Conditional Disease-Free and Overall Survival of 1,858 Young Women with Non-Metastatic Breast Cancer and with Participation in a Post-Therapeutic Rehab Programme according to Clinical Subtypes

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Keywords

Survival · Non-metastatic breast cancer · Young adults

Abstract

Background: Breast cancer in young women is associated with unfavourable tumour biology and is the main cause of death in this group. Conditional survival analysis estimates survival rates under the pre-condition of already having survived a certain time. **Objectives:** To describe conditional disease-free and overall survival of female breast cancer patients according to clinical subtypes and age. **Methods:** This study analyses information from 1,858 breast cancer patients aged between 21 and 54 years, who were taking part in a post-therapeutic rehab programme (time between diagnosis and rehab start: maximum 24, median 11 months). Mean follow-up time was 3.6 years. We describe biological, clinical and pathological features in regard to different age groups (<40 and ≥40 years) and report conditional 5-year survival rates for overall and disease-free survival, and Cox proportional hazard models. **Results:** Very young and young patients differed in regard to hormone receptor negativity, tumour grade, lymphovascular invasion, and molecular sub-

types. Young women bore triple-negative and HER2-like disease more frequently. Conditional 5-year overall survival did not differ substantially between women <40 and 40–54 years of age (95 vs. 96%). It was highest for women with cancer of the luminal A subtype (98%) and lowest for the triple-negative subtype (91%). Lymphangiosis was a significant predictor of death. Results for disease-free survival were comparable. **Conclusions:** Conditional 5-year overall survival after non-metastatic breast cancer was as high as 95.5%, and disease-free survival was 85.2%. When controlling for time between diagnosis and rehab start, molecular subtypes influenced overall and disease-free survival prospects. When additionally controlling for clinical characteristics, this effect only remained stable for disease-free survival.

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Introduction

With 69,000 new cases and a median age of 64 years at diagnosis in 2014, breast cancer among women is still the most frequent type of malignancies in Germany. Survival after breast cancer has recently increased due to new

treatment strategies and early detection measures. Nowadays, the overall absolute 5-year survival rate is estimated to be as high as 88% (irrespective of age and stage at diagnosis) [1]. However, as many breast cancer patients die shortly after diagnosis, this overall survival rate may be too pessimistic for cancer survivors. Conditional survival analysis takes survivorship into account and estimates survival rates under the pre-condition that patients have already survived a certain time period.

Approximately 7–9% of all cancer cases are diagnosed in women <40 years with an accumulative lifetime-risk to contract cancer of 0.45% [1–4]. Based on the GLOBOCAN 2012 data, Fidler et al. [5] estimated recently that about 30.2% of all cancers occurring in women aged 20–39 years are malignant neoplasms of the breast. This proportion equals an amount of about 191,100 incident cases worldwide. Breast cancer in young women is associated with advanced stage at diagnosis and unfavourable tumour biology and worse pathological features [3, 6–10]. Young breast cancer patients have an increased risk for lymphovascular invasion, oestrogen and progesterone receptor negativity, as well as a higher expression of proliferation marker Ki67 and growth factor HER2 [4, 9, 11–14].

Due to these disadvantageous tumour characteristics, young women proved to be at increased risk for local and systemic recurrences. For example, compared to an age group >40, young women show both a worse 5-year disease-free survival and a worse 5-year overall survival [2, 15, 16]. Although breast cancer in young women <40 years is rather rare, it is the most common cause of death in this age group [17]. It was estimated recently, that about 25% of all cancer-related deaths occurring in women aged 20–39 years are due to malignant neoplasms of the breast (equalling an estimated amount of about 48,775 deaths worldwide) [5].

Many studies suggest a link between tumour subtypes and young age at the time of diagnosis concerning survival [11, 13, 14, 18]. The triple-negative subtype, which is associated with worse outcomes and presents itself more often in young women than it does in older women, exemplifies this. In contrast, luminal A disease, which is associated with better outcomes, is more frequently found in older women [11, 13, 14]. As there is no indication for consistent evidence in recent studies and insufficient Germany-specific data, we analysed data of 1,858 young breast cancer patients and aimed to describe tumour characteristics like tumour stage, grading, receptor status, and molecular subtypes. As our study cohort consists of women who participated in a rehab programme which started after initial treatment was terminated (maximum of 2 years after diagnosis), we analysed conditional 5-year overall and disease-free survival for subgroups according to tumour characteristics and age.

Table 1. Definition of tumour subtypes by clinical features according to Brouckaert et al. [19]

	ER	PR	HER2	Ki67 (if available)	Grading (if Ki67 missing)
Luminal A	+	+/-	-	<14%	<3
Luminal B1	+	+/-	-	≥14%	3
Luminal B2	+	+/-	+		
HER2 like	-	-	+		All values
Triple-negative	-	-	-		

Materials and Methods

Study Population

This study is a sub-study of a larger cohort study which started in 2009 [6]. The cohort study includes young mothers with non-metastatic breast cancer who participate in a 3-week in-patient mother-child rehabilitation programme. To be eligible for the programme, the patient's child had to be under the age of 12 and the patient's primary cancer treatment had to be concluded at least 6 weeks prior to the start of the rehab programme. Women with distant metastases at diagnosis were not eligible for the rehab programme and were thus not included in our analysis.

The present study comprises data from 1,858 women aged between 21 and 54 years with invasive non-metastatic breast cancer (ICD-10 code C50 or D05). They took part in the rehab programme between 2010 and 2017 which started within a maximum timespan of 24 months after diagnosis. All women resided in Germany; there was no evidence that women from a particular region or a particular federal state were overrepresented in our study cohort.

Data Sources

Sociodemographic and basic clinical data were provided by the patients. These data were supplemented by data derived from patient record files. Tumour specimens had been worked up locally at the time of diagnosis. A further centralised work-up of the tumour material at the time of recruitment was not conducted. That is, information on tumour biology and pathology was derived from patient's record files as well.

Follow-up information was provided by the women themselves (e.g., on recurrences or metastasis) in the years 2015 and 2018. The study questionnaire included a question on tumour-related changes after the end of the rehab stay (i.e., local recurrence in the same breast, a tumour in the contralateral breast, local or distant metastasis) and on the date of diagnosis of the disease progression. Additionally, the respective registration offices provided the information whether a woman was alive or dead, including date of death. In case the woman had moved, the office provided the updated address, thus allowing to contact the new corresponding registration office. Vital status was obtained, if applicable, in 2011, 2013, 2015 and winter 2017/2018.

Statistics

We defined subgroups as follows: tumour subtypes were classified as luminal A, luminal B1, luminal B2, HER2 like, and triple-negative following subtype categories by Brouckaert et al. [19] (Table 1). Further, "very young" women were in the age-range 21–39 years, while "young" women were 40–54 years old. Hormone receptors and growth factor HER2 were divided in positive and negative. Tumour size was subdivided into 3 groups (Tis/T0/T1; T2; T3/T4). Infiltration of regional lymph nodes was divided into 3 groups (N0; N1; N2/N3) and the grading was classified as "low"

(G1), “intermediate” (G2), “high” (G3), and “missing” (Gx). Finally, we differentiated women who started their rehab programme within the first year from those who started it within 13–24 months after diagnosis.

We used absolute and relative frequencies to describe the overall cohort and age-specific subgroups and χ^2 tests to assess statistically significant differences between the age groups.

For deceased patients, survival time was measured as days from the date of diagnosis up to the date of death from any cause. Alive patients were censored at the date of the last follow-up contact (follow-up survey or information from the registration office). As women in our cohort had survived already a certain time (time interval between diagnosis and rehab start) before they entered the study the reported survival rates are conditional survival rates. The latter describe the further survival probability given that a patient has already survived a specific time period.

We present conditional 5-year survival for overall and disease-free survival stratified by molecular subtypes, age, stage, and tumour characteristics.

Cox proportional hazard models were computed to describe the impact of tumour subtypes, age, tumour characteristics (stage, grading, lymphangiosis, and receptor status) on overall survival/death and disease-free survival. In the first step of our analysis, we ran several models with death as the dependent variable and each clinical factor as the independent variable while adjusting for the time period between diagnosis and rehab start to control for survivorship bias (model 1). In the second step (model 2), we ran a full model and included age, tumour subtypes, stage, grading, and lymphangiosis as potential clinical predictors while still adjusting for the time period. Hazard ratios (HR) and 95% confidence intervals (CIs) are reported.

For the analysis, SPSS software version 22 and R (version 4.2.1) with the package periodR were used [20, 21]. All *p* values reported are two-sided and were considered to be statistically significant if <0.05 .

Results

Patient Characteristics

The study population consisted of 1,858 young women with a mean age of 39.6 years (SD 5.6, range 21–54) of whom 49.6% were younger than 40 years and 50.4% were 40 years or older. Of all women, 63.3% started their rehab programme within the first year after diagnosis with the median time span between diagnosis and rehab start being 11 months. Women aged <40 years were slightly more likely when compared to women aged 40–54 years to start their rehab programme within the second year after diagnosis (38.5 vs. 34.9%, $p = 0.103$), but the median time span between diagnosis and rehab start was 11 months for both subgroups. Characteristics of our study cohort, overall and divided by age group, are shown in Table 2. Very young women showed less favourable tumour characteristics compared to young women: Cancer cases of the very young women (<40 years) proved to be poorly differentiated. In addition, they presented oestrogen negative or progesterone negative more frequently than the older age group. In contrast, the growth factor HER2 was more fre-

quently positive in very young patients. This translates to a lower proportion of luminal A subtype, and a higher proportion of the triple-negative and HER2-like subtype in very young women. Most of the described differences were of statistical significance.

Deaths during Follow-Up

Median follow-up time was 3.6 years (range 81 days to 8 years since diagnosis). Overall, 3.8% (70/1,858) of non-metastatic breast cancer patients died during follow-up. The first death occurred 14 months after the rehab programme had been started.

When data were stratified according to tumour biology, the percentage of deaths ranged between 2.1% (luminal A subtype) and 7.3% (triple-negative subtype). Stratification by age and time between diagnosis and rehab start, respectively, revealed that the percentage of deaths was higher in the group of very young women (4.2%) than in the older group (3.3%; $p = 0.295$) and that the percentage of deaths was lower in the group of women with an early start of the rehab programme compared to women with rehab start 13–24 months after diagnosis (3.5 vs. 4.3%; $p = 0.403$).

Survival Analysis

The 5-year conditional overall survival rate (COS) of women who participated in the rehab programme was 95.5% as shown in Table 3, and 5-year conditional disease-free survival (DFS) was 85.2% (Table 4).

Taking the time period between diagnosis and rehab start into account, the 5-year COS for women starting the rehab in the first year after diagnosis was lower (94.7 vs. 96.6%), and the DFS was higher (86.4 vs. 84.2%) than for women who had already survived another year since diagnosis and who started the rehab 13–24 months after diagnosis. The younger age group proved to be associated with worse 5-year COS (94.9 vs. 96.1%) as well as worse 5-year DFS (83.9 vs. 86.5%) as compared to the older age group. Among the tumour subtypes, triple-negative disease showed the worst 5-year survival rates (COS 94.4%; DFS 78.6%). The 5-year survival rates were worse in advanced tumours than in tumours with modest growth for conditional overall survival (T2: 94.8%, T3 or T4: 86.0 vs. 96.7%, reference group) and for disease-free survival (T2: 85.0%, T3 or T4: 75.3 vs. 85.9%, reference group). Patients with regional lymph node category N2 or N3 showed an inferior 5-year survival rate for both, COS (89.3%) and DFS (77.0%) when compared to patients without infiltration (COS: 97.5%; DFS: 87.6%, reference group) and patients with lymphangiosis had inferior 5-year survival rates (COS 92.3%; DFS 80.3%) when compared with to patients without lymphangiosis (COS 97.1%; DFS 88.3%). Finally, we observed a lower 5-year COS and DFS for less differentiated tumours (G3; COS 93.5%; DFS 81.5%) compared to differentiated tumours (G1; COS 97.3%; DFS 85.7%; Tables 3, 4).

Table 2. Tumour characteristics of young women with breast cancer in Germany overall and according to age groups

	Overall 1,858 (100)	<40 years 921 (49.6)	≥40 years 937 (50.4)	<i>p</i> value (χ^2)
Primary tumour (T)				
Tis	69 (3.7)	29 (3.1)	40 (3.9)	0.168*
T0	208 (11.2)	137 (14.9)	71 (3.3)	
T1	851 (45.8)	407 (44.2)	444 (49.3)	
T2	603 (32.5)	282 (30.6)	321 (37.0)	
T3	91 (4.9)	45 (4.9)	46 (5.2)	
T4	8 (0.4)	3 (0.3)	5 (0.9)	
Tx (unknown)	28 (1.5)	18 (2.0)	10 (0.4)	
Regional lymph nodes (N)				
N0	1,127 (60.7)	567 (61.6)	560 (59.8)	0.827
N1	488 (26.3)	234 (25.4)	254 (27.1)	
N2	141 (7.6)	67 (7.3)	74 (7.9)	
N3	65 (3.5)	34 (3.7)	31 (3.3)	
Nx (unknown)	37 (2.0)	19 (2.1)	18 (1.9)	
Histologic grade				
1	106 (5.7)	46 (5.0)	60 (6.4)	<0.001
2	800 (43.1)	343 (37.2)	457 (48.4)	
3	844 (45.4)	484 (52.6)	360 (38.4)	
Gx (unknown)	108 (5.8)	48 (5.2)	60 (6.4)	
ER status				
Positive	1,298 (69.9)	570 (61.9)	728 (77.7)	<0.001
Negative	548 (29.5)	348 (37.8)	200 (21.3)	
Unknown	12 (0.6)	3 (0.3)	9 (1.0)	
PR status				
Positive	1,171 (63.1)	507 (55.0)	664 (70.9)	<0.001
Negative	670 (36.1)	409 (44.4)	261 (27.9)	
Unknown	16 (0.9)	5 (0.5)	11 (1.2)	
HER2 status				
Positive	491 (26.4)	281 (30.5)	210 (22.4)	0.001
Negative	1,319 (71.0)	623 (67.7)	696 (74.3)	
Unknown	47 (2.5)	16 (1.7)	31 (3.3)	
Lymphangiosis				
Yes	434 (23.4)	227 (24.6)	207 (22.1)	0.197
No	1,141 (61.4)	547 (59.4)	594 (63.5)	
Unknown	282 (15.2)	147 (16.0)	135 (14.4)	
Tumour subtype				
Luminal A	607 (32.7)	223 (24.2)	384 (41.0)	<0.001
Luminal B1	275 (14.8)	126 (13.7)	149 (15.9)	
Luminal B2	347 (18.7)	188 (20.4)	159 (17.0)	
HER2 like	129 (6.9)	81 (8.8)	48 (5.1)	
Triple-negative	368 (19.8)	235 (25.5)	133 (14.2)	
Unknown	132 (7.1)	68 (7.4)	64 (6.8)	

Data are presented as *n* (%). * Grouped T categories Tis/T0/T1 vs. T2 vs. T3/T4 vs. unknown were used for χ^2 test.

Univariate Cox proportional hazard regression analyses indicated that conditional overall survival and conditional disease-free survival prospects were altered by the time between diagnosis and rehab start: the hazard to die during follow-up was increased for those who started their rehab during the early phase after diagnosis and

treatment as compared to those who had already survived for 2 years (i.e., for COS HR 1.55, 95% CI 0.94–2.57, $p = 0.087$; for DFS HR 1.95, 95% CI 1.40–2.71, $p < 0.001$). Thus, all further regression models included time between diagnosis and rehab start as a confounding variable.

Table 3. Conditional 1-, 3-, and 5-year observed overall survival (COS) with corresponding standard errors (SE), and hazard risks for death (HR) with corresponding 95% confidence intervals (95% CI)

Category	Women, <i>n</i>	1-year COS	SE	3-year COS	SE	5-year COS	SE	Model 1: HR ¹	95% CI		Model 2: HR ¹	95% CI	
									lower	upper		lower	upper
Overall	1,858	100	0	97.5	0.4	95.5	0.6						
Time between diagnosis and rehab start													
13–24 months	682	100	0	98.4	0.5	96.6	0.8						
≤12 months	1,176	100	0	96.9	0.6	94.7	0.9						
Age													
≥40 years	937	100	0	98.0	0.5	96.1	0.8	Ref.			Ref.		
<40 years	921	100	0	97.1	0.6	94.9	0.9	1.34	0.84	2.15	1.07	0.65	1.75
Tumour subtype													
Luminal A	607	100	0	99.2	0.4	98.0	0.7	Ref.			Ref.		
Luminal B1	275	100	0	97.6	1.1	95.6	1.5	2.41	1.10	5.30	1.15	0.36	3.74
Luminal B2	347	100	0	97.9	0.9	96.4	1.4	2.09	0.95	4.59	1.36	0.51	3.61
HER2 like	129	100	0	97.6	1.7	95.5	2.6	1.40	0.40	4.92	1.00	0.23	4.28
Triple- negative	368	100	0	94.4	1.4	90.5	1.9	3.88	1.99	7.55	2.58	0.90	7.46
ER status													
Positive	1,298	100	0	98.4	0.4	96.9	0.6	Ref.			–		
Negative	548	100	0	95.3	1.1	92.1	1.5	1.96	1.22	3.16			
PR status													
Positive	1,171	100	0	99.0	0.3	97.9	0.6	Ref.			–		
Negative	670	100	0	94.9	1.0	91.5	1.4	2.81	1.73	4.57			
HER2 status													
Positive	491	100	0	97.8	0.8	96.3	1.2	Ref.			–		
Negative	1,319	100	0	97.3	0.5	95.1	0.7	1.15	0.65	2.04			
Lymphangiosis													
Yes	4,434	100	0	96.7	1.0	92.3	1.6	Ref.			Ref.		
No	1,141	100	0	98.2	0.5	97.1	0.6	0.42	0.25	0.69	0.53	0.30	0.93
Primary tumour													
Tis/T0/T1	1,128	100	0	98.4	0.5	96.7	0.7	Ref.			Ref.		
T2	603	100	0	96.6	0.8	94.8	1.1	1.42	0.83	2.41	1.42	0.83	2.41
T3/T4	99	100	0	93.8	2.7	86.0	4.5	2.21	0.98	4.97	2.22	0.98	5.00
Regional lymph nodes													
N0	1,127	100	0	98.6	0.4	97.5	0.6	Ref.			Ref.		
N1	488	100	0	96.7	0.9	93.8	1.4	1.65	0.93	2.93	1.65	0.92	2.94
N2/N3	206	100	0	93.9	1.9	89.3	2.6	2.06	1.01	4.19	2.03	0.99	4.14
Histologic grade													
G1	106	100	0	97.3	1.9	97.3	1.9	Ref.			Ref.		
G2	800	100	0	99.3	0.3	97.6	0.7	1.20	0.28	5.16	0.78	0.18	3.42
G3	844	100	0	96.0	0.8	93.5	1.1	3.20	0.78	13.2	1.64	0.32	8.50

¹ The multivariate model 1 included time period between diagnosis and rehab start (as continuous variable) to correct for survivorship bias. Model 2 additionally included age groups, tumour biology, lymphangiosis, T and N category, and histologic grade as predictor variables.

All effect estimators were comparable in size, direction, and statistical significance (the only exception: tumour categories T2 and T3/T4 were significant predictors of DFS but not of COS) in regression analyses with either disease-free or overall survival as the dependent variable (model 1; Tables 3, 4).

The results of the multivariate analysis with the fully adjusted model 2 on COS confirmed, in principle, the results from the analysis adjusted only for time between diagnosis and rehab start (model 1), but all effect estimators found to be statistically significant in model 1 analyses (i.e., those for progressed lymph node infiltration, tumour biology luminal B1 and triple-negative) lost statistical significance in the

Table 4. Conditional 1-, 3-, and 5-year disease-free survival (DFS) with corresponding standard errors (SE), and hazard risks for death (HR) with corresponding 95% confidence intervals (95% CI)

Category	Women, <i>n</i>	1-year DFS	SE	3-year DFS	SE	5-year DFS	SE	Model 1: HR ¹	95% CI		Model 2: HR ¹	95% CI	
									lower	upper		lower	upper
Overall	1,858	99.6	0.2	92.9	0.7	85.2	1.1						
Time between diagnosis and rehab start													
13–24 months	682	99.7	0.2	93.1	1.1	84.2	1.6						
≤12 months	1,176	99.5	0.2	92.7	0.9	86.4	1.4						
Age													
≥40 years	937	99.8	0.2	93.3	0.9	86.5	1.5	Ref.			Ref.		
<40 years	921	99.4	0.3	92.4	1.0	83.9	1.6	1.29	0.97	1.72	1.13	0.84	1.52
Tumour subtype													
Luminal A	607	99.5	0.3	96.1	0.9	90.3	1.5	Ref.			Ref.		
Luminal B1	275	99.2	0.5	91.6	1.9	81.9	3.1	2.05	1.31	3.19	1.59	0.82	3.11
Luminal B2	347	100	0	93.9	1.6	87.4	2.5	1.52	0.95	2.41	1.28	0.74	2.21
HER2 like	129	99.2	0.8	93.4	2.6	83.8	4.7	1.63	0.86	3.08	1.53	0.74	3.17
Triple-negative	368	99.7	0.3	87.3	2.0	78.6	2.7	2.42	1.65	3.55	2.14	1.18	3.38
ER status													
Positive	1,298	99.6	0.2	94.2	0.8	86.8	1.3	Ref.			–		
Negative	548	99.6	0.3	89.4	1.5	81.3	2.2	1.48	1.10	1.98			
PR status													
Positive	1,171	99.5	0.2	95.1	0.7	88.8	1.2	Ref.			–		
Negative	670	99.7	0.2	88.8	1.4	78.9	2.0	1.89	1.42	2.51			
HER2 status													
Positive	491	99.8	0.2	93.9	1.3	86.8	2.1	Ref.			–		
Negative	1,319	99.5	0.2	92.5	0.8	84.6	1.3	1.09	0.77	1.54			
Lymphangiosis													
Yes	434	99.8	0.2	91.6	1.5	80.3	2.5	Ref.			Ref.		
No	1,141	99.4	0.2	94.1	0.8	88.3	1.2	0.52	0.38	0.72	0.58	0.40	0.82
Primary tumour													
Tis/T0/T1	1,128	99.7	0.2	94.2	0.8	85.9	1.4	Ref.			Ref.		
T2	603	99.3	0.3	90.9	1.3	85.0	1.8	1.35	1.00	1.81	1.22	0.89	1.67
T3/T4	99	100	0	88.3	3.7	75.3	5.5	1.82	1.07	3.09	1.39	0.79	2.45
Regional lymph nodes													
N0	1,127	99.7	0.2	93.5	0.9	87.6	1.3	Ref.			Ref.		
N1	488	99.4	0.4	93.1	1.3	83.6	2.2	1.28	0.92	1.79	1.15	0.81	1.64
N2/N3	206	99.5	0.5	88.4	2.5	77.0	3.6	2.04	1.41	2.95	1.76	1.15	2.69
Histologic grade													
1	106	99.0	1.0	93.7	2.8	85.7	4.6	Ref.			Ref.		
2	800	99.7	0.2	96.5	0.7	90.1	1.4	0.93	0.46	1.87	0.65	0.32	1.32
3	844	99.5	0.2	89.7	1.2	81.5	1.7	1.75	0.89	3.45	0.86	0.38	1.95

¹ The multivariate model 1 included time period between diagnosis and rehab start (as continuous variable) to correct for survivorship bias. Model 2 additionally included age groups, tumour biology, lymphangiosis, T and N category, and histologic grade as predictor variables.

full model (Table 3). The only clinical factor that remained as a significant predictor in both models was lymphangiosis (model 1 HR 0.42 and model 2 HR 0.53 for the group without lymphangiosis when compared to the group with lymphangiosis). The results for DFS were comparable, but advanced regional lymph node involvement (N2, N3) remained in addition as a significant predictor in the model.

Discussion/Conclusion

Breast cancer in very young women is associated with unfavourable tumour characteristics and worse outcomes [2, 3, 6, 11–16]. As the literature on young breast cancer patients in Germany is relatively sparse, we assessed 5-year conditional overall and disease-free survival of

1,858 young women with non-metastatic breast cancer stratified by tumour biology and further clinical characteristics. Further, we wanted to explore whether age had an additional effect on survival in our young cohort and thus stratified our sample into “very young” (<40 years) and “young” women (40–54 years of age). Finally, we aimed to identify predictors for death during the follow-up period.

In brief, the main findings are:

1. In our study population, observed 5-year conditional overall survival is as high as 95.5% and 5-year disease-free survival equals 85.2%. In the group of women who started rehab within 12 months after diagnosis, survival was lower than in women who started rehab 13–24 months after diagnosis.
2. Molecular subtypes and biological, pathological, and clinical characteristics that are associated with poorer prognosis are more frequently found in very young (<40 years) than in young breast cancer patients (40–54 years).
3. In addition to known risk factor for poor survival such as advanced infiltration of regional lymph nodes, lymphangiosis, and triple-negative subtype proved to be independent risk factors for death and progression of disease (in simple regression models when only adjusting for time period between diagnosis and rehab start), while age had no further additional statistical significant effect in our young study population. However, in the fully adjusted model, only lymphangiosis remained as a statistically significant predictor for conditional overall survival, while the analysis for disease-free survival identified lymph node involvement as well as lymphangiosis as significant predictors.

Differently than expected and described in previous studies [7, 8, 22], infiltration of regional lymph nodes does not differ significantly between very young and young women in our cohort. This fact contradicts the assumption of later diagnosis in (very) young women but is supported by results of further studies [4, 23]. Evidently, patients with more advanced stage disease (N2/N3, T3/T4) are characterised by poor 5-year survival. In our analyses (model 1), advanced lymph node involvement was statistically significantly associated with death and disease progression during follow-up, and advanced tumour growth showed a trend for significance (COS) and a significant effect on disease progression.

As observed in other studies, hormone receptor status in young women expresses itself differently and is associated with worse outcomes. Thus, very young women are more often oestrogen receptor negative and/or progesterone negative than women aged >40 years, as it has already been described in precedent studies [7, 8, 13]. Additionally, patients with hormone receptor negativity proved to be at increased risk for disease progression, death and

lower survival, which has already been reported in former studies [8, 24, 25], as an indication of the link between unfavourable tumour biology and poor survival in young women. Different to the hormone receptors, the expression of the growth factor HER2 is higher in young women below 40, which is comparable to other studies [26]. In our analysis, there is no difference in disease-free and overall survival comparing the groups with and without overexpression of HER2 and – moreover – there is an inconsistent evidence regarding the prognostic significance of HER2 [25, 27, 28].

In line with other study findings, young women show the unfavourable histological grade G3 as well as an increased lymphovascular invasion more frequently [4, 12, 16, 29]. For both, poor histological grade and involvement of lymphatic vessels, COS as well as DFS take a worse course as has been shown in previous studies [29–31].

In the current literature, non-uniform classification systems for tumour subtypes result in an inappropriate comparison between different studies. Our study, applying subtype categories by Brouckaert et al. [19] with 5 subtypes, shows considerable differences according to age.

Our study indicates that tumour subtypes significantly influence the outcome for women with non-metastatic breast cancer. Patients with B1 tumours and those with triple-negative disease proved to be subject to worse 5-year conditional overall survival and disease-free survival rates (model 1 of Cox proportional regression models). When controlling for further clinical characteristics, the effect was still visible for the triple-negative subtype but lost its significance. Using the same classification system for tumour subtypes and different age groups, Brouckaert et al. [19] showed very similar results in frequency and survival. Another study focussing on women under 40 years with only 4 different subtypes deduced similar results as well [31].

Our study indicates that diagnosis at very young age compared to young age is a risk factor for worse 5-year survival, but the hazard risks from regression analyses fail to reach statistical significance. These findings coincide with those of many other studies [2, 3, 9, 15]. Compared to similar studies, conditional 5-year overall survival with 95.5% and disease-free survival with 85.2% are much better in our cohort than in the study of Ito et al. [32] who reported conditional 5-year survival for 5-year survivors of breast cancer of 90.5%. Our survival rates are higher than those of the cohort of Lian et al. [16] who reported an absolute breast cancer-specific survival rate for patients ≤40 years of 84.9% and a disease-free survival for patients ≤40 years of 62.5%, as well as those of the study by Yu et al. [33] who reported conditional 5-year relative survival of 88.8% for patients with breast cancer 1 year

after diagnosis. Considerable reasons for generally better outcomes in our study are the exclusion of metastasised breast cancer cases and the survivorship cohort (patients had survived already up to 2 years after diagnosis before they started with their rehab programme) in our study, in addition to a nationwide healthcare infrastructure and treatments with high guideline conformity in Germany [34].

Our study detects that there certainly is a link between higher prevalence of subtypes, which are associated with worse outcomes, in (very) young women. These findings correlate with the results of various other studies [9, 14, 18].

In an additional analysis, we stratified molecular subtypes by age groups, similar to a comparable Chinese study [16], to discuss whether young age is an independent risk factor for women with breast cancer. Considering 2 different age groups with the same tumour subtype, no significant differences between the age groups could be shown in our study (data not shown). Astonishingly, there is a trend for women aged <40 years affected by subtype luminal B2 (a subtype with generally better outcome) to be at increased risk to die compared to women aged ≥40 (HR 1.65, 95% CI 0.49–5.12). Lian et al. [16] observed that for young women with luminal A and luminal B2 subtypes, young age could be an independent risk factor.

Partridge et al. [10] concluded based on a study with 3,401 HER2-positive breast cancer patients that age (≤40 vs. ≥41 years) was not a prognostic factor for disease-free or overall survival. In a more recent analysis, based on 17,575 women with stage I–III breast cancer (among them were 1,916 women ≤40 years), very young women (≤40 years) were more likely to die compared to the reference group (51–60 years; HR 1.9, 95% CI 1.6–2.3) [35]. Comparable to the results of Lian et al. [16] and our analysis especially for subtypes with generally better outcomes, Partridge et al. [35] detected that for patients with luminal A disease, very young age might have a poor prognostic effect on mortality (HR 2.1, 95% CI 1.4–3.2). The same was true for young women (≤40 years) with luminal B disease, which had an increased risk to die (HR 1.4, 95% CI 1.1–1.9) compared to the reference group (51–60 years).

Our study has several strengths and weaknesses worth mentioning. First of all, the large study population allowed stratification with respect to molecular subtypes with reasonable sample sizes. Second, although breast cancer in young women is rare, the rehab setting which is targeted at mothers with breast cancer predominantly attracts young women, thus allowing to describe differences between very young (<40 years) and young breast cancer patients (40–54 years). Third, women from all over Germany who have been diagnosed and treated in

many different settings take part in the rehab programme. Thus, our study population is most likely to be representative of young breast cancer patients in Germany. However, we did not aim for a centralised work-up of tumour specimens or a centralised second reading of images. Thus, there may be variation in the expertise of the local clinicians and pathologists leading to smaller deviations in the interpretation of the pathological and clinical findings.

Among the weaknesses of our study, we further have to mention that the exclusion of patients with metastatic disease and the recruitment of patients in a rehab setting may give an overly optimistic picture of survival, as only relatively healthy patients will take part in a rehab programme (confounding by indication). Moreover, only women who had finished their treatment were allowed to participate in the rehab programme; thus, the observed survival in our cohort represents conditional survival rather than absolute survival, and our results might be hampered by the survivorship bias as only women who had survived a certain time period since diagnosis were included in our study. However, we restricted our analysis to women with a maximum time period of 24 months between diagnosis and rehab start and adjusted for the time interval in our Cox proportional hazard models. Further, median follow-up time was 3.6 years with a maximum of 8 years since diagnosis. This follow-up period may be too short, given that breast cancer-associated deaths can occur also at a significantly later date. Recently, Haberland et al. [36] demonstrated that the excess mortality of breast cancer patients remains for a time span of >10 years.

In conclusion, our study revealed that with a maximum time period of 2 years since diagnosis, conditional 5-year overall survival after non-metastatic breast cancer is as high as 95.5%, and disease-free survival is 85.2%. Young women in our study proved to be at lower risk to die in general, compared to other studies with the same age structure, which may be due to confounding by indication.

Differences between our 2 age subgroups were found in biological, pathological and clinical features. Especially those features associated with worse outcomes like oestrogen and progesterone negativity as well as lymphangiosis were observed more often in very young women. This translates to a higher proportion of supposedly more aggressive molecular subtypes such as HER2-like and triple-negative subtypes in very young women. The latter as well as nodal involvement and lymphangiosis proved to be significant risk factors for death during follow-up, but when adjusting for several clinical characteristics, only lymphangiosis remained as a statistically significant predictor of death during follow-up.

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Statement of Ethics

The Ethics Committee of the University Lübeck approved the study protocol, and all women gave written consent for study participation. From 2010 on, written consent included not only the primary survey during the rehab but also the follow-up survey.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.W., D.F., and J.P. developed the research question. A.W., D.F., and A.K. made substantial contributions to the conception and design of the study. J.P. and A.W. analysed the data. J.P., A.W., F.H., and T.P. made substantial contributions to data interpretation. All authors reviewed, edited, and approved the final manuscript.

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