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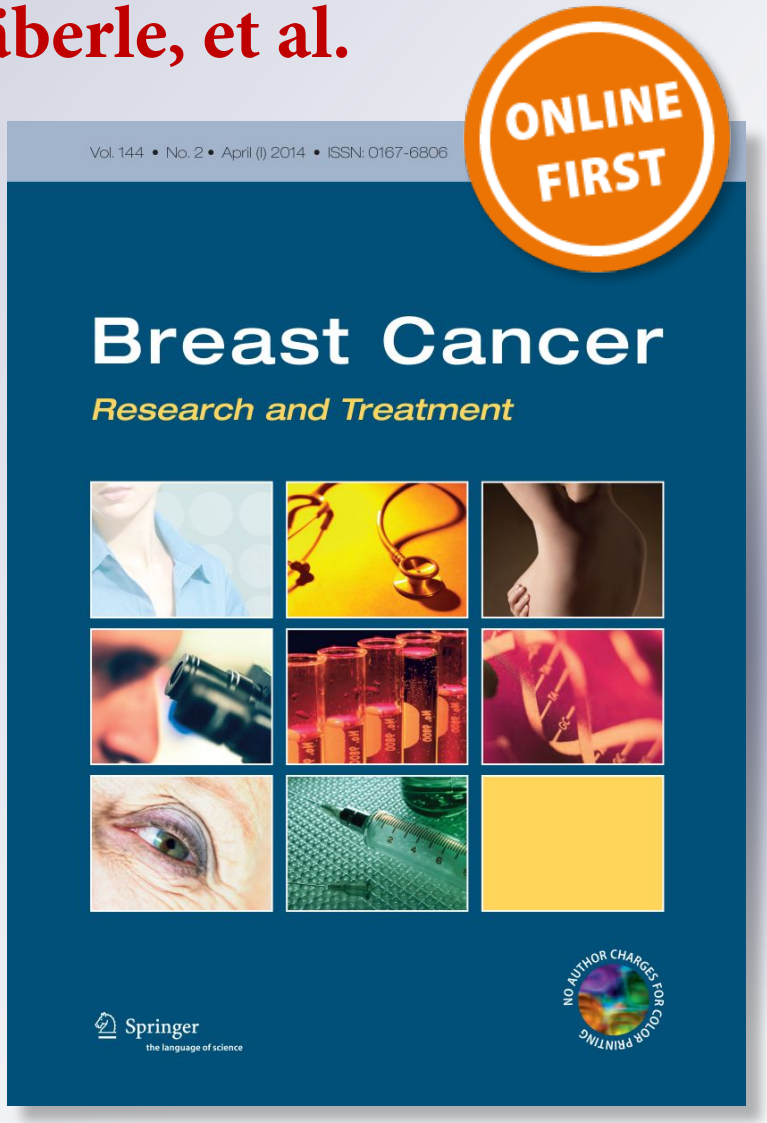


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CLINICAL TRIAL

# Association between breast cancer risk factors and molecular type in postmenopausal patients with hormone receptor-positive early breast cancer

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## Abstract

**Purpose** Evidence shows that genetic and non-genetic risk factors for breast cancer (BC) differ relative to the molecular subtype. This analysis aimed to investigate associations between epidemiological risk factors and immunohistochemical subtypes in a cohort of postmenopausal, hormone receptor-positive BC patients.

**Methods** The prospective, single-arm, multicenter phase IV PreFace study (Evaluation of Predictive Factors Regarding the Effectivity of Aromatase Inhibitor Therapy) included 3529 postmenopausal patients with hormone receptor-positive early BC. Data on their epidemiological risk factors were obtained from patients' diaries and their medical histories. Data on estrogen receptor, progesterone receptor, and HER2 receptor status were obtained from pathology reports. Patients with incomplete information were excluded. Data were analyzed using conditional inference regression analysis, analysis of variance, and the chi-squared test.

**Results** In a cohort of 3392 patients, the strongest association with the molecular subtypes of BC was found for hormone replacement therapy (HRT) before diagnosis of early BC. The analysis showed that patients who took HRT at diagnosis had luminal A-like BC more often (83.7%) than those who had never taken HRT or had stopped taking it (75.5%). Luminal B-like BC and HER2-positive BC were diagnosed more often in women who had never taken HRT or had stopped taking it (13.3% and 11.2%, respectively) than in women who were taking HRT at diagnosis of BC (8.3% and 8.0%, respectively).

**Conclusions** This analysis shows an association between HRT and the distribution of molecular subtypes of BC. However, no associations between other factors (e.g., age at diagnosis, body mass index, smoking status, age at menopause, number of deliveries, age at first delivery, breastfeeding history, or family history) were noted.

**Keywords** Breast cancer · Molecular subtype · Risk factors · Hormone replacement therapy · Prognosis

## Introduction

With 1.67 million new cases diagnosed in 2012, breast cancer (BC) is the most common type of cancer diagnosed in women worldwide [1]. Several different molecular subtypes of BC, distinguished by different gene expression patterns, were identified nearly two decades ago: one estrogen receptor (ER)-positive (ER+/luminal) subtype and three

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ER-negative subtypes (basal-like, HER2-positive, and normal-like) [2]. The ER-positive subtype was further classified into the luminal A and luminal B subtypes, with the latter having a lower prevalence and a poorer prognosis [3, 4]. To allow these molecular subtypes to be used in clinical routine, immunohistochemical markers are employed to approximate the classification with gene expression patterns [5, 6]. Treatments and drug development are currently mainly directed at these molecular subtypes [7, 8].

There is evidence that age, family history, obesity, as well as reproductive and hormonal factors such as early menarche, late menopause, no breastfeeding or only brief breastfeeding, late age at first full-term delivery, nulliparity, and administration of hormone replacement therapy (HRT) are risk factors for developing BC [9–11]. It has also been demonstrated that the risk factors associated with different molecular subtypes of BC vary [12–19]. Moreover, there is evidence that genetic risk factors differ depending on the molecular tumor type and that they have an impact on the prognosis [20–29]. One of the most important risk factors, with an up to fivefold increase in the risk for BC, is mammographic density (MD) [18, 30, 31]. It has been shown that MD is inversely associated with estrogen receptor expression [32, 33]. It has also been reported that the association between MD and HRT administration interacts with Ki-67 expression [33].

The molecular mechanisms that link risk factors to the development of a specific molecular subtype are still not well understood. It would be of great interest to examine whether the known risk factors are relevant for all molecular subtypes, or whether they are only important for the development of a specific subtype. This could lead to a better understanding of tumor development and might possibly lead to new cancer prevention strategies and new targeted therapeutic options [19, 34].

The objective of this analysis was therefore to investigate the association between BC risk factors and the three molecular subtypes—luminal A-like, luminal B-like, and HER2-positive tumors—in a cohort of postmenopausal patients with hormone receptor-positive early BC who were treated with the aromatase inhibitor letrozole.

## Methods

### Patient recruitment and conduct of the study

The PreFace study (Evaluation of Predictive Factors Regarding the Effectivity of Aromatase Inhibitor Therapy, NCT01908556) is a prospective, single-arm, multicenter phase IV study investigating the influence of pharmacogenetic markers on efficacy and side effects in patients with hormone receptor-positive BC who are postmenopausal and have received adjuvant therapy with letrozole 2.5 mg for a period of 5 years. The study included 3529 postmenopausal women with steroid receptor-positive BC at 250 study sites in Germany between February 2009 and November 2010. In all, 137 patients with missing data for estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor status were excluded. Data for a total of 3392 patients were therefore analyzed.

### Data collection

The epidemiological risk factors were collected by using diaries kept by the patients and from their medical histories and were documented prospectively in an electronic case report form. Tumor and histopathological characteristics, as well as tumor treatment data, were documented in the electronic case report form.

### Pathological data

Data on tumor type, tumor grading, ER, PR, and HER2 status were obtained from the routine pathology reports. Tumors were considered hormone receptor-positive when ER-expression or PR-expression was observed in 10% or more of the tumor cells. This threshold was chosen because at the time when the trial started, a tumor with $< 10\%$ of its cells staining positive for steroid hormone receptors was not regarded as hormone receptor-positive but as a tumor of uncertain endocrine responsiveness [35].

The HER2 status was reported as 0, 1+, 2+, or 3+ according to immunohistochemical staining. HER2 expression in tumors with 2+ staining was regarded as being uncertain and requiring further testing using chromogen in situ hybridization (CISH) or fluorescence in situ hybridization (FISH). Tumors were defined as HER2-negative if the score was 0 or 1+ or 2+ with negative FISH or CISH; as HER2-positive if the score was 2+ or 3+ and FISH- or CISH-positive. The three molecular subtypes were defined as luminal A-like (HER2-negative, grading 1 or 2, positive hormone receptor status), luminal B-like (HER2-negative, grading 3, positive hormone receptor status), and HER2-positive (HER-positive, regardless of hormone receptor status).

### Statistical considerations

Descriptive characteristics for patients in the different molecular subgroups (luminal A-like, luminal B-like, and HER2-positive) are given as means plus or minus standard deviation (SD) or as frequencies and percentages.

The heterogeneity of the risk factors of age at first delivery and breastfeeding status between the molecular subgroups was evaluated using analysis of variance (ANOVA) for the quantitative variable age at first delivery and with the

chi-squared test for the dichotomous variable breastfeeding status.

The association between molecular subgroups and risk factors was analyzed using a conditional inference tree [36], a method which partitions the dataset in homogeneous subgroups by finding optimal 'splits' in the predictor variables. Furthermore, multinomial regression analysis was performed, resulting in adjusted odds ratios (ORs) for molecular subgroups. Predictor variables included in the analysis were age at diagnosis, body mass index (BMI), hormone replacement therapy (HRT until diagnosis, previous HRT, or no HRT ever), smoking status (until diagnosis, former, never), age at menopause, number of deliveries, age at first delivery, breastfeeding history (yes, no), and family history (positive, negative). Positive family history was defined as at least one first-degree relative with BC irrespective of age. Data analyses were performed using the R system for statistical computing (version 3.3.3, 2017) [37].

## Results

The analysis included a total of 3392 women. The women's mean age at the time of BC diagnosis was 63.7 years (SD 8.0 years). The majority of patients were diagnosed with pT1 tumors ($n = 2148$, 63.3%) and with no lymph nodes affected ($n = 2384$, 70.3%). The patients' characteristics are listed in Table 1. With regard to molecular types, there were 2581 (76.1%) patients with luminal A-like tumors, 441 (13.0%) with luminal B-like tumors, and 370 (10.9%) patients with HER2-positive tumors.

The characteristics of the study population in relation to molecular subtypes are shown in Table 2. The patients' mean ages were, 63.7 (SD 7.9) years in those with luminal A-like tumors, 64.3 (SD 8.3) years in those with luminal B-like tumors, and 62.8 (SD 8.0) years in women with HER2-positive tumors. The mean BMI at diagnosis was 27.2 (SD 5.2) kg/m$^2$. There were no significant differences between the different molecular subtypes. With regard to tobacco consumption, 83.8% of the women were non-smokers at the time of diagnosis (64.0% had never smoked and 19.8% had formerly smoked), 13.4% were currently smoking at the time of diagnosis, and no information about smoking was given by 2.8%. The patients' mean age at menopause was 49.4 (SD 5.4) years and their mean age at the first live delivery was 24.1 (SD 4.7) years. There were no differences between the different molecular subtypes in relation to these characteristics.

With regard to HRT, 10.3% of the women took HRT until diagnosis, 22.8% had taken HRT at some time, 59.6% had never taken HRT, and no information was available for 7.3%. Information on type and duration of HRT was available for 61.9% and 69.1% of patients. Of these, 57.3% were treated with a combination of estrogen and progestin, while 42.7%

**Table 1** Patient and tumor characteristics

| | *n* or mean | % or SD |
|---|---|---|
| Overall (*n*) | 3392 | |
| Age (mean, SD) | 63.7 | 8.0 |
| BMI (mean, SD) | 27.2 | 5.2 |
| HRT administration (*n*, %) | | |
| Until diagnosis | 350 | 10.3 |
| Former | 772 | 22.8 |
| Never | 2022 | 59.6 |
| N/A | 248 | 7.3 |
| Smoking history (*n*, %) | | |
| Until diagnosis | 455 | 13.4 |
| Former | 671 | 19.8 |
| Never | 2172 | 64.0 |
| N/A | 94 | 2.8 |
| Age at menopause (mean, SD) | 49.4 | 5.5 |
| Age at first live delivery (mean, SD) | 24.1 | 4.7 |
| Number of live deliveries (*n*, %) | | |
| 0 | 312 | 9.2 |
| 1 | 816 | 24.1 |
| 2 | 1322 | 39.0 |
| ≥ 3 | 641 | 18.9 |
| N/A | 301 | 8.9 |
| Breastfeeding history (*n*, %) | | |
| Ever | 1859 | 54.8 |
| Never | 837 | 24.7 |
| N/A | 696 | 20.5 |
| Family history of BC (*n*, %) | | |
| Positive | 602 | 17.7 |
| Negative | 2579 | 76.0 |
| Unknown | 211 | 6.2 |
| Grading (*n*, %) | | |
| G1 | 621 | 18.3 |
| G2 | 2206 | 65.0 |
| G3 | 565 | 16.7 |
| pT (*n*, %) | | |
| pT0, pTis | 47 | 1.4 |
| pT1 | 2148 | 63.3 |
| pT2 | 1018 | 30.0 |
| pT3 | 127 | 3.7 |
| pT4 | 42 | 1.2 |
| pTx | 10 | 0.3 |
| pN (*n*, %) | | |
| pN0 | 2384 | 70.3 |
| pN1 | 668 | 19.7 |
| pN2 | 190 | 5.6 |
| pN3 | 122 | 3.6 |
| pNx | 28 | 0.8 |
| cM (*n*, %) | | |
| cM0 | 3295 | 97.1 |
| cMx | 97 | 2.9 |

**Table 1** (continued)

*BC* breast cancer, *HRT* hormone replacement therapy, *BMI* body mass index, *SD* standard deviation, *N/A* not available

received estrogen monotherapy. The median duration of HRT was 66 months (interquartile range 30–138 months; mean 97.9 months).

Luminal A-like tumors were more frequent in women who were taking HRT at the time of diagnosis (83.7%) in comparison with women who had formerly used or had never used HRT (75.5%). Luminal B-like BC was diagnosed less frequently in women who were taking HRT at the time of diagnosis (8.3%), whereas luminal B-like BC was diagnosed in 13.3% of cases in women who had formerly used HRT or had never used it. HER2-positive BC was also less frequently diagnosed in women who were using HRT up to the time of diagnosis (8.0%) in comparison with women who had formerly received or never received it (11.2%).

The conditional inference regression analysis (Fig. 1) showed that the distribution of molecular subtypes was dependent on previous HRT use ($p = 0.049$). No association was found in relation to age at diagnosis, BMI, smoking status, age at menopause, number of deliveries, family history, breastfeeding, or age at first live delivery. Adjusted category-specific ORs (Table 3) also indicated a difference between women taking HRT at time of diagnosis and women who had never or previously used it with regard to higher odds of being diagnosed with luminal A-like BC vs. HER2-positive BC (OR 1.65, $p = 0.07$).

**Table 2** Patient characteristics, stratified by molecular subtypes of breast cancer

| | HER2-positive BC | | Luminal A-like BC | | Luminal B-like BC | |
|---|---|---|---|---|---|---|
| Overall (*n*) | 370 | | 2581 | | 441 | |
| Age (mean, SD) | 62.8 | 8.0 | 63.7 | 7.9 | 64.3 | 8.3 |
| BMI (mean, SD) | 27.0 | 4.6 | 27.2 | 5.2 | 27.4 | 5.0 |
| HRT administration (*n*, %) | | | | | | |
| Until diagnosis | 28 | 7.6 | 293 | 11.4 | 29 | 6.6 |
| Former | 90 | 24.3 | 592 | 22.9 | 90 | 20.4 |
| Never | 224 | 60.5 | 1516 | 58.7 | 282 | 63.9 |
| N/A | 28 | 7.6 | 180 | 7.0 | 40 | 9.1 |
| Smoking history (*n*, %) | | | | | | |
| Until diagnosis | 49 | 13.2 | 351 | 13.6 | 55 | 12.5 |
| Former | 77 | 20.8 | 502 | 19.4 | 92 | 20.9 |
| Never | 231 | 62.4 | 1658 | 64.2 | 283 | 64.2 |
| N/A | 13 | 3.5 | 70 | 2.7 | 11 | 2.5 |
| Age at menopause (mean, SD) | 49.3 | 5.0 | 49.4 | 5.5 | 49.6 | 5.5 |
| Age at first live delivery (mean, SD) | 24.2 | 4.9 | 24.1 | 4.7 | 24.1 | 4.6 |
| Number of live deliveries (*n*, %) | | | | | | |
| 0 | 37 | 10.0 | 245 | 9.5 | 30 | 6.8 |
| 1 | 88 | 23.8 | 621 | 24.1 | 107 | 24.3 |
| 2 | 144 | 38.9 | 1009 | 39.1 | 169 | 38.3 |
| ≥ 3 | 62 | 16.8 | 485 | 18.8 | 94 | 21.3 |
| N/A | 39 | 10.5 | 221 | 8.6 | 41 | 9.3 |
| Breastfeeding history (*n*, %) | | | | | | |
| Ever | 194 | 52.4 | 1,411 | 54.7 | 254 | 57.6 |
| Never | 91 | 24.6 | 638 | 24.7 | 108 | 24.5 |
| N/A | 85 | 23.0 | 532 | 20.6 | 79 | 17.9 |
| Family history of BC (*n*, %) | | | | | | |
| Positive | 74 | 20.0 | 443 | 17.2 | 85 | 19.3 |
| Negative | 276 | 74.6 | 1972 | 76.4 | 331 | 75.1 |
| Unknown | 20 | 5.4 | 166 | 6.4 | 25 | 5.7 |

*BC* breast cancer, *BMI* body mass index, *HRT* hormone replacement therapy, *SD* standard deviation, *N/A* not available

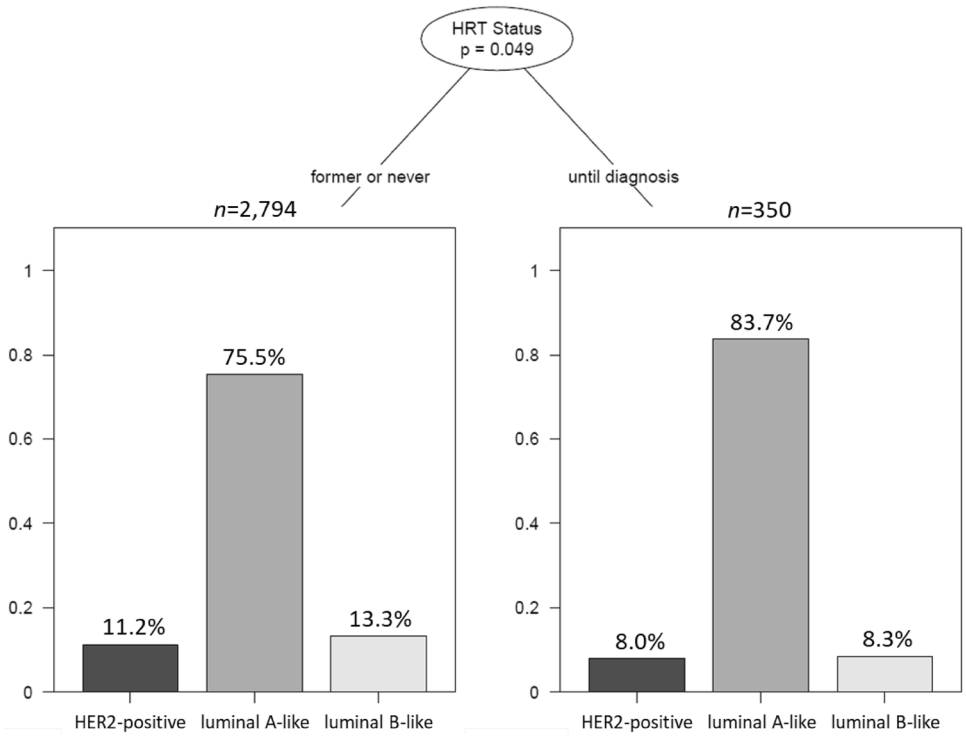


**Fig. 1** Conditional inference tree for the classification of breast cancer patients with different molecular subgroups (HER2-positive, luminal A-like, luminal B-like) and influence of hormone replacement therapy (HRT)

**Table 3** Adjusted category-specific ORs from multinomial regression model with reference category HER2-positive breast cancer

| | Luminal A-like BC | *p* value | Luminal B-like BC | *p* value |
|---|---|---|---|---|
| Age | 1.02 | 0.07 | 1.02 | 0.07 |
| BMI | 1.02 | 0.28 | 1.02 | 0.24 |
| HRT administration | | | | |
| Until diagnosis | 1.65 | 0.07 | 0.79 | 0.52 |
| Former | 0.95 | 0.75 | 0.73 | 0.15 |
| Never | 1 (ref) | – | 1 (ref) | – |
| Smoking history | | | | |
| Until diagnosis | 1.34 | 0.22 | 1.41 | 0.25 |
| Former | 1.03 | 0.87 | 1.02 | 0.92 |
| Never | 1 (ref) | – | 1 (ref) | – |
| Age at menopause | 1.00 | 0.74 | 1.00 | 0.81 |
| Age at first live delivery | 1.01 | 0.52 | 1.00 | 0.97 |
| Number of live deliveries | 1.08 | 0.35 | 1.09 | 0.41 |
| Breastfeeding history | | | | |
| Ever | 1.13 | 0.48 | 1.01 | 0.95 |
| Never | 1 (ref) | – | 1 (ref) | – |
| Family history of BC | | | | |
| Positive | 0.74 | 0.10 | 0.67 | 0.10 |
| Negative | 1 (ref) | – | 1 (ref) | – |

*BC* breast cancer, *BMI* body mass index, *HRT* hormone replacement therapy, *Ref* reference

## Discussion

This analysis of patients with postmenopausal, hormone receptor-positive early BC shows that using HRT before a diagnosis of BC is associated with the distribution of molecular type of early BC.

It is known that current administration of HRT increases the risk of developing BC [9, 38–41]. HRT use has also been reported to be associated with smaller tumors [42–44], lower grading [44–47], and a better prognosis [44, 48]. These results are in line with the present finding that luminal A-like tumors are more frequently diagnosed in the group of patients who are currently receiving HRT in comparison with those who have never received HRT or had stopped receiving it.

Several studies have reported an association between the use of HRT and the risk of specifically developing luminal BC [12, 49–53]. In a multiethnic cohort study of postmenopausal women, current HRT administration was associated with the development of ER-positive/PR-positive tumors (hazard ratio, HR 2.28; 95% CI 1.97 to 2.64) and ER-positive/PR-negative tumors (HR 1.63, 95% CI 1.15 to 2.33) [50]. A case-control study showed that receiving HRT was associated with a higher risk of developing a luminal BC (OR 1.7; 95% CI 1.3 to 2.1) in women aged between 55 and 79 years [49]. The association between risk factors and molecular subtypes of BC was investigated in a subset of 2022 BC cases from the Nurses' Health Study. HRT administration in general resulted in an increased risk for luminal

A-like tumors, but not luminal B-like tumors [12]. Another recent case–control study showed that receiving HRT was associated with luminal A-like BC in a large group of 4748 women who had BC (OR 2.92; 95% CI 2.36 to 3.62) [53]. On the other hand, no association between HRT and HER2-positive BC was found in some of the above-mentioned studies [12, 49, 53].

The present analysis provides evidence that patients who were using HRT at diagnosis of BC were more likely to develop luminal A-like BC and less likely luminal B-like BC or HER2-positive BC. On the contrary, patients who had stopped HRT or had never used it were less likely to be diagnosed with luminal A-like BC and were more likely to be diagnosed with luminal B-like BC or HER2-positive BC (Fig. 1). A partly similar trend has been described in the above-mentioned analysis of BC cases from the Nurses' Health Study [12]. Nevertheless, to the best of our knowledge, the distinction between different BC subtypes depending on the time of HRT intake, as shown here, has not been reported in other studies of this size.

No significant association between breastfeeding history and luminal A-like, luminal B-like, and HER2-positive molecular subtypes was found in the present analysis. In the literature, breastfeeding has been reported to be inversely associated with hormone receptor-positive BC, although less consistently than other reproductive risk factors [38].

In our study, no significant association was found between age at first live delivery and the different molecular subtypes of BC. A recent meta-analysis showed that advanced age at first delivery is associated with the development of luminal-like BC, although with significant heterogeneity, whereas an association between age at first live delivery and HER2-positive BC was not found [14]. The majority of the trials included in this meta-analysis divided the women into two groups: those who were $\leq 24$ years at first live delivery and those who were $> 24$ years when their first child was born. A case–control study also found that women aged $\geq 30$ years at first delivery are at greater risk of developing hormone-positive BC in comparison with women aged between 20 and 24 at first delivery [54].

In the population included in the present study, previous use of HRT was associated with a higher prevalence of luminal A-like BC. This patient population may therefore have a more favorable prognosis. Our group showed in a retrospective cohort study that patients with previous use of HRT had a more favorable prognosis [44]. It may therefore be postulated that patients with previous HRT may not only have a different molecular subtype, but also a different prognosis. This could have several implications in relation to the prevention and treatment of BC. It is not known whether HRT also has an influence on novel therapies, many of which focus on anti-endocrine treatment [55]. It might be worthwhile to include documentation of HRT administration in future clinical trials, for subgroup analyses in connection with the efficacy of anti-endocrine treatments.

This study has some limitations and strengths. One strength is the prospective nature of the trial. Additionally, the trial has a large sample size. The analysis is limited by its design as a case–case analysis. Although it shows an association between the intake of HRT and the distribution of the luminal A-like, luminal B-like, and HER2-positive molecular subtypes, it is not possible to draw any conclusions regarding which way the distribution is influenced—either by increasing the risk for one subtype or decreasing the risk for another. The molecular tumor types were only based on pathological hormone receptor status, since gene expression profiles of the tumors were not available. Another limitation of the analysis is that the results are applicable to the present study population with early BC and no severe secondary diagnoses or other carcinomas according to the inclusion/exclusion criteria of the PreFace study.

In conclusion, this analysis shows an association between HRT administration and the molecular subtypes of BC. The majority of the tumors were luminal A-like, especially if women received HRT until diagnosis of BC. If HRT was never or formerly taken, but not until diagnosis, this was associated with a relatively decreased number of luminal A-like tumors and a relatively increased number of luminal B-like tumors and HER2-positive tumors. However, further research will be needed—e.g., case–control studies—in order to elucidate which way the influence of HRT acts.

**Author contributions** MW, JP, PAF, and CR contributed to the acquisition and interpretation of data, to the conception, drafting, and critical revision of the manuscript. CF and LH performed statistical analyses and contributed to critical revision of the manuscript. SYB, BV, AH, AH, SMJ, MPL, WJ, CRL, ADH, CBW, GB, AF, WM, RW, NH, OH, SK, BM, CT, HG, CW, CMB, CCH, KA, PG, FH, TFB, NN, CL, HCK, PK, MW, DSB, AK, CB, VS, GF, VP, DW, BR, TF, AR, NM, and MWB were involved in the acquisition of patient and tumor data and in critical revision of the manuscript. All authors have read the manuscript and have given their final approval for publication of this study.

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## Compliance with ethical standards

**Conflict of interest** A Hartmann received honoraria from BMS, Roche, MSD, Novartis, AstraZeneca, NanoString, and BioNTech and funding from NanoString, BioNTech, and Janssen-Cilag. MPL received honoraria from Pfizer, Roche, MSD, Hexal, Novartis, AstraZeneca, Celgene, Eisai, Medac, and Thieme for advisory boards, lectures, and travel support. WJ received research grants from Novartis. ADH participated on advisory boards for Novartis. RW participated on advisory boards for Novartis, AstraZeneca, Pfizer, and Lilly. SK participated on advisory boards for Roche/Genentech, Genomic Health, Novartis, AstraZeneca, Amgen, Celgene, SOMATEX, Daiichi Sankyo, Puma Biotechnology, pfm medical, Pfizer, and MSD Oncology and received funding from Roche and Daiichi Sankyo. CT received honoraria from Amgen, AstraZeneca, Celgene, Genomic Health, Lilly, Na-

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**Ethical approval** Approval for the study was obtained from the ethics committee of the Faculty of Medicine at Friedrich Alexander University of Erlangen-Nuremberg and all of the relevant local ethics committees. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Written informed consent was obtained from the patients as part of the inclusion criteria before they entered the study.

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