Influence of Family History of Breast or Ovarian Cancer on Pathological Complete Response and Long-Term Prognosis in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

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Keywords

Breast cancer · Ovarian cancer · Family history ·
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Abstract

Purpose: In breast cancer, a pathological complete response (pCR) has been described as generally resulting in a favorable prognosis. However, there are subgroups, such as patients with a mutation in *BRCA1* or *BRCA2*, in which the effect of pCR on the prognosis is suspected to be weaker. Patients with a family history of breast and/or ovarian cancer may therefore react differently in relation to pCR and prognosis, and this is investigated in this study. **Patients and Methods:** Breast cancer patients were identified from a clinical breast cancer registry. The study subjects had been treated with neoadjuvant chemotherapy from 2001 to 2018 and their

pathological and clinical information as well as medical family history were available. They were considered to have a positive family history if they had at least 1 first-degree relative with breast and/or ovarian cancer. Multivariate logistic regression analyses were performed to study the association between family history, pCR (ypT0; ypN0), and disease-free survival (DFS). **Results:** Of 1,480 patients, 228 (15.4%) had a positive family history. The pCR rates were 24.9% in all patients, and 24.4% and 27.6% in those without/with a family history, respectively. Family history was not associated with a higher pCR rate (adjusted odds ratio [OR] 1.23; 95% confidence interval [CI] 0.85–1.76; $p = 0.27$) or a different disease-free survival (DFS; adjusted hazard ratio [HR] 1.15; 95% CI 0.88–1.52; $p = 0.30$). pCR did not affect the prognosis differently in relation to family history. **Conclusions:** In this retrospective analysis, family history was not associated with pCR and DFS. pCR improved survival, independently of family history.

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Introduction

With the aim of individualizing treatments for patients with breast cancer (BC), recent studies have been focusing on molecular and genetic subgroups in BC as well as on neoadjuvant therapy. The neoadjuvant setting appears to be ideal for learning about the response pattern of tumors as well as for investigating the predictors of tumor response [1, 2]. Certain factors have been identified that predict the pathological complete response (pCR) very consistently across studies. These include hormone receptor status, HER2 receptor status, grading, tumor proliferation (Ki-67), tumor stage, and intrinsic molecular subtypes of BC. Other factors such as age, body mass index (BMI), familial or genetic background, and other patient characteristics are under discussion [1, 3–6]. Germline *BRCA1/2* mutations have been associated with better pCR rates across different studies [7–12]. This treatment effect appears to be most prominent in patients with triple-negative breast cancer (TNBC) when platinum chemotherapies are used [8–11].

pCR generally correlates very well with an excellent prognosis in patients with HER2 receptor-positive, hormone receptor-negative and triple-negative BC [1, 2, 6, 13, 14]. In hormone receptor-positive, low-grade BC, the pCR rate is lower and the association with a favorable prognosis is not as clear [14]. With regard to *BRCA1/2* mutation carriers, some studies have demonstrated improved survival in patients with a pCR [10, 11, 15]. However, a small-scale study reported that in *BRCA1* mutation carriers with TNBC, pCR may not be predictive of prognosis [7]. Another analysis from the GeparQuinto Trial confirmed that pCR is a strong predictor of disease-free survival (DFS) in patients without *BRCA1/2* mutations, but not in patients with *BRCA1/2* mutations [12].

It is therefore important to understand in which group of patients pCR translates clearly into a long-term survival benefit, and in which group of patients pCR needs to be used more carefully as a surrogate end point in clinical studies. In addition to *BRCA1/2* mutation status, it has been discussed whether a family history of BC and/or ovarian cancer (OC) might serve as a surrogate for a genetically enriched population and play a major role in predicting pCR.

In an analysis of TNBC patients from the GeparSixto trial, patients with a positive family history had a moderately increased pCR rate, but the multivariable analysis showed that family history was not a predictor of pCR [11]. As there are only a few published studies about this issue, the aim of this study was to analyze whether family history has an impact on pCR overall, particularly in molecular subtypes in addition to commonly known predictors of pCR, and whether the effect of pCR on the long-term prognosis differs between groups with and without a family history of BC or OC.

Patients and Methods

Study Population

This retrospective observational study included patients with primary BC from the Erlangen Neoadjuvant Study of the Breast (ERNEST-B) who were at least 18 years old and had undergone neoadjuvant chemotherapy between 2001 and 2018, followed by definitive surgery ($n = 1,614$). Information on the following parameters had to be available from the pretreatment assessment: age, tumor size, estrogen receptor (ER) status, progesterone receptor (PgR) status, HER2 receptor status, grading, proliferation status as assessed by Ki-67 staining, and the number of first-degree relatives affected with BC and/or OC. Patients were excluded for the reasons shown in Figure 1. The final study population consisted of 1,480 patients.

Clinical Data

Clinical data were collected in a prospective database as part of a continuous quality control process required for compliance with the certification requirements for breast centers in Germany (www.onkozeit.de). Patient and tumor characteristics must be documented as well as exact treatment information concerning surgery, radiotherapy, and systemic therapies. Patients are followed up for a period of 10 years. All data are audited annually on site by an external expert review panel. This process ensures quality control of treatment in accordance with the German guidelines and has been reported to improve the prognosis for patients as a consequence of treatment in conformity with the guidelines [16–18].

Systemic Treatments

Patients mainly received anthracycline/taxane-based chemotherapy, while some received cyclophosphamide/methotrexate/fluorouracil or other regimens. TNBC patients were partly treated with a platinum/taxane-based regimen. HER2-positive BC patients received additional neoadjuvant and adjuvant anti-HER2 therapy. Hormone receptor-positive BC patients were treated with an adjuvant antihormone therapy. Treatments were administered in accordance with the standard guidelines in the respective years. Systemic treatments in the study population have been described previously [3, 10, 19].

Epidemiological Data

Information on risk factors for BC was collected using an epidemiological questionnaire developed for studies concerned with identifying genetic and nongenetic risk factors and prognostic factors in BC [20–22]. The data collected with the questionnaire were harmonized in order to make the information available to large international consortia and have been previously published [23–25]. In this analysis, family history is regarded as positive if the patient had at least 1 first-degree relative with a diagnosis of BC and/or OC.

Pathology Data

The histopathological information was directly documented from the original pathology reports, which were reviewed by 2 investigators. Grading, tumor type, ER status, PgR status, HER2 receptor status, and Ki-67 staining were assessed as part of clinical routine testing on formalin-fixed, paraffin-embedded tumor tissue at the time of the initial diagnosis, as described previously [3]. HER2 was positive when immunohistochemical staining indicated a 3+ result or the tumor showed HER2 amplification, as determined by chromogene in situ hybridization (CISH; ZytoDot, 2C SPEC HER2/CEN17, Zyto Vision Ltd., Bremerhaven, Germany). The immunohistochemical evaluation was quality-controlled and validated in annual round-robin tests.

Fig. 1. Patient selection. BC, breast cancer; ERNEST-B, Erlangen Neoadjuvant Study Breast; OC, ovarian cancer; pCR, pathological complete response.

Tumor molecular subtype was defined consistently with the guidelines in the respective years. Luminal A-like tumors were ER-positive or PgR-positive, HER2-negative, and had low Ki-67 values (<14%). Luminal B-like tumors were ER-positive or PgR-positive, HER2-negative, and had high Ki-67 values ($\geq 14\%$). TNBCs were required to be negative or weakly positive ($\leq 10\%$) for ER and PgR and constantly negative for HER2. All HER2-positive tumors were grouped together, regardless of hormone receptor status [26, 27].

pCR was defined as a complete absence of invasive tumor cells or carcinoma in situ cells from the breast and lymph nodes after chemotherapy at the time of surgery (ypT0; ypN0).

Statistical Analysis

The primary objective was to investigate whether information about a family history of BC and/or OC has an impact on pCR overall and particularly in molecular subtypes, in addition to other well-known predictive factors. For this purpose, a multiple lo-

gistic regression model was fitted with pCR status as a binary outcome (Yes vs. No) and the following predictors: a family history of BC/OC (Yes vs. No), age at diagnosis (continuous), body mass index (BMI; continuous), clinical tumor stage (ordinal; cT1 to cT4), tumor type (categorical; ductal, lobular, and other), grade (ordinal; G1 to G3), ER status, PgR status, HER2 status (each categorical; positive vs. negative), and Ki-67 (categorical; high vs. low).

Subsequently, an additional logistic model (the full model) was fitted containing the predictor family history of BC/OC (Yes vs. No), the predictors of the previous basic model, and the interactions between a family history of BC/OC and ER, PgR, HER2, and Ki-67. Both models were compared using the likelihood ratio test. A significant test result indicates that a family history of BC/OC influences pCR, either across all patients or at least within 1 of the subgroups defined by the interaction terms. In cases of significance, molecular subtype-specific adjusted odds ratios (ORs) were

estimated, using the full model. Otherwise, an adjusted overall OR for a family history of BC/OC was estimated, using a reduced full model in which the interaction terms were excluded.

DFS was defined as the time from the date of diagnosis to the earliest date of disease progression (local recurrence, invasive contralateral BC, distant metastasis, or death from any cause) or the date of censoring. Patients who were lost to follow-up before the maximum observation period of 10 years, or were disease-free after the maximum observation time, were censored at the last date on which they were known to be disease-free, or at the maximum observation time.

The secondary objective was to study whether the impact of a family history of BC/OC on DFS varied between patients with and without pCR. A Cox regression model was fitted with the predictors described above and additionally pCR (Yes vs. No). Next, another Cox model was fitted containing these predictors and in addition the interaction of pCR relative to a family history of BC/OC. The 2 models were compared using the likelihood ratio test. A significant test result means that the impact of a family history of BC/OC on DFS is different in patients who achieve a pCR and those who do not. In cases of significance, pCR status-specific hazard ratios (HRs) for a family history of BC/OC were estimated using the interaction model. Otherwise, an overall HR for a family history of BC/OC was estimated using the first Cox model described. The proportional hazards assumptions were checked using the Grambsch-Therneau method.

Patients who did not achieve a pCR, or for whom information about family history of BC/OC was lacking, were excluded from both analyses. Missing values for other predictors were imputed, and continuous predictors were used as natural cubic spline functions (as in [28]).

For sensitivity analyses, unadjusted ORs and HRs were estimated using simple logistic and Cox regression models. Survival rates, especially 5- and 10-year survival rates, were estimated using the Kaplan-Meier product limit method. In addition, analyses were repeated with a family history of BC (Yes vs. No) as the variable of interest instead of a family history of BC/OC (Yes vs. No), and ORs and HRs are shown.

All of the tests were two-sided, and $p < 0.05$ was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (v3.4.1; R Development Core Team, Vienna, Austria, 2017).

Results

Patient and Tumor Characteristics

Of the 1,480 patients who were included in this analysis, a total of 228 (15.4%) had a family history including a first-degree relative with BC and/or OC. Of these, 198 (86.8%) had a family history of BC and 40 (17.5%) had a family history of OC. The patient and tumor characteristics of individuals with and without a family history were similar. Patient and tumor characteristics relative to a family history of BC/OC are shown in Table 1.

Family History of BC/OC and pCR

Of 7,880 patients with primary BC being treated between 2001 and 2018 at the Breast Center of the Erlangen University Hospital, 1,614 (20.5%) received neoadjuvant chemotherapy as part of ERNEST-B. Of these, 369 (22.9%)

Table 1. Patient and tumor characteristics relative to a family history of breast cancer and/or ovarian cancer

Characteristic	No family history (n = 1,252)		Family history (n = 228)	
	n or mean	% or SD	n or mean	% or SD
Age, years	51.6	12.1	52.8	11.5
BMI, kg/m ²	25.9	5.2	26.4	5.4
Tumor stage				
cT1	272	21.7	58	25.4
cT2	789	63.0	139	61.0
cT3	65	5.2	16	7.0
cT4	126	10.1	15	6.6
Lymph node stage				
cN0	557	44.5	113	49.6
cN+	695	55.5	115	50.4
Tumor type				
Ductal	899	71.8	157	68.9
Lobular	92	7.3	23	10.1
Other	261	20.8	48	21.1
Grade				
G1	37	3.0	5	2.2
G2	462	36.9	93	40.8
G3	753	60.1	130	57.0
ER status				
ER–	399	31.9	82	36.0
ER+	853	68.1	146	64.0
PgR status				
PgR–	724	57.8	136	59.6
PgR+	528	42.2	92	40.4
HER2 status				
HER2–	940	75.1	179	78.5
HER2+	312	24.9	49	21.5
Ki-67 status				
Ki67 <14%	170	13.6	26	11.4
Ki67 ≥14%	1,082	86.4	202	88.6
Molecular subtype				
Luminal A-like	141	11.3	19	8.3
Luminal B-like	524	41.9	102	44.7
HER2-positive	312	24.9	49	21.5
Triple-negative	275	22.0	58	25.4
pCR				
No	946	75.6	165	72.4
Yes	306	24.4	63	27.6

Mean and SD are shown for continuous characteristics and *n* and % for categorical characteristics. BMI, body mass index; ER, estrogen receptor; pCR, pathological complete response; PgR, progesterone receptor.

achieved a pCR. In patients without a family history of BC/OC, 306 of 1,252 (24.4%) had a pCR. In patients with a family history, 63 of 228 (27.6%) had a pCR. It was not found that a family history of BC/OC had an impact on pCR, neither across all patients nor within the molecular subtypes luminal A-like, luminal B-like, HER2-positive, and triple-negative ($p = 0.07$, likelihood ratio test). The adjusted overall OR was 1.23 (95% confidence interval

Fig. 2. Kaplan-Meier curves for disease-free survival relative to pathological complete response (pCR) and a family history of breast cancer and/or ovarian cancer.

[CI] 0.85–1.76; $p = 0.27$); the unadjusted overall OR was 1.18 (95% CI 0.86–1.62; $p = 0.31$).

Family History of BC/OC and DFS

The median follow-up period for DFS was 4.1 years, both for patients with a family history of BC/OC and those without. The study did not show different effects of the family history on DFS in patients who achieved a pCR and patients who did not achieve a pCR ($p = 0.15$, likelihood ratio test). Moreover, family history status in gen-

eral was not associated with DFS. The adjusted HR for patients with a family history of BC/OC versus patients without a family history was 1.15 (95% CI 0.88–1.52; $p = 0.30$); the unadjusted HR was 1.12 (95% CI 0.85–1.46; $p = 0.42$). Kaplan-Meier curves are shown in Figure 2. The 5- and 10-year survival rates are presented in Table 2.

Family History of BC

Sensitivity analyses with a family history of BC as the variable of interest, instead of a family history of BC/OC,

Table 2. Number of events and rates of disease-free survival

Subgroup	Number of at-risk patients	Number of events	5-year DFS (95% CI)	10-year DFS (95% CI)
No pCR and no FH	946	288	0.71 (0.68–0.74)	0.58 (0.55–0.63)
No pCR and FH	165	59	0.67 (0.59–0.76)	0.50 (0.42–0.61)
pCR and no FH	306	31	0.88 (0.84–0.93)	0.84 (0.78–0.90)
pCR and FH	63	4	0.98 (0.95–1.00)	0.82 (0.67–1.00)

CI, confidence interval; DFS, disease-free survival; FH, a family history of breast and/or ovarian cancer; pCR, pathological complete response.

yielded similar results. The adjusted and unadjusted ORs for a family history of BC were 1.16 (95% CI 0.79–1.72; $p = 0.45$) and 1.08 (95% CI 0.77–1.52; $p = 0.64$), respectively. The adjusted and unadjusted HRs for a family history of BC were 1.12 (95% CI 0.84–1.49; $p = 0.45$) and 1.08 (95% CI 0.81–1.44; $p = 0.61$).

Discussion

This study did not show that a family history of BC/OC has an impact on pCR, neither across all patients nor within a molecular subtype, in addition to age, BMI, tumor stage, tumor type, grading, hormone receptor status, HER2 status, and Ki-67 proliferation index.

Recently, the effect of family history and *BRCA1/2* mutation status on pCR was reported in a subgroup analysis of TNBC patients from the GeparSixto study. The pCR rate (ypT0; ypN0) was 42.0% in patients without a family history and 48.2% in those with a family history. The addition of platinum increased the pCR rate both in patients with a family history and those without, but it did not increase the already high pCR rate in *BRCA1/2* mutation carriers. In the multivariate analysis, neither *BRCA1/2* mutation status (OR 1.44; 95% CI 0.54–3.82; $p = 0.46$) nor family history (OR 1.04; 95% CI 0.58–1.87; $p = 0.91$) was associated with the pCR rate [11]. In the study group overall, the pCR rates were 24.4% in patients without a family history and 27.6% in those with at least 1 first-degree relative with BC and/or OC. The higher pCR rates recorded in the GeparSixto study might be attributable to the triple-negative subgroup, half of whom were treated with platinum-containing systemic therapy.

It has been suggested that genetic alterations in *BRCA1/2* or other loci can be found in <40% of BC patients with a positive family history [6, 29]. These include high-penetrance loci such as *TP53*, *PTEN*, *STK11*, *CDH1*, and *PALB2*, and medium-to-low-penetrance loci such as *CHEK2*, *ATM*, *RAD51D*, *RAD51C*, *BARD1*, *BRIP1*, *MSH6*, and others [29–31]. Recently, in a large genotyping effort, common low-penetrance polymorphisms (sin-

gle-nucleotide polymorphisms [SNPs]) have been identified and validated that modify the risk for BC in *BRCA1/2* mutation carriers [32, 33]. In addition, a total of around 170 common SNPs have been reported to influence the risk of BC in unselected populations (summarized in [29, 34]). As many of these genes have a function in DNA damage sensitizing and repair, cell cycle control, and tumor suppression [29–31], genetic alterations may result in a distinct group of BC patients who show a different response to systemic treatments. There may also be other reasons, not conclusively explained, including epigenetic factors, specific behavioral patterns, and other risk factors that could be familial [34, 35].

With regard to the prognosis, this study shows that pCR is predictive of DFS in patients with and without a family history of BC/OC. pCR has been associated with a favorable prognosis in several studies [1, 2, 6, 13, 14]. This finding has also been supported for *BRCA1/2* mutation carriers in some studies [10, 11, 15]. In contrast, in a cohort of 80 TNBC patients with a known *BRCA1* mutation status who were treated with neoadjuvant anthracycline- and taxane-containing chemotherapy, the pCR rate was higher in patients with a *BRCA1* mutation (67 vs. 37%). However, pCR was not predictive of the prognosis in *BRCA1* mutation carriers, while it was prognostic in patients without a *BRCA1* mutation [36]. These results could be due to chance, but an analysis of the GeparQuinto study also reported that pCR was a predictor of DFS in patients without a *BRCA1/2* mutation (HR 0.18; 95% CI 0.11–0.31), but not in those with a *BRCA1/2* mutation (HR 0.74; 95% CI 0.32–1.69) [12]. Moreover, a study on 77 heterogeneously treated TNBC patients showed a better prognosis for the 15 *BRCA1/2* mutation carriers than for the 62 noncarriers [37]. Together, these data imply that in *BRCA1/2* mutation carriers, the prognosis may not be mediated by the response to chemotherapy, but rather by additional factors such as different *BRCA1/2* mutation patterns, alterations in other risk-modifying genes, etc. [32, 33, 35]. The question of how *BRCA1/2* mutations have an effect on pCR and prognosis will remain unsolved until larger-scale studies become

available, with possibly prospectively collected data from clinical trials.

Independently of pCR status, some studies on *BRCA1* mutation carriers have demonstrated a better [15, 38–40] or similar prognosis [38, 41, 42], but 2 meta-analyses suggested poorer survival [43, 44]. *BRCA2* mutation carriers appear to show no difference in comparison with noncarriers [39, 41, 43, 44] or a poorer prognosis [44, 45]. In addition, large trials have reported a similar long-term prognosis for the whole group of *BRCA1/2* mutation carriers in comparison with noncarriers [15, 38, 39, 41, 46]. Even fewer data are available regarding the prognosis with other BC susceptibility genes such as *PALB2*, *CHEK2*, and others [47–50].

A few studies have also investigated the influence of a positive family history on the overall survival (OS). One study estimated that the 10-year OS rate was 73% in patients with sporadic BC, 75% in intermediate-risk patients, and 82% in high-risk patients (log-rank $p < 0.0001$) [40]. Correspondingly, a meta-analysis reported a better OS in BC patients with a first-degree family history of BC/OC (OR 0.89; 95% CI 0.83–0.95) [51].

This study has several strengths and limitations. Firstly, it was retrospective, although the data documented in the database are maintained prospectively. One strength of the study was also the quality-controlled assessment of biomarkers such as ER, PgR, HER2, and Ki-67, which have been shown to be of clinical value in previous publications [3]. A limitation was the small sample size of patients with a positive family history and the heterogeneity of tumor types and different treatments. Due to the study's retrospective nature, the analyses of DFS were limited.

Conclusion

This study did not use *BRCA1/2* mutation status, but the surrogate marker for a genetically enriched cohort “family history.” Family history of BC/OC was not associated with pCR after neoadjuvant chemotherapy. The study confirms that pCR influences DFS regardless of family history. As there is growing evidence that pCR does not have the same impact on prognosis in all patients, it continues to be difficult to identify patients who

may benefit more from pCR. It is not unlikely that certain hereditary BCs may show a good response to chemotherapy, while others do not, and that therapy effects may be mediated through different mechanisms.

Statement of Ethics

Approval for the analyses conducted in the study was received from the ethics committee of the University of Erlangen-Nuremberg. All procedures were in accordance with the ethics standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable standards. Informed consent was obtained from all patients included in the study.

Conflict of Interest Statement

M.P.L. reports personal fees from Pfizer, Roche, Merck Sharp & Dohme, Hexal, Novartis, AstraZeneca, Tesaro, Eisai, medac, and Lilly. C.C.H. reports personal fees from Roche. N.N. reports personal fees from Janssen-Cilag, Novartis, and Teva. A. Hartmann reports personal fees from Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Novartis, AstraZeneca, NanoString, BioNTech, and Janssen-Cilag. P.A.F. reports research grants from Novartis and BioNTech and personal fees from Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, TEVA, AstraZeneca, Puma, Eisai, Merck Sharp & Dohme, and Myelo Therapeutics. P.G. reports personal fees from Novartis, Roche, and PharmaMar. All the other authors declare that they have no conflicts of interest.

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Author Contributions

M.W., P.A.F., and P.G. contributed to conception and design of the study. M.W., A. Hein, S.M.J., M.P.L., C.C.H., J.E., F.H., N.N., C.R.L., R.S.-W., A. Hartmann, M.W.B., P.A.F., and P.G. contributed to the acquisition of clinical data. L.H. performed the statistical analysis. L.H., M.W., P.A.F., and P.G. performed interpretation of data. M.W., P.A.F., and P.G. were involved in drafting the manuscript. All authors gave final approval of the version to be published, revised the manuscript critically and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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