI trials indicate a significant biological difference between estrogen-only and estrogen–progestin combination HT: combination therapies associated with larger, progesterone receptor-negative tumors, whereas in the estrogen-only group, tumors were more often HER2 positive, moderately differentiated (grade 2) and of lobular histology [7].

Women with a family history of breast cancer have an elevated baseline risk of breast cancer. The interaction of family history and HT has been evaluated in several studies, with mixed results. Some studies have reported association between HT use and increased risk of breast cancer also among women with positive family history, while others have failed to observe such an interaction [4, 24, 25]. The 2015 WHI study included a substantial fraction (11.8–14.2%) of cases with family history, but association between family history and tumor characteristics in the estrogen-only and estrogen–progestin groups was not investigated [7].

Tumor characteristics and prognosis have not been extensively studied in cases developing during HT in women with a family history of breast cancer. A study by Sellers et al. reported that women with a family history of breast cancer who used HT had a significantly lower any-cause mortality than did women who had never used HT, but this effect was not replicated when death from breast cancer was used as the end-point of the analysis [24]. The relationship between HT use and prognosis in patients with a family history of breast cancer survival therefore remains unclear at this time.

The aim of the present study was to investigate whether HT use associates with the tumor characteristics and prognosis of breast cancer in women with family history, by linking a well characterized cohort of breast cancer patients with data to a comprehensive database of previous HT use recorded in the Finnish National Medical Reimbursement registry.

Methods

Study population

The breast cancer cases in this study have been recruited in four patient series containing 2815 patients in total. Three of these series are unselected (consecutively recruited, including both familial and sporadic cases), and the fourth is based on family history. The first two series of 884 unselected cases were collected at the Department of Oncology between April 1997 to March 1998 and from January 2000 to June 2000 [26, 27], covering 79% of all newly diagnosed cases treated at the Department during the collection period. The third series of 986 unselected patients was collected at the Department of Surgery from November 2001 to February 2004 [28], with 87% coverage of all newly diagnosed cases. The study population also includes an additional series of

945 familial breast cancer patients (both index cases and relatives) from an ongoing collection at the Helsinki University Hospital's Departments of Oncology and Clinical Genetics starting in 1995 [29, 30]. The median time between diagnosis and study entry was 9.7 months among the familial cases. All patients were recruited with written informed consent.

From these cases a sample of 1536 postmenopausal familial and non-familial patients with invasive breast cancer (ICD C50; malignant neoplasm of breast) diagnosed at the age of 50 or later has been selected for this study. Cases with breast cancer in-situ only were excluded as well as cases with diagnosis of breast cancer later than 1.1.2010. Cases with germline BRCA-1 or BRCA-2 mutations were excluded from cases with family history, as previously described [31]. The selection process of these 1536 cases, of whom 727 were classified as current users of HT at the time of diagnosis, is described in detail in Fig. 1.

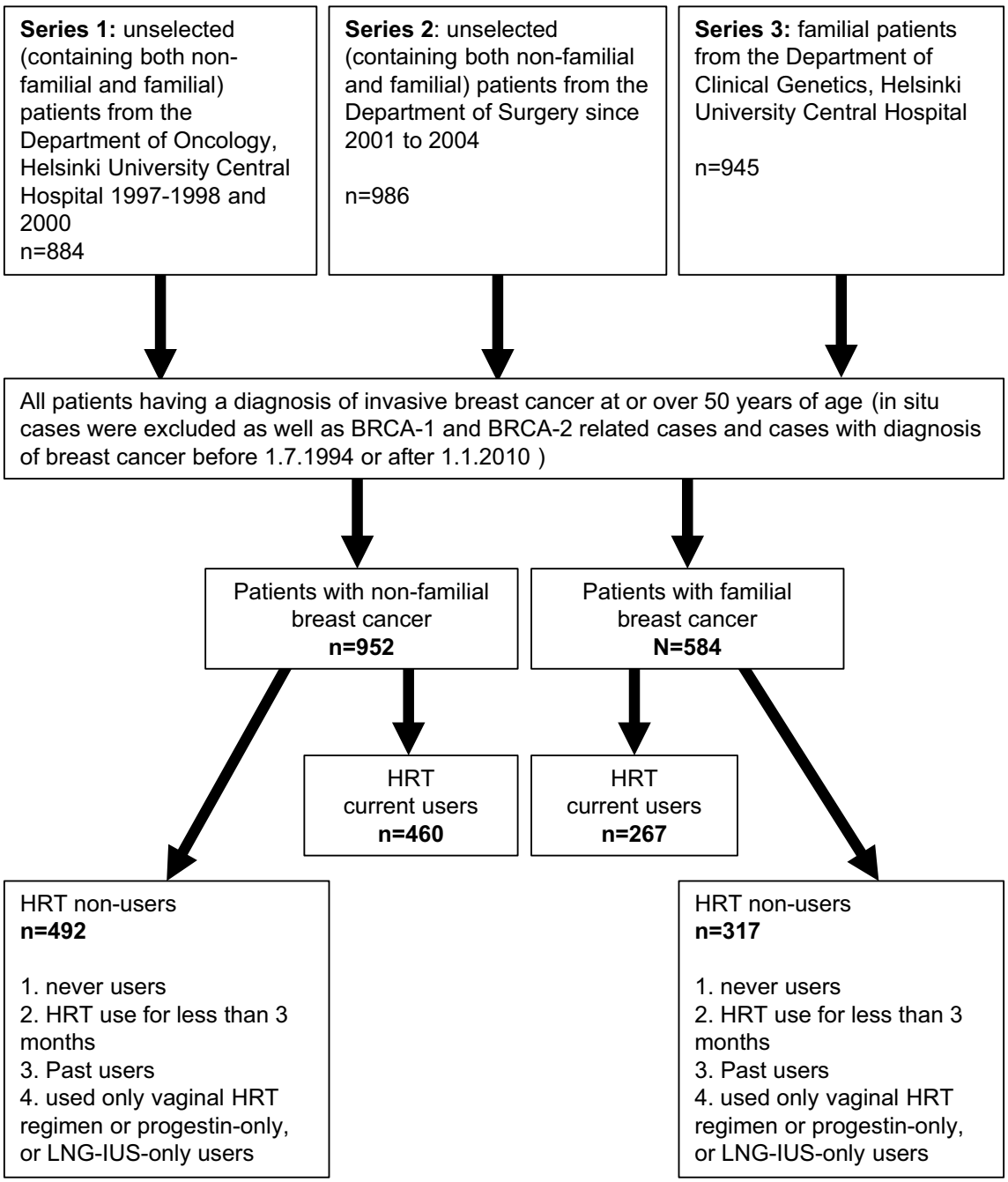

Fig. 1 Flow diagram describing the collection and selection of cases in the study

Out of the 1536 patient sample, 952 were cases with non-familial breast cancer and 584 with familial breast cancer. Family history was ascertained by patient interviews first, with verification by population registry, hospital records and/or the Finnish Cancer Registry as previously described [31]. Breast cancer families were identified by the selection criterion of at least two first- or second-degree relatives with breast or ovarian cancer in the family.

This study has been approved by the ethics committee of the Helsinki University Hospital.

Characterization of HT use

The users of HT were identified using the National Medical Reimbursement Registry of the Social Insurance Institution during the period from the beginning of 1994 to the end of 2009. The registry covers practically 100% of all HT users because HT is available only with medical prescription in Finland and women themselves finance a part of it. Of all these patients, we included all women who used HT at least 6 months (who had bought HT regimens at least twice at 3 months intervals) in this study. Patients who had bought a HT regimen only once (a dose for 3 months or less) were considered as non-users, because this group of women might include individuals who had only bought HT regimens, but not used them.

In this study, we compared non-users and current-users of systemic HT (use at the time of or within 12 months before breast cancer diagnosis). Patients who had used only vaginal estrogen were considered as non-users since vaginal HT has no documented effect on breast cancer risk [32]. Progestin-only users and levonorgestrel intrauterine system (LNG-IUS) only users were also considered as non-users. Prescriptions were sorted according to the Anatomical Therapeutic Chemical (ATC) Classification System; estrogen-only drugs, ATC group G03C and combined estrogen–progestin drugs, ATC group G03F.

Tumor histopathology

Information on tumor histology, grade, tumor size (T), nodal status (N), distant metastases (M), and hormone receptor (estrogen and progesterone; ER, PR) status were collected from pathology reports. For those cases from which tumor tissue microarray samples were available (42.6% of the cases in the current study), grade and histological type were further verified by an experienced breast cancer pathologist (P.H.). Tumors were categorized histologically as ductal, lobular, and "other" for the purposes of this analysis. Grading was based on a modification of Scarff-Bloom-Richardson into grade 1–3 [33]. Ki67 expression was determined using immunohistochemistry, and scored as follows: 0 (negative; <5% cells positive), 1 (weak; 5–19%), 2 (intermediate; 20–29%) and 3 (strong; >29%) [34]. HER2 amplification was detected from tumor tissue samples using chromogenic in situ hybridization (CISH) or, in the absence of a CISH result, immunohistochemical staining of the Her-2 protein was used (in total, 87.8% of all HER2 data originated from CISH).

Follow-up data

The genealogies were confirmed through population registries and cancer diagnoses were confirmed through The Finnish Cancer Registry, a centralized registry that collects comprehensive diagnostic, mortality, and cause-of-death information on all cancer cases in Finland. Cancer diagnoses were also checked through hospital records. The survival was calculated as the time from the diagnosis of the first invasive breast cancer to diagnosis of a relapse (local recurrence free survival; LRFS), or of a distant metastasis (distant disease free survival; DDFS), or until death from breast cancer before March 1, 2011 (BCS). Survival times were censored at the date of last clinical follow-up for LFRS and DDFS, the date of last Finnish Cancer Registry update (March 1, 2011) for BCS, or the diagnosis date of a second primary cancer for all end-points.

Statistical analysis

The data were analyzed using SPSS Statistics 22 and R 3.0.2. P values for comparisons of HT usage and tumor characteristics were calculated using linear and logistic regression as tests of heterogeneity and trend where appropriate. Heterogeneity between familial and sporadic cases was assessed by z-tests between coefficients from the corresponding regression models in Table 1, and as the significance of the beta of the interaction-term in the interaction analyses in Tables 2 and 3. P values < 0.05 were considered statistically significant and all p values are two-sided.

We used Cox regression analysis to estimate the association between HT and survival among familial and non-familial cases, adjusted for age at diagnosis. Follow-up times were left-truncated to account for case recruitment latency (time between diagnosis and study entry). Cases with metastases at the time of diagnosis were excluded from the analysis. To investigate the effects of known prognostic factors, we also calculated additional Cox models that included ER, T, N, and grade, as well as age at diagnosis. The end points in the survival analyses were BCS (death from breast cancer), distant disease free survival (DDFS) and local recurrence free survival (LRFS). The follow-up times for DDFS and LRFS were right-censored at 6 years; this threshold was chosen based on the observation that while regular clinical follow-up continues for 5 years after diagnosis, in principle, in actual

Table 1 Clinicopathological features of breast cancer tumours of postmenopausal non-familial and familial breast cancer patients

	Non-familial cases					Familial cases					
	No HT	(%)	HT	(%)	p value	no HT	(%)	HT	(%)	p value	p (het)
Total	492	(51.7)	460	(48.3)		317	(54.3)	267	(45.7)		0.32
Age at dg											
(Mean)	64.6		61.5		< 0.0001	63.6		61.0		0.0009	0.50
ER status											
Negative	88	(18.3)	58	(12.9)	0.02	45	(15.2)	54	(21.6)	0.051	**0.004**
Positive	392	(81.7)	393	(87.1)		251	(84.8)	196	(78.4)		
Missing[a]	12	(2.4)	9	(1.95)		21	(6.62)	17	(6.36)		
PgR status											
Negative	166	(34.6)	170	(37.7)	0.32	94	(31.9)	98	(39.2)	0.076	0.41
Positive	314	(65.4)	281	(62.3)		201	(68.1)	152	(60.8)		
Missing	12	(2.43)	9	(1.95)		22	(6.94)	17	(6.36)		
Grade											
1	128	(26.8)	158	(35.8)	< 0.0001	75	(25.0)	80	(31.6)	0.35	0.067
2	214	(44.9)	208	(47.2)		149	(49.7)	107	(42.3)		
3	135	(28.3)	75	(17.0)		76	(25.3)	66	(26.1)		
Missing	15	(3.04)	19	(4.13)		17	(5.36)	14	(5.24)		
T											
T1	262	(53.8)	324	(70.9)	< 0.0001	198	(64.1)	179	(67.8)	0.28	**0.029**
T2	186	(38.2)	109	(23.9)		90	(29.1)	71	(26.9)		
T3	15	(3.1)	13	(2.8)		12	(3.9)	9	(3.4)		
T4	24	(4.9)	11	(2.4)		9	(2.9)	5	(1.9)		
Missing	5	(1.01)	3	(0.65)		8	(2.52)	3	(1.12)		
N											
N0	239	(49.5)	278	(61.0)	0.0004	163	(53.1)	150	(56.8)	0.37	0.14
N1	244	(50.5)	178	(39.0)		144	(46.9)	114	(43.2)		
Missing	9	(1.82)	4	(0.86)		10	(3.15)	3	(1.12)		
Histology											
Ductal	356	(72.4)	274	(59.6)		215	(67.8)	164	(61.4)		
Lobular	80	(16.3)	130	(28.3)	< 0.0001	63	(19.9)	60	(22.5)	0.29	0.05
Other	56	(11.4)	56	(12.2)	0.2	39	(12.3)	43	(16.1)	0.13	0.74
Missing	0	(0.0)	0	(0.0)		0	(.00)	0	(0.0)		
Ki67 score											
0	64	(14.6)	117	(27.8)	< 0.0001	64	(23.5)	62	(27.2)	0.63	**0.001**
1	184	(41.9)	202	(48.0)		116	(42.6)	90	(39.5)		
2	96	(21.9)	46	(10.9)		46	(16.9)	38	(16.7)		
3	95	(21.6)	56	(13.3)		46	(16.9)	38	(16.7)		
Missing	53	(10.77)	39	(8.47)		45	(14.19)	39	(14.6)		
Her2 status											
Negative	196	(87.1)	166	(85.6)	0.65	179	(84.4)	156	(88.1)	0.29	0.28
Positive	29	(12.9)	28	(14.4)		33	(15.6)	21	(11.9)		
Missing	267	(54.26)	266	(57.82)		105	(33.12)	90	(33.7)		

[a]Percent of total, not included in the statistical analysis

practice the last follow-up date is often during the 6th year. BCS follow-up times were right-censored at 10 years to avoid statistical problems relating to a diminishing pool or survivors (and an increasing rate of any-cause mortality at long follow-up times). To maximize statistical power, it was considered ideal to investigate estrogen-only and estrogen–progestin combinations as a single group in the survival analysis. The feasibility of this approach was tested using a sensitivity analysis where HT use was split into three subcategories: estrogen-only, estrogen–progestin, and mixed HT (e.g. estrogen-only followed by estrogen–progestin at a later date). Kaplan–Meier curves were

Table 2 Interaction analysis of the combined effect of HT use and family history

Breast cancer specific (BCS)	HR	95% CI	p value
Model without interaction term			
HT	0.84	(0.61–1.17)	0.31
Family history	0.88	(0.63–1.23)	0.451
Age at diagnosis	1.05	(1.03–1.06)	< 0.0001
Model with interaction term			
HT	0.61	(0.41–0.92)	0.02
Family history	0.56	(0.35–0.92)	0.022
Age at diagnosis	1.05	(1.03–1.06)	< 0.0001
HT * Family history	2.6	(1.3–5.18)	0.007
Distant disease free (DDFS)	HR	95% CI	p value
Model without interaction term			
HT	0.75	(0.55–1.02)	0.07
Family history	0.77	(0.55–1.09)	0.14
Age at diagnosis	1.03	(1.01–1.05)	0.0002
Model with interaction term			
HT	0.57	(0.39–0.83)	0.004
Family history	0.5	(0.31–0.82)	0.006
Age at diagnosis	1.03	(1.01–1.05)	0.0002
HT * Family history	2.6	(1.3–5.19)	0.007
Local recurrence free (LRFS)	HR	95% CI	p value
Model without interaction term			
HT	0.88	(0.5–1.55)	0.67
Family history	1.26	(0.71–2.24)	0.43
Age at diagnosis	1.01	(0.98–1.04)	0.60
Model with interaction term			
HT	0.56	(0.27–1.18)	0.13
Family history	0.71	(0.3–1.68)	0.43
Age at diagnosis	1.01	(0.98–1.04)	0.59
HT * Family history	3.25	(0.99–10.66)	0.05

Separate models are presented for 10-year BCS (death from breast cancer; deaths from other causes are censored), 6-year distant disease free survival (distant metastasis; DDFS) and 6-year local recurrence free survival (LRFS). All analyses are adjusted for age at diagnosis

used to further visualize the association between HT and survival in relation to family status.

Results

Of all the study participants, 1536 cases were classified as postmenopausal women with diagnosis of invasive breast cancer at or over 50 years of age and included to this analysis, as previously explained. Women were considered to be users of HT (n = 813) if they reported use of HT for more than 3 months. They were considered to be current-users (n = 727; 89%) if they reported use at date of diagnosis or within 12 months prior to the date of diagnosis of breast cancer. Of the current HT users, 166 (23%) had used an estrogen-only regimen, 246 (34%) had used estrogen–progestin combination therapy, and 314 (43%) had used mixed regimens (switched between estrogen-only and estrogen–progestin regimens. Although there was no statistically significant heterogeneity in HT regimen distribution between familial and sporadic cases (p = 0.057, Chi square test), estrogen-only regimens appeared to be somewhat more common among familial cases (27 vs. 20% in sporadics). Within the mixed category, estrogen-only preparations were also slightly more common (proportion of purchases as reported by the National Medical Reimbursement Registry) among familial cases, but the difference was not statistically significant (44% of all purchases in sporadic, 50% in familial cases; p = 0.1028, Student's *t* test). The mean age of the patients at the time of diagnosis of first invasive breast cancer was 62.6 years (SD 9.1 years). Of all invasive tumors, 1149 (66.3%) were ductal, 358 (20.7%) lobular and 225 (13.0%)

Table 3 BCS interaction analysis adjusted for standard prognostic factors

	HR	95% CI	p value
Model without interaction term			
HT	1.04	(0.73–1.48)	0.81
Family history	0.67	(0.47–0.97)	0.04
Age at diagnosis	1.04	(1.02–1.06)	< 0.0001
Year of diagnosis	0.89	(0.83–0.95)	0.0005
ER status	0.32	(0.21–0.48)	< 0.0001
Grade	1.32	(1.01–1.73)	0.04
Tumor size	1.90	(1.57–2.29)	< 0.0001
Nodal metastasis	2.68	(1.83–3.92)	< 0.0001
Model with interaction term			
HT	0.81	(0.53–1.25)	0.35
Family history	0.46	(0.27–0.79)	0.005
Age at diagnosis	1.04	(1.02–1.06)	< 0.0001
Year of diagnosis	0.89	(0.83–0.95)	0.0004
ER status	0.33	(0.22–0.50)	< 0.0001
Grade	1.31	(1.00–1.71)	0.05
Tumor size	1.90	(1.57–2.30)	< 0.0001
Nodal metastasis	2.68	(1.83–3.91)	< 0.0001
HT * Family history	2.20	(1.05–4.63)	0.04

Interaction analysis between HT use and family history using 10-year BCS (death from breast cancer; deaths from other causes are censored). Standard prognostic factors included are estrogen receptor status (ER), histological grade, tumor size coded as T stage, nodal metastasis coded as 0/1, and age at diagnosis. Additionally, year of diagnosis has been included as an additional covariate to account for different case recruitment periods

other. Age at diagnosis was significantly associated with HT use, with mean age at diagnosis being lower in current-users compared to non-users (61.7 vs. 63.3 years). This association between HT use and age at diagnosis was similar between familial and non-familial cases (no heterogeneity; Table 1). The likelihood of HT use did not associate with family history of breast cancer. Among non-familial patients, 460 (48.3%) were current users of HT, and 267 (45.7%) of the familial cases were current users of HT. Mean starting age of HT use could not be accurately determined for the whole data set, as the information in the National Medical Reimbursement Registry starts in 1994, and a substantial proportion of the cases may have started HT before 1994. Among cases starting in 1995 or later, the mean starting age was 53 years in both familial and sporadic cases.

Analysis of clinicopathological features of breast cancers in familial and non-familial by HT use

See Table 1 for a detailed breakdown of the clinicopathological features of breast cancer tumors among non-familial and familial breast cancer patients according to HT use. Among non-familial patients, current use of HT was associated with more favorable characteristics. Current users of HT were more likely to present with ER-positive tumors ($p = 0.02$), lobular histological type ($p < 0.0005$), tumors of lower grade ($p = 0.001$), less advanced T-stage ($p < 0.0005$), lower rate of nodal metastasis ($p = 0.0004$), and lower Ki-67 proliferative index ($p < 0.0005$).

In contrast, among familial cases HT use did not strongly associate with tumor phenotype. However, there was a significant heterogeneity in HT-phenotype association when comparing familial and non-familial cases, particularly in the case of ER status ($p_{(het)} = 0.0036$), where non-familial HT-associated tumors tended to be ER-positive, and in Ki67 index ($p_{(het)} = 0.0012$), where familial HT-associated tumors had lower proliferation rates, as well as in tumour stage, where familial HT-associated cases had more advanced tumors ($p = 0.03$).

HT use associates with better prognosis among non-familial but not among familial cases

Sensitivity analysis did not indicate significant heterogeneity between the prognostic values of estrogen-only, estrogen–progestin, and mixed HT either among familial ($p = 0.44$, Woolf's test for heterogeneity) or non-familial ($p = 0.92$) cases (Supplementary Fig. 1). The regimens were therefore combined into a single category to define current HT use.

Among the non-familial cases, postmenopausal HT use was associated with better survival in BCS (HR 0.63, 95% CI 0.41–0.94, $p = 0.03$) and DDFS (HR 0.58, 95% CI 0.40–0.85, $p = 0.005$), with a similar but statistically non-significant effect in LRFS (Fig. 2). This favorable prognosis was not observed among familial cases, however. Among familial cases, HT was not associated with survival to a statistically significant degree, and the observed hazard ratios were in the opposite direction compared to non-familial cases. See Fig. 3 for a visual depiction of absolute BCS rates among familial and non-familial cases in relation to HT use.

Based on the results above, we tested for interaction between HT and family history (Table 2). The apparent heterogeneity between familial and non-familial cases was confirmed in the interaction analysis, with $p_{(interaction)}$ values of 0.007 (BCS), 0.007 (DDFS). Again, LRFS statistics followed a similar pattern but did not reach statistical significance ($p = 0.05$).

In a multivariate interaction analysis (BCS), we observed a statistically significant ($p = 0.04$) increased hazard associated with the combination of HT and family history, despite adjustment for year of diagnosis and standard prognostic factors (ER, T, N, Grade, and age; Table 3).

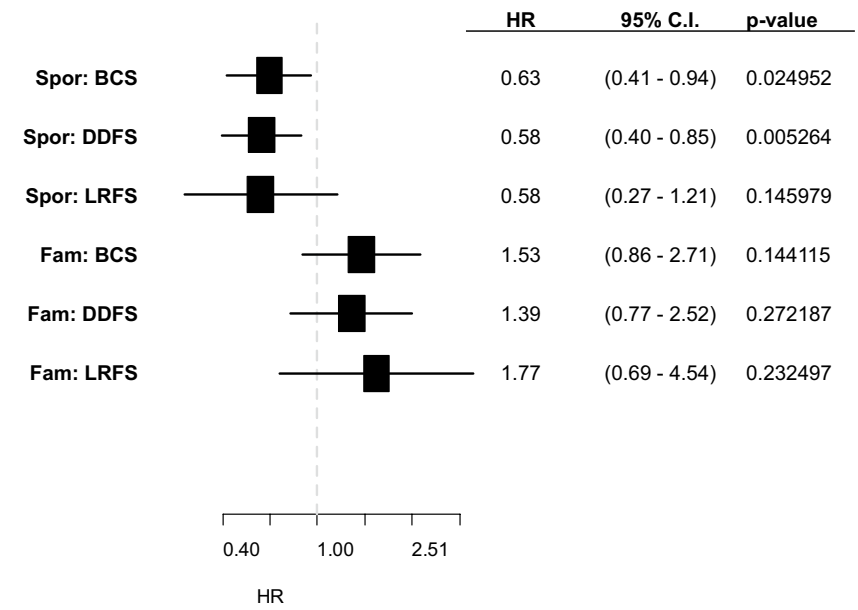

Fig. 2 Survival statistics for HT users compared to non-users among sporadic and familial breast cancer cases. The end points in the analyses are BCS (death from breast cancer; deaths from other causes are censored; all follow-up times are censored at 10 years), distant disease free survival (distant metastasis; DDFS) and local recurrence free survival (LRFS). For DDFS and LRFS, follow-up times are censored at 6 years. All analyses are adjusted for age at diagnosis

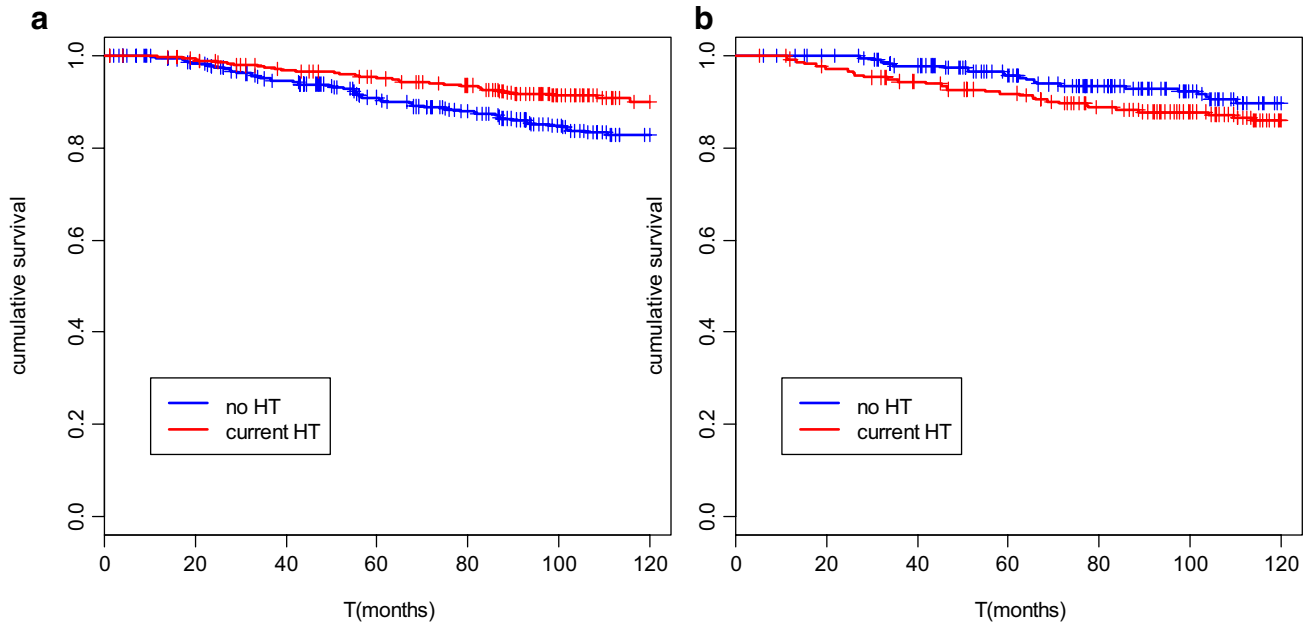

Fig. 3 Kaplan–Meier curves illustrating breast cancer specific survival according to HT use. Breast-cancer specific (BCS) survival curves are depicted for **a** sporadic and **b** familial breast cancer cases according to HT use at the time of diagnosis. Follow-up times are left-truncated to account for recruitment latency, and right-censored at a maximum of 10 years of follow-up

A sensitivity analysis (Supplementary Fig. 1) did not indicate any major difference between HT-regimens and prognostic interaction.

Discussion

We have investigated the relationship between hormone therapy, family history, and breast cancer prognosis. Our results suggest that the association between HT and prognosis may be influenced by family history: while sporadic breast cancers developing during HT tend to have favorable prognosis, in familial cases HT use either does not associate with prognosis at all, or may lead to slightly worse survival. Consistent with our findings in sporadic cases, most previous observational studies indicate that the breast cancers diagnosed during HT are less aggressive with higher histological differentiation [4, 9–23]. HT has been associated

with low-grade, mostly hormone-receptor positive invasive cancers and lobular histology, and HT-related breast cancers tend to have better prognosis. In the studies where information on regimen was available [13, 16, 18, 21] both patients on estrogen only and estrogen combined with progestin were included; the majority, approximately 80%, had combination therapy. However, these findings were not confirmed in the first randomized placebo-controlled trial, he Women's Health Initiative (WHI), where combined HT was associated with more advanced cancer at diagnosis and worse prognosis, while estrogen only was associated with an improved prognosis and more favorable tumor characteristics [7]. The reason for the discrepancy between breast cancer characteristics in the combined HT group in the WHI study and the majority of previous observational studies remains unclear. Although a randomized study, the WHI trial did not include a randomization between estrogen only and combined HT. Instead, the treatment arm was chosen based on previous history of hysterectomy. It is therefore possible that the difference in tumor characteristics and prognosis between these two HT regimens may be influenced by confounding factors in addition to the effect of the HT regimen per se.

There is little previous data available on the effect of previous HT use in women with a family history of breast cancer. The Iowa Women's health study was the first to investigate the role of family history in combination with HT: in this study, HT users with a family history had a significantly lower hazard of all-cause mortality than never-users, but not when death from breast cancer was used as the end-point. The breast-cancer specific hazard in fact appeared to have increased in association with HT use, although this was not statistically significant, and the statistical confidence intervals were wide (RR 1.9; 95% CI 0.6–5.7) [24].

Our results are consistent with most previous observational studies in that HT use appears to associate with more favorable tumor characteristics and better prognosis in cases without family history. However no such protective effect was seen among cases with family history. Indeed, in familial cases HT use appeared to associate with increased hazard, although not to a statistically significant degree. This observation was statistically verified by an interaction test, which indicated that the prognosis associated with HT use is modulated by family history using either death from breast cancer (BCS) or distant metastasis (DDFS) as survival end-points. We also detected statistically significant phenotypic heterogeneity between familial and non-familial cases, particularly in the case of ER status and Ki67 proliferative index. As the association between HT and tumor characteristics differed between familial and non-familial cases, the association between HT and survival can be partially expected to arise from differences in tumor histopathology: the tumors of familial HT users exhibit markers of worse prognosis (ER-negativity and proliferation). The association between HT and survival does not appear to be entirely explained by these prognostic markers, however, since multivariate analysis still showed a statistically significant interaction.

The large randomized WHI study indicated biological differences between estrogen-only and estrogen–progestin therapy: estrogen-only therapy may be associated with an improved breast cancer prognosis, whereas combined estrogen–progestin therapy may in contrast be associated with increased mortality and adverse prognostic features [7, 8]. The WHI trial included a substantial proportion of women with familial history, between 11.8 and 14.2% in the different treatment groups, but no separate analyses of familial cases were reported. It was therefore important to consider the possibility that our results may be confounded by differences in HT regimens between familial and sporadic cases. Our study included patients on estrogen therapy alone, estrogen–progestin combination therapy, and a large subset (43%) of cases who had switched one or more times between estrogen and estrogen–progestin regimens (mixed category). The mixed category may in reality be even larger, since we do not have data from before 1994. Due to the smaller number of patients in the regimen-specific subgroups, it was not feasible to conduct comprehensive analyses of these groups separately with sufficient statistical power. However, a sensitivity analysis (Supplementary Fig. 1) did not indicate any major differences in prognosis between these categories. It must be noted that while the distributions of HT regimens were similar between familial and sporadic cases, estrogen-only regimens were nevertheless somewhat more common among the familial cases in our study. Similarly, the distributions of specific HT drug types within the "mixed" category were also very similar between familial and non-familial cases, yet estrogen-only preparations were slightly more common among familial cases. These minor differences are unlikely to have biased our results towards worse prognosis among familial cases, given that estrogen-only HT has been reported to associate with better prognosis compared to combination therapies.

A major strength of the present study is the availability of accurate patient data through the uniform, centralized Finnish health care system. Detailed data on tumor histopathology and follow-up data could be obtained from clinical records and the nationwide Finnish Cancer Registry, and reliable, detailed information on systemic hormone therapy obtained from the National Medical Reimbursement Registry of the Social Insurance Institution during the period of 16 years, ranging from beginning of 1994 until the end of 2009. Data from National Medical Reimbursement Registry cover practically 100% of all HT users because HT is available only on medical prescription in Finland. Moreover, since HT use was based on registry data in contrast to patient reported data, the effect of patient recall bias is eliminated. One minor

limitation of this study is that accurate time of exposure to HT regimen could not be calculated for patients who were using HT already in 1994, when the Reimbursement Registry of the Social Insurance Institution was established. For these patients we cannot be sure of the accurate time of exposure to HT, which prevents the reliable inclusion of past use and the duration of use as parameters in the analyses. We have therefore restricted our analyses to current-use only, and to patients diagnosed after 1994.

The most important limitations of this study arise from the observational nature of this investigation. Lifestyle factors cannot be entirely accounted for or excluded as confounders. It must also be noted that we cannot rule out a degree of potential selection bias in our study since the majority of our familial cases have been collected specifically from patients attending clinical genetics counseling due to the suspicion of familial disease, whereas the sporadic patients were recruited as unselected consecutive patients during a limited time-period. All these sporadic cases have, however, been interviewed for family history. Both family history and HT use can also influence the patients' lifestyle, such as the frequency of mammography screening, for which we do not have available data. However, population-based mammography screening has been available in Finland since 1987 among women aged 50–69, which probably minimizes any bias in breast screening between HT users and non-users in our cohort. Moreover, the cancers in the familial and non-familial HT users in our study display differential biological characteristics, notably ER status, in addition to differences in survival times, which is not to be expected had the adverse prognosis of HT users in the familial cases been due to lifestyle factors.

Conclusions

Our results suggest that a positive family history of breast cancer may predispose users of postmenopausal hormone therapy to breast cancer with a more aggressive phenotype and worse prognosis compared to HT users without family history. If confirmed by further studies, our results suggest that family history should be taken into consideration in clinical counseling before beginning a HT regimen. Physicians should discuss the benefits and risks of HT with women in the context of their own personal or family history, so that they can make informed decisions about initiating or continuing HT use.

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Author Contributions RF prepared the manuscript and performed most of the statistical analyses. MF classified the treatment data and patient material, performed initial statistical analyses. KA assisted in manuscript preparation. KA coordinated clinical case data acquisition from the Department of Clinical Genetics. PH reviewed the histopathological and immunohistochemical data. MH assisted in manuscript preparation and interpretation of the statistical findings in a clinical context. HN coordinated and supervised the study, participated in study design. CB designed the study, coordinated and supervised the study. All authors participated in the interpretation of the results and the preparation of the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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