CLINICAL TRIAL

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

Marius Wunderle[1] · Jutta Pretscher[1] · Sara Y. Brucker[2] · Bernhard Volz[1] · Arndt Hartmann[3] · Cornelia Fiessler[4] · Alexander Hein[1] · Lothar Häberle[1] · Sebastian M. Jud[1] · Michael P. Lux[1] · Wolfgang Janni[5] · Christian R. Loehberg[1] · Andreas D. Hartkopf[2] · Christina B. Walter[2] · Gerold Baake[6] · Alexander Fridman[7,8] · Wolfram Malter[7] · Rachel Wuerstlein[9] · Nadia Harbeck[9] · Oliver Hoffmann[10] · Sherko Kümmel[11] · Bernhard Martin[12] · Christoph Thomssen[13] · Heiko Graf[14] · Christopher Wolf[15] · Christian M. Bayer[1] · Carolin C. Hack[1] · Katrin Almstedt[16] · Paul Gass[1] · Felix Heindl[1] · Tobias F. Brodkorb[1] · Naiba Nabieva[1] · Christoph Lindner[17] · Hans-Christian Kolberg[18] · Petra Krabisch[19] · Michael Weigel[20] · Dieter Steinfeld-Birg[21] · Andreas Kohls[22] · Cosima Brucker[23] · Volker Schulz[24] · Gunnar Fischer[25] · Volker Pelzer[26] · Diethelm Wallwiener[2] · Brigitte Rack[5] · Tanja Fehm[27] · Achim Rody[28] · Nicolai Maass[29] · Matthias W. Beckmann[1] · Peter A. Fasching[1] · Claudia Rauh[1]

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

✉ Peter A. Fasching
peter.fasching@uk-erlangen.de

Extended author information available on the last page of the article

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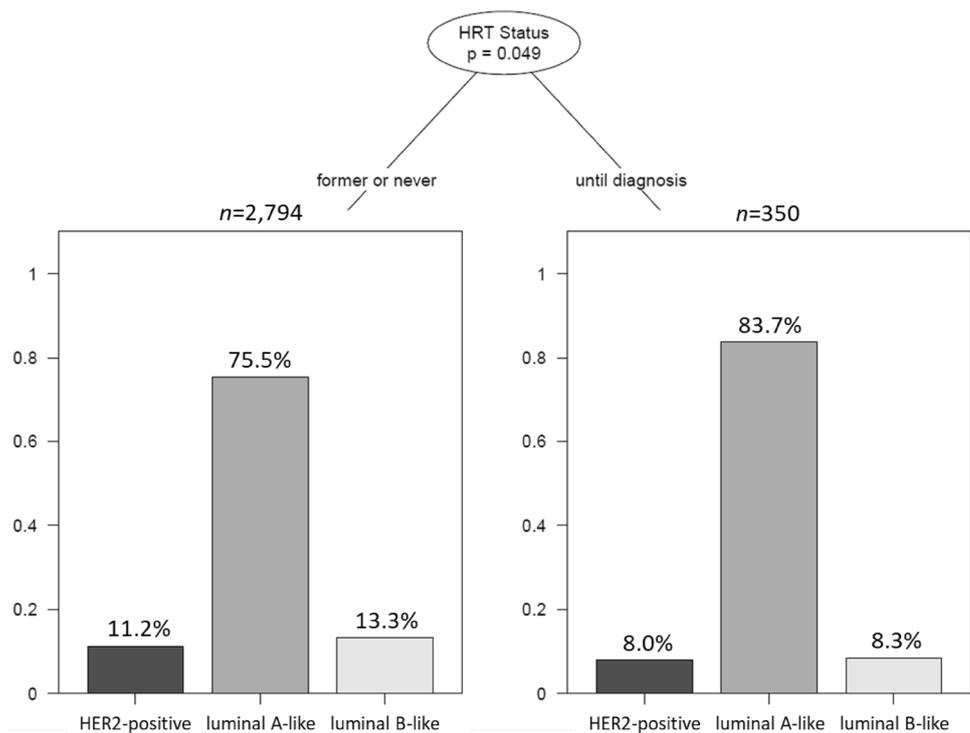
Table 3 Adjusted category-specific ORs from multinomial regression model with reference category HER2-positive breast cancer

	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 ≤ 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 ≥ 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.

Compliance with ethical standards

References

1. Ferlay J et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386
2. Perou CM et al (2000) Molecular portraits of human breast tumours. Nature 406(6797):747–752
3. Sorlie T et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98(19):10869–10874
4. Ades F et al (2014) Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. J Clin Oncol 32(25):2794–2803
5. Sotiriou C, Pusztai L (2009) Gene-expression signatures in breast cancer. N Engl J Med 360(8):790–800
6. Cheang MC et al (2009) Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst 101(10):736–750
7. Taran FA et al (2018) Update breast cancer 2018 (Part 1)—primary breast cancer and biomarkers. Geburtshilfe Frauenheilkd 78(3):237–245
8. Schneeweiss A et al (2018) Update breast cancer 2018 (Part 2)—advanced breast cancer, quality of life and prevention. Geburtshilfe Frauenheilkd 78(3):246–259
9. Collaborative Group on Hormonal Factors in Breast C (2002) Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 360(9328):187–195
10. McPherson K, Steel CM, Dixon JM (2000) ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ 321(7261):624–628
11. Renehan AG et al (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371(9612):569–578
12. Tamimi RM et al (2012) Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat 131(1):159–167
13. Rauh C et al (2015) Association of molecular subtypes with breast cancer risk factors: a case-only analysis. Eur J Cancer Prev 24(6):484–490
14. Lambertini M et al (2016) Reproductive behaviors and risk of developing breast cancer according to tumor subtype: a systematic review and meta-analysis of epidemiological studies. Cancer Treat Rev 49:65–76
15. Sisti JS et al (2016) Reproductive risk factors in relation to molecular subtypes of breast cancer: results from the nurses' health studies. Int J Cancer 138(10):2346–2356
16. Colditz GA et al (2004) Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 96(3):218–228
17. Sherman ME et al (2007) Variation in breast cancer hormone receptor and HER2 levels by etiologic factors: a population-based analysis. Int J Cancer 121(5):1079–1085
18. Fasching PA et al (2011) Breast cancer risk—genes, environment and clinics. Geburtshilfe Frauenheilkd 71(12):1056–1066
19. Fasching PA et al (2013) Breast cancer risk—from genetics to molecular understanding of pathogenesis. Geburtshilfe Frauenheilkd 73(12):1228–1235
20. Antoniou AC et al (2010) A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nat Genet 42(10):885–892
21. Garcia-Closas M et al (2013) Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 45(4):392–398
22. Fasching PA et al (2012) The role of genetic breast cancer susceptibility variants as prognostic factors. Hum Mol Genet 21(17):3926–3939
23. Haberle L et al (2017) Predicting triple-negative breast cancer subtype using multiple single nucleotide polymorphisms for breast cancer risk and several variable selection methods. Geburtshilfe Frauenheilkd 77(6):667–678
24. Fagerholm R et al (2015) The SNP rs6500843 in 16p13.3 is associated with survival specifically among chemotherapy-treated breast cancer patients. Oncotarget 6(10):7390–7407
25. Fagerholm R et al (2017) TP53-based interaction analysis identifies cis-eQTL variants for TP53BP2, FBXO28, and FAM53A that associate with survival and treatment outcome in breast cancer. Oncotarget 8(11):18381–18398
26. Hein A et al (2014) Polymorphisms in the RANK/RANKL genes and their effect on bone specific prognosis in breast cancer patients. Biomed Res Int 2014:842452
27. Hein A et al (2017) Genetic Breast Cancer Susceptibility Variants and Prognosis in the Prospectively Randomized SUCCESS A Study. Geburtshilfe Frauenheilkd 77(6):651–659
28. Wunderle M et al (2018) Risk, Prediction and Prevention of Hereditary Breast Cancer - Large-Scale Genomic Studies in Times of Big and Smart Data. Geburtshilfe Frauenheilkd 78(5):481–492
29. Wunderle M et al (2018) BRCA mutations and their influence on pathological complete response and prognosis in a clinical cohort of neoadjuvantly treated breast cancer patients. Breast Cancer Res Treat 171(1):85–94
30. Heusinger K et al (2011) Mammographic density as a risk factor for breast cancer in a German case-control study. Eur J Cancer Prev 20(1):1–8
31. Boyd NF et al (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med 356(3):227–236

32. Heusinger K et al (2012) Association of mammographic density with hormone receptors in invasive breast cancers: results from a case-only study. Int J Cancer 131(11):2643–2649

33. Heusinger K et al (2012) Association of mammographic density with the proliferation marker Ki-67 in a cohort of patients with invasive breast cancer. Breast Cancer Res Treat 135(3):885–892

34. Lux MP et al (2017) Update Breast Cancer 2017 - Implementation of Novel Therapies. Geburtshilfe Frauenheilkd 77(12):1281–1290

35. Goldhirsch A et al (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 16(10):1569–1583

36. Hothorn T, Hornik K, Zeileis A (2006) Unbiased Recursive Partitioning: A Conditional Inference Framework. J Comput Gr Stat 15:651–674

37. R Core Team (2017) R A Language and Environment for Statistical Computing. https://www.r-project.org

38. Anderson KN, Schwab RB, Martinez ME (2014) Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat 144(1):1–10

39. Chlebowski RT et al (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 289(24):3243–3253

40. Cui Y et al (2014) Interactions of hormone replacement therapy, body weight, and bilateral oophorectomy in breast cancer risk. Clin Cancer Res 20(5):1169–1178

41. Barnard ME, Boeke CE, Tamimi RM (2015) Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochim Biophys Acta 1856(1):73–85

42. Holli K, Isola J, Cuzick J (1998) Low biologic aggressiveness in breast cancer in women using hormone replacement therapy. J Clin Oncol 16(9):3115–3120

43. Daling JR et al (2003) Association of regimens of hormone replacement therapy to prognostic factors among women diagnosed with breast cancer aged 50–64 years. Cancer Epidemiol Biomarkers Prev 12(11 Pt 1):1175–1181

44. Rauh C et al (2015) Hormone Therapy and its Effect on the Prognosis in Breast Cancer Patients. Geburtshilfe Frauenheilkd 75(6):588–596

45. Schairer C et al (1999) Estrogen replacement therapy and breast cancer survival in a large screening study. J Natl Cancer Inst 91(3):264–270

46. Esteve J et al (2002) Does a better grade of tumour occurring in women under hormone replacement therapy compensate for their lower probability of detection by screening mammography. J Med Screen 9(2):70–73

47. Bonnier P et al (1998) Impact of menopausal hormone-replacement therapy on clinical and laboratory characteristics of breast cancer. Int J Cancer 79(3):278–282

48. Schuetz F et al (2007) Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. Am J Obstet Gynecol 196(4):342 e1–e9

49. Phipps AI et al (2008) Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer. Cancer 113(7):1521–1526

50. Setiawan VW et al (2009) Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. Am J Epidemiol 169(10):1251–1259

51. Ritte R et al (2012) Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Breast Cancer Res 14(3):R76

52. Bao PP et al (2011) Association of hormone-related characteristics and breast cancer risk by estrogen receptor/progesterone receptor status in the shanghai breast cancer study. Am J Epidemiol 174(6):661–671

53. Ellingjord-Dale M et al (2017) Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res 19(1):10

54. Rosenberg LU et al (2006) Risk factors for hormone receptor-defined breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 15(12):2482–2488

55. Untch M et al (2017) Initial Treatment of Patients with Primary Breast Cancer: Evidence, Controversies, Consensus: Spectrum of Opinion of German Specialists at the 15th International St. Gallen Breast Cancer Conference (Vienna 2017). Geburtshilfe Frauenheilkd 77(6):633–644

Affiliations

Marius Wunderle[1] · Jutta Pretscher[1] · Sara Y. Brucker[2] · Bernhard Volz[1] · Arndt Hartmann[3] · Cornelia Fiessler[4] · Alexander Hein[1] · Lothar Häberle[1] · Sebastian M. Jud[1] · Michael P. Lux[1] · Wolfgang Janni[5] · Christian R. Loehberg[1] · Andreas D. Hartkopf[2] · Christina B. Walter[2] · Gerold Baake[6] · Alexander Fridman[7,8] · Wolfram Malter[7] · Rachel Wuerstlein[9] · Nadia Harbeck[9] · Oliver Hoffmann[10] · Sherko Kümmel[11] · Bernhard Martin[12] · Christoph Thomssen[13] · Heiko Graf[14] · Christopher Wolf[15] · Christian M. Bayer[1] · Carolin C. Hack[1] · Katrin Almstedt[16] · Paul Gass[1] · Felix Heindl[1] · Tobias F. Brodkorb[1] · Naiba Nabieva[1] · Christoph Lindner[17] · Hans-Christian Kolberg[18] · Petra Krabisch[19] · Michael Weigel[20] · Dieter Steinfeld-Birg[21] · Andreas Kohls[22] · Cosima Brucker[23] · Volker Schulz[24] · Gunnar Fischer[25] · Volker Pelzer[26] · Diethelm Wallwiener[2] · Brigitte Rack[5] · Tanja Fehm[27] · Achim Rody[28] · Nicolai Maass[29] · Matthias W. Beckmann[1] · Peter A. Fasching[1] · Claudia Rauh[1]

1   Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich Alexander University of Erlangen-Nuremberg, Universitätsstrasse 21-23, 91054 Erlangen, Germany

2   Department of Obstetrics and Gynecology, University of Tübingen, Tübingen, Germany

3   Institute of Pathology, Comprehensive Cancer Center Erlangen-EMN, Erlangen University Hospital, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

4   Department of Medical Informatics, Biometry and Epidemiology, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

[5] Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany

[6] Oncological Medical Practice Pinneberg, Pinneberg, Germany

[7] Breast Center, Department of Gynecology and Obstetrics, University Hospital of Cologne, Cologne, Germany

[8] Department of Gynecology and Obstetrics, Evangelic Hospital Kalk, Cologne, Germany

[9] Breast Center and Comprehensive Cancer Center, Department of Gynecology and Obstetrics, University of Munich (LMU), Munich, Germany

[10] Department of Gynecology and Obstetrics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[11] Breast Unit, Kliniken Essen-Mitte, Essen, Germany

[12] Department of Gynecology and Obstetrics, Tuttlingen Clinic, Tuttlingen, Germany

[13] Department of Gynecology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

[14] Breast Center, Helios Clinic Meiningen, Meiningen, Germany

[15] Ulm Medical Center, Ulm, Germany

[16] Department of Obstetrics and Gynecology, Johannes Gutenberg University, Mainz, Germany

[17] Department of Gynecology and Obstetrics, Agaplesion Diakonie Clinic Hamburg, Hamburg, Germany

[18] Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany

[19] Department of Gynecology and Obstetrics, Klinikum Chemnitz, Chemnitz, Germany

[20] Department of Gynecology and Obstetrics, Leopoldina Hospital Schweinfurt, Schweinfurt, Germany

[21] Gynecological Oncological Practice Augsburg, Augsburg, Germany

[22] Department of Gynecology and Obstetrics, Evangelic County Hospital Ludwigsfelde-Teltow, Ludwigsfelde-Teltow, Germany

[23] Department of Gynecology and Obstetrics, Paracelsus Private Medical University of Nuremberg, Nuremberg, Germany

[24] Gynecological Practice abts+partner Kiel, Kiel, Germany

[25] Department of Gynecology and Obstetrics, Mittweida Hospital, Mittweida, Germany

[26] Department of Gynecology and Obstetrics, St. Marien Hospital Bonn, Bonn, Germany

[27] Department of Gynecology and Obstetrics, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany

[28] Department of Gynecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

[29] Department of Gynecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany