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European Perspectives

Real-World Clinical Outcomes in Biological Subgroups of Breast Cancer in the Hospital District of Southwest Finland

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Subgroups • Clinical outcomes • Real-world evidence • Registry-study

Abstract

Background. Comparing breast cancer survival trends globally, Finland is among the top three countries in Europe. However, outcome data on breast cancer subgroups in the Finnish population are limited. This retrospective, registry-based study aimed to assess patient characteristics and clinical outcomes of different breast cancer subgroups in early (EBC) and metastatic breast cancer (MBC) in a real-life clinical setting.

Materials and Methods. The study consisted of 6,977 adult, female patients with breast cancer diagnosed in Southwest Finland during 2005–2018. Patients were divided into four mutually exclusive groups: human epidermal growth factor receptor 2 positive (HER2+), triple negative, HER2−/hormone receptor positive (HR+), and HER2 and/or HR status unknown, and further into patients with EBC and MBC. Overall survival (OS) was assessed as a clinical outcome, as well as the following real-world (rw) clinical outcomes: disease-free survival (rwDFS), progression-free survival (rwPFS), and distant recurrence-free interval (rwDRFI).

Results. Within EBC, 5-year survival was the highest (88%) in HER2−/HR+, followed by 85% in HER2+, and 75% in triple negative. The rwDFS varied significantly in EBC (5-year rwDFS HER2 -/HR+, HER2+, triple negative: 87%, 80%, 71% respectively). In MBC, median survival was 2 years for both HER2−/HR+ and HER2+ and markedly shorter for triple negative (0.8 years). Independent predictors of mortality were age (hazard ratio [HR], 1.1), other subgroups than HER2−/HR+ (HR, 1.2–1.9), metastatic disease (HR, 9.8), and other malignancies (HR, 2.7).

Conclusion. This registry-based study demonstrates significant differences in breast cancer outcomes on the subgroup level, as well as poorer outcomes compared with clinical trials, giving complementary insight on clinical characteristics in an unselected patient population. ***The Oncologist*** 2021;25:1–9

Implications for Practice: This retrospective, registry-based study assessed the clinical outcomes of different breast cancer subgroups in 6,977 adult, female patients with breast cancer diagnosed in Southwest Finland during 2005–2018. Results demonstrated significant variation in the survival between subgroups in both early breast cancer and metastatic breast cancer, as well as differences between unselected patients representing the standard of care and randomized clinical trials. Although, according to the global comparison of survival trends, the net survival of patients with breast cancer in Finland is generally high, there is great variation between subgroups. These real-life breast cancer data provide tools to further evaluate medical need in different breast cancer subgroups.

Introduction

Breast cancer is a highly heterogeneous disease that can be classified according to distinct clinical, histopathological, and molecular features, which also vastly affect the disease course and outcome. The four intrinsic breast cancer subtypes, originally identified through a comprehensive gene expression profiling effort, are luminal A, luminal B, human epidermal growth receptor 2 positive (HER2+), and basal-like (also called triple negative

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Table 1. Patient characteristics stratified by biological subgroup and cancer stage

Variable	HER2+ ($n = 832$, 14.2%[a]), *n* (%)	Triple negative ($n = 352$, 6%[a]), *n* (%)	HER2−/HR+ ($n = 4{,}680$, 79.8%[a]), *n* (%)	HER2 NA/HR NA (unknown) ($n = 1{,}113$, 16.0%[b]), *n* (%)	*p* value[d] for difference between all BC subgroups	*p* value[d] for difference between HER2+, triple negative, and HER2−/HR+
Early-stage breast cancer						
Patients	767 (92.2)	337 (95.7)	4,528 (96.8)	985 (88.5)		
Age at index, yr						
≤39	58 (7.6)	22 (6.5)	78 (1.7)	19 (1.9)	<.001	<.001
40–49	113 (14.7)	63 (18.7)	466 (10.3)	51 (5.2)		
50–59	199 (25.9)	84 (24.9)	1,079 (23.8)	193 (19.6)		
≥60	397 (51.8)	168 (49.9)	2,905 (64.2)	722 (73.3)		
LN status						
Negative	322 (52.5)	183 (65.1)	2,645 (66.4)	53 (75.7)		
Positive	291 (47.5)	98 (34.9)	1,341 (33.6)	17 (24.3)		
Missing	154	56	542	915		
HR status						
Negative	159 (21.4)	337 (100.0)	0 (0.0)	7 (10.9)		
Positive	584 (78.6)	0 (0.0)	4,528 (100.0)	57 (89.1)		
Missing	24	0	0	921		
Grade						
I	27 (3.6)	9 (2.8)	890 (19.8)	105 (24.9)	<.001	<.001
II	218 (29.2)	47 (14.4)	2,710 (60.4)	220 (52.3)		
III	502 (67.2)	271 (82.9)	886 (19.8)	96 (22.8)		
Missing	20	10	42	564		
Proliferation						
Low	177 (24.3)	47 (14.3)	2,927 (65.5)	75 (65.8)	<.001	<.001
High	552 (75.7)	281 (85.7)	1,542 (34.5)	39 (34.2)		
Missing	38	9	59	871		
Metastatic breast cancer						
Patients[c]	65 (7.8)	15 (4.3)	152 (3.2)	128 (11.5)		
Age at index, yr						
≤39	6 (9.2)	1 (6.7)	2 (1.3)	1 (0.8)	<.001	.031
40–49	7 (10.8)	2 (13.3)	14 (9.2)	5 (3.9)		
50–59	13 (20.0)	0 (0.0)	30 (19.7)	14 (10.9)		
≥60	39 (60.0)	12 (80.0)	106 (69.7)	108 (84.4)		
LN status						
Negative	1 (5.6)	1 (33.3)	9 (19.1)	1 (100.0)	.071	.186
Positive	17 (94.4)	2 (66.7)	38 (80.9)	0 (0.0)		
Missing	47	12	105	127		
HR status						
Negative	18 (31.0)	15 (100.0)	0 (0.0)	2 (10.5)		
Positive	40 (69.0)	0 (0.0)	152 (100.0)	17 (89.5)		
Missing	7	0	0	109		
Grade						
I	2 (3.8)	1 (9.1)	19 (15.6)	9 (15.0)	<.001	<.001
II	15 (28.3)	2 (18.2)	62 (50.8)	42 (70.0)		
III	36 (67.9)	8 (72.7)	41 (33.6)	9 (15.0)		
Missing	12	4	30	68		

(continued)

Table 1. (continued)

Variable	HER2+ ($n = 832$, 14.2%[a]), n (%)	Triple negative ($n = 352$, 6%[a]), n (%)	HER2−/HR+ ($n = 4{,}680$, 79.8%[a]), n (%)	HER2 NA/HR NA (unknown) ($n = 1{,}113$, 16.0%[b]), n (%)	p value[d] for difference between all BC subgroups	p value[d] for difference between HER2+, triple negative, and HER2−/HR+
Proliferation						
Low	8 (14.3)	4 (28.6)	58 (42.0)	7 (53.8)	<.001	<.001
High	48 (85.7)	10 (71.4)	80 (58.0)	6 (46.2)		
Missing	9	1	14	115		

Percentages for all variables except patient numbers are calculated from the total number of patients with data available for the corresponding variable.
[a]Of breast cancers with well-defined subtype (excluding HER2 NA/HR NA cancers).
[b]Of all breast cancers.
[c]Proportions indicate the proportion of early-stage or metastatic breast cancers relative to all breast cancers within the breast cancer subgroup.
[d]χ^2 test, if values in each cell were at least 5, Fisher's exact test otherwise. Only testing difference between patients with nonmissing values.
Abbreviations: BC, breast cancer; HER2+, human epidermal growth factor receptor 2 positive; HER2−, human epidermal growth factor receptor 2 negative; HR, hormone receptor; LN, lymph node; NA, not available.

Table 2. Types of treatments used in patients with early and metastatic breast cancer

	Patients with early breast cancer				Patients with metastatic breast cancer			
Type of treatment	HER2+ ($n = 489$; 98.6%), n (%)	Triple negative ($n = 226$; 99.1%), n (%)	HER2−/ HR+ ($n = 3{,}027$; 99.1%), n (%)	HER2 NA/ HR NA ($n = 180$; 44.0%), n (%)	HER2+ ($n = 58$; 89.2%), n (%)	Triple negative ($n = 24$; 72.7%), n (%)	HER2−/ HR+ ($n = 160$; 85.1%), n (%)	HER2 NA/ HR NA ($n = 49$; 56.3%), n (%)
Surgery	434 (88.8)	211 (93.4)	2,882 (95.2)	73 (40.6)	8 (13.8)	2 (8.3)	16 (10.0)	3 (6.1)
Anti-HER2	374 (76.5)	0 (0.0)	10 (0.3)	0 (0.0)	45 (77.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cytotoxic	371 (75.9)	180 (79.6)	1,521 (50.2)	58 (32.2)	42 (72.4)	23 (95.8)	102 (63.8)	38 (77.6)
Hormonal	335 (68.5)	13 (5.8)	2,377 (78.5)	83 (46.1)	35 (60.3)	2 (8.3)	129 (80.6)	25 (51.0)
Radiotherapy	298 (60.9)	160 (70.8)	2,149 (71.0)	47 (26.1)	13 (22.4)	9 (37.5)	48 (30.0)	4 (8.2)
Neoadjuvant[a]	38 (8.8)	11 (5.2)	77 (2.7)	4 (5.5)				

The number and percentage of patients treated in each subgroup are shown in parentheses.
[a]Any treatment received prior to surgery; percentage calculated from patients receiving surgery.
Abbreviations: HER2+, human epidermal growth factor receptor 2 positive; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; NA, not available.

because of lack of hormone receptor [HR] and HER2 receptors) breast cancer [1]. However, traditional histological assessment of the HR status, (i.e., estrogen receptor [ER] and progesterone receptor [PR]) , HER2 expression, and proliferation rate of the tumor tissue still forms the core of the disease diagnostics [2,3].

Breast cancer subgroup information is central for treatment design and estimating disease prognosis [4,5]. Patients with HR positive/HER2 negative (HR+/HER2−) breast cancer generally have better prognosis than patients with HER2 + or triple-negative breast cancer. The triple-negative subgroup often manifests the most aggressive disease, whereas HER2+ tumors show improved outcomes since the introduction of HER2 targeted treatments [6]. Other general prognostic factors for invasive carcinomas include tumor size, lymph node involvement, degree of histological differentiation, invasion to blood vessel or epidermis, and cell proliferation determined by Ki67 staining [2,3].

Overall, the survival of patients with breast cancer has steadily increased. Currently, approximately 90% of patients with breast cancer are alive 5 years after diagnosis. The global cancer CONCORD-3 surveillance shows that Finnish patients with breast cancer have the third best survival in Europe and are among the top 10 globally [7]. The prognosis is not, however, the same across all patient subgroups, and the occurrence of metastasis after the initial diagnosis is not systematically updated to national cancer registries, making it difficult to find population-based information on metastasis risk among patients with early-stage breast cancer [8,9]. Therefore, outcome data on breast cancer subgroups in the Finnish population are limited, especially in the metastatic patient population.

Clinical trials may give valid estimates of treatment effects providing a basis for clinical recommendations. However, these trials are often not fully representative of the general population that the health services are set to care for and usually have limited follow-up times [10]. The aim of this study was to assess clinical outcomes in both early and metastatic breast cancer in a setting reflecting everyday clinical practice. Specifically, the real-life patient characteristics in stratified subgroups, provided treatments and outcomes were explored.

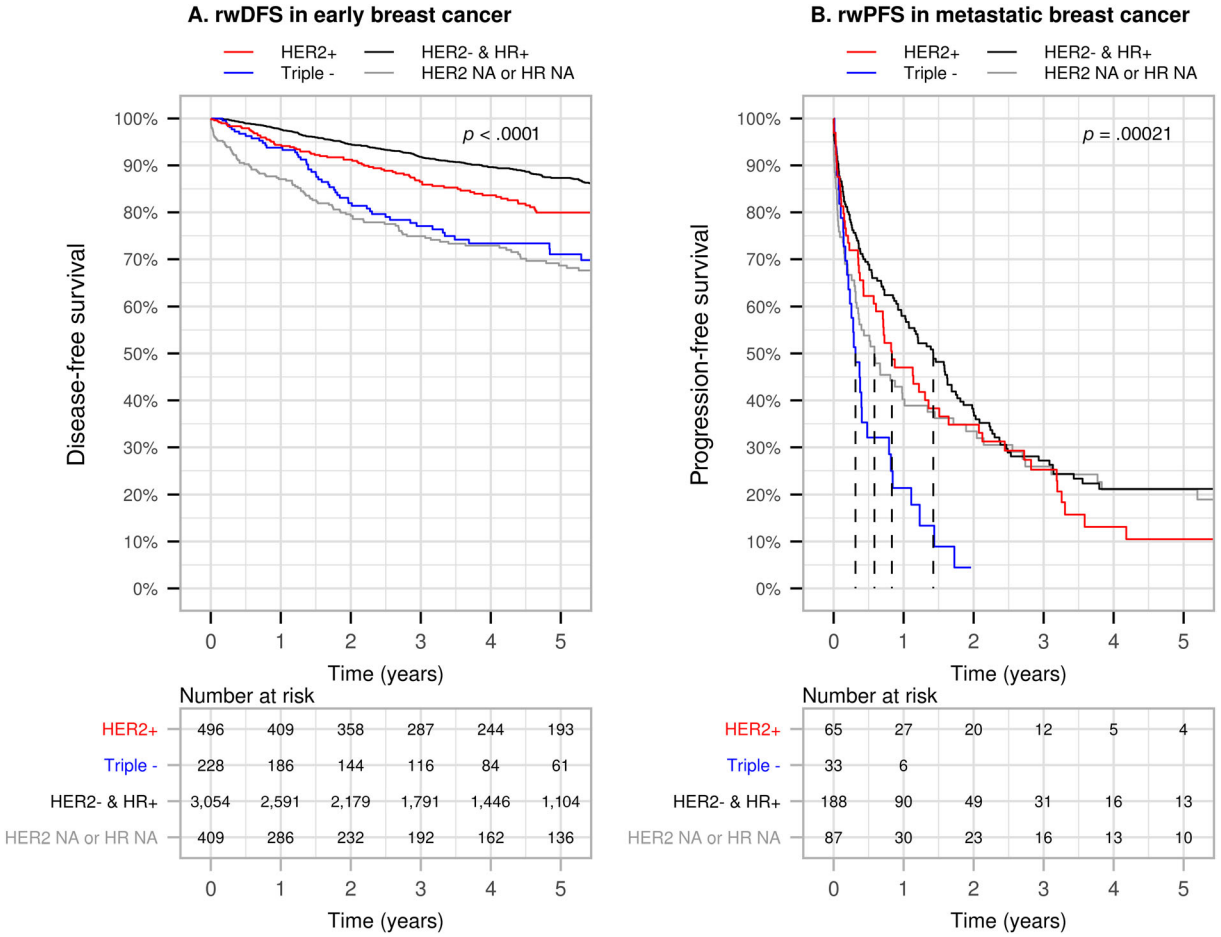

Figure 1. rwDFS in early, and rwPFS in metastatic breast cancer. Kaplan-Meier curves of rwDFS in early breast cancer **(A)**, and rwPFS in metastatic breast cancer **(B)**. The *p* value at the top right corners of each panel indicate the significance from log-rank test for the difference in survival rates among the subgroups.
Abbreviations: HER2+, human epidermal growth receptor 2 positive; HR, hormone receptor; NA, not available; rwDFS, real-world disease-free survival; rwPFS, real-world progression-free survival.

Patients, Materials, and Methods

This study was a population-based, non-interventional, retrospective registry study, using hospital medical record data accessible via Auria Clinical Informatics (Turku, Finland). Data used for the study consisted of electronic hospital records (EHR) collected during clinical practice, representing standard of care. All adult, female patients, resident in the municipality of Southwest Finland and diagnosed with breast cancer (i.e., *International Classification of Diseases, 10th edition* [ICD-10] code C50 present in their electronic health record), during January 1, 2005, to December 31, 2018, were included in the study. Patients with other cancer diagnoses were included. Index was defined to be the date of the first recorded breast cancer diagnosis. The corresponding base population of the area is approximately 0.5 million people.

Patient Characteristics and Patient Subgroups

HER2 receptor status by in situ hybridization, hormone receptor (ER and PR) status, and tumor cell proliferation (Ki67) by immunohistochemistry together with pathologist's assessment of cancer grade and lymph node (LN) positivity were collected from structurally available pathology data. Additionally, text mining of these outcomes from the EHR data was applied. The values closest to index were used, excluding all values more than 6 months apart from the index, as these were considered likely to represent something else than the primary tumor.

All patients were divided into four mutually exclusive patient groups based on HER2 and HR status: HER2+, triple negative, HER2−/HR+, and status unknown. The status-unknown group included patients with missing HER2 status, or HER2− patients with missing HR status. A patient was determined HR+ if at least 1% of the malignant cells stained positive for either ER or PR. The tumor was considered highly proliferative if at least 20% of the malignant cells were positive for Ki67 [11,12].

The patient subgroups were further divided into early breast cancer (EBC) and metastatic breast cancer (MBC). A patient was determined to have EBC if no metastasis was detected within 3 months after the index, and MBC if metastasis was detected within 3 months of the index or at some point during the follow-up. Metastases were based on the following: (a) the first record of ICD-10 diagnosis code C78 or C79 (secondary malignant neoplasm of respiratory and digestive organs, secondary malignant neoplasm

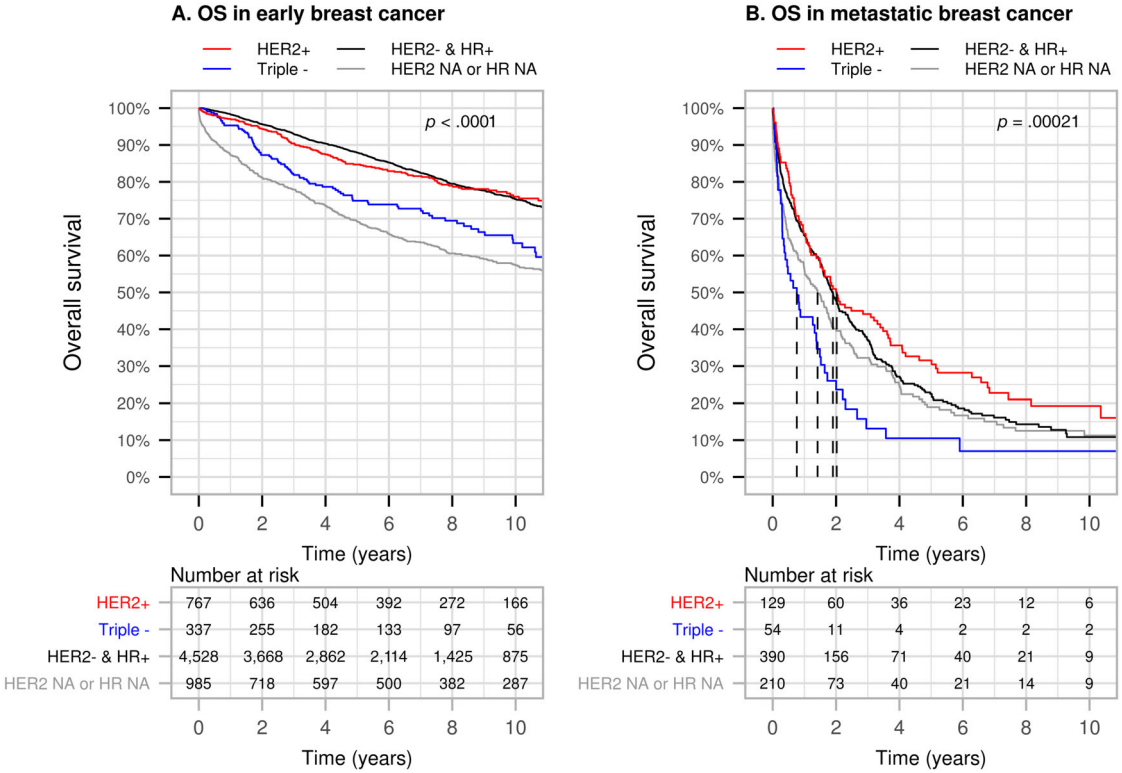

Figure 2. OS in early and metastatic breast cancer. OS stratified by biological subgroup in patients with early breast cancer **(A)**, and in patients with metastatic breast cancer **(B)**. The *p* values at the top right corners of each panel indicate the significance from log-rank test for the difference in survival rates among the subgroups. Dashed black lines in **(B)** indicate the median survival times. Abbreviations: HER2+, human epidermal growth receptor 2 positive; HR, hormone receptor; NA, not available; OS, overall survival.

of other and unspecified sites); (b) tumor-node-metastasis staging; (c) information on metastases in the unstructured EHR through text mining.

Treatment Patterns

Treatment patterns, real-world disease-free survival (rwDFS), and progression-free survival (rwPFS) analyses included data from 2010 to 2018, because medication data prior to 2010 were not comprehensively available. The analysis was restricted to medical treatments prescribed at or from the hospital, relevant to breast cancer. The total numbers of treated patients were based on those receiving at least one of the following: breast cancer surgery or radiation therapy or anti-HER2, hormonal, or cytotoxic treatment. The results are reported separately for EBC and MBC. Treatments before a detection of metastasis in EBC and treatments starting at or after the metastasis detection in MBC were included. A patient could contribute to both analyses if a metastasis was detected during the follow-up. Neoadjuvant treatment in patients with EBC was defined as any breast cancer related treatment given at or after index and prior to the first breast cancer surgery.

Statistical Analysis

Outcomes of rwDFS, rwPFS, overall survival (OS) and real-world distant recurrence-free interval (rwDRFI) were analyzed using Kaplan-Meier fits. The Kaplan-Meier curves are reported alongside the survival estimates and the 95% confidence intervals (CIs) at 1, 2, 3, and 5 years. When reached, the median survivals are reported. The differences in survival curves were compared using the log-rank test. For rwDFS, rwDRFI, and rwPFS analyses patients were censored at time of diagnosis of other malignancy, as applicable.

In EBC, rwDFS was analyzed and defined as metastasis (event) or death (all-cause, event) or other malignancy (censoring event). In addition to rwDFS, for patients with EBC, rwDRFI, differing from rwDFS in measuring time to metastasis without death as an event, was assessed and defined as the time from index until the first detection of metastasis (event), death (censoring event), or other malignancy (censoring event). rwPFS was defined as the time from the detection of metastasis until medication switch (event), death (event), or other malignancy (censoring event). The rwPFS analyses included all patients with a metastasis at diagnosis and those who developed metastasis after index. OS was defined as the time from index until death (all-cause) for patients with EBC and time since detection of metastasis until death (all-cause) for patients with MBC. The end of study (December 31, 2018) was considered a censoring event in all survival analyses. The analyses were stratified by the patient subgroups.

Multivariable Cox regression models were used to assess the impact of breast cancer subgroup, age, sex, metastasis, and other cancer on overall survival (model 1). For the analyses both metastasis and other cancers were included as time varying covariables. In model 2, lymph node status at diagnosis was also included in the model. All statistical analyses were run using R v. 3.5.1 on RStudio Server v. 1.1.463 under Ubuntu v. 16.04.4 LTS (R Group, Vienna, Austria).

Table 3. Multivariable Cox regression model of factors associated with overall survival

Variable	HR (95% CI)	*p* value
Model 1, *n* = 7,955		
Age at index, yr	1.08 (1.07–1.08)	<.001
Subgroup		
HER2− and HR+ (ref.)	1.00	
HER2 NA or HR NA	1.89 (1.67–2.13)	<.001
HER2+	1.18 (1.01–1.38)	.043
Triple−	1.85 (1.50–2.28)	<.001
Metastatic[a]	9.75 (8.79–10.81)	<.001
Other malignancy[a]	2.74 (2.42–3.10)	<.001
Model 2, *n* = 5,765		
Age at index (years)	1.08 (1.09–1.09)	<.001
Subgroup		
HER2− and HR+ (ref.)	1.00	
HER2 NA or HR NA	1.78 (1.06–2.97)	.029
HER2+	0.94 (0.77–1.16)	.576
Triple−	1.75 (1.37–2.24)	<.001
Metastatic[a]	13.85 (11.82–16.22)	<.001
Other malignancy[a]	2.82 (2.43–3.28)	<.001
LN status		
Negative (ref.)	1.00	
Positive	1.28 (1.10–1.48)	.001

[a]Time varying covariates.
Abbreviations: CI, confidence interval; HER2−, human epidermal growth receptor 2 negative; HER2+, human epidermal growth receptor 2 positive; HR, hazard ratio; HR+, hormone receptor positive; LN, lymph node; NA, not available.

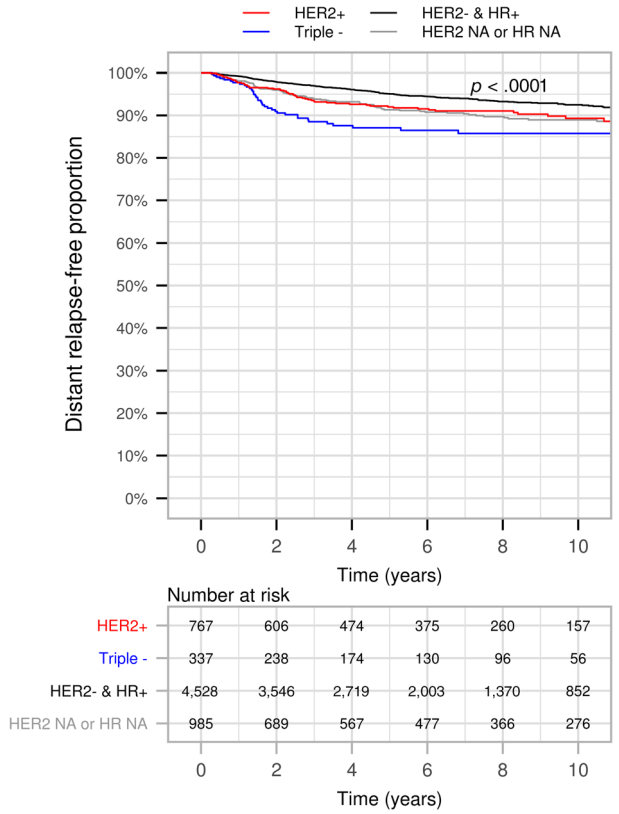

Figure 3. rwDRFI in early breast cancer. Kaplan-Meier fit of rwDRFI stratified by biological subgroup in patients with early breast cancer. The *p* value above the survival curves indicates the significance from log-rank test for the difference in metastasis development probabilities among the subgroups.
Abbreviations: HER2+, human epidermal growth receptor 2 positive; HR, hormone receptor; NA, not available; rwDRFI, real-world distant recurrence-free interval.

Results

The study population consisted of 6,977 adult (≥18 years of age), female patients with breast cancer diagnosed between 2005 and 2018, in the Hospital District of Southwest Finland. The overall breast cancer incidence during the study period was 130.8 per 100,000 person-years in Southwest Finland. Phenotype information regarding HER2 and HR status was available for 5,864 (84%) of the identified patients. Four out of five patients with breast cancer (79.8%) presented with HER2−/HR+, 14.2% presented with HER2+, and 6% presented with triple-negative breast cancer (Table 1). At the time of breast cancer diagnosis, 6% of patients in the HER2−/HR+, HER2+, and triple-negative subgroups, and 20% of those with unknown receptor status, had been diagnosed with a previous malignancy. Clinical characteristics for the patients with EBC and MBC were assessed in the different subgroups. The majority of patients with EBC were older than 50 years of age at index, even if differences in the age distribution were observed between subgroups (Table 1).

Treatment Patterns

Real-life clinical treatment patterns were assessed for patients with EBC and patients with MBC in different subgroups for patients diagnosed after 2010. Almost all patients with EBC in HER2+ (98.6%), triple-negative (99.1%), and HER2−/HR+ (99.1%) groups received treatment, but in the status-unknown group only 44.0%. The majority of the patients with early breast cancer underwent surgery, excluding the status-unknown group, in which 40.6% of the patients were operated on. Depending on the subgroup 2.7%–8.8% of patients received neoadjuvant treatment prior to surgery. Besides surgery, the most common treatments included chemotherapy and anti-HER2 therapy in HER2+, chemotherapy and radiotherapy in triple negative, and hormonal and radiotherapy in HER2−/HR+ patients with early breast cancer (Table 2). Out of early HER2+ patients those who did not receive anti-HER2 therapy were older and had more cardiovascular complications (supplemental online Table 1).

The proportions of treated patients were smaller among patients with MBC. Out of HER2+ patients, 89.2% received treatment, with corresponding proportions of 72.7% in triple-negative and 85.1% in HER2−/HR+ patients. The most common treatment regimens were the same as in the patients with EBC (Table 2).

Real-World Disease-Free Survival and Progression-Free Survival

The rwDFS varied significantly between different subgroups in patients with EBC and rwPFS in patients with MBC (Fig. 1A, B). In EBC, 5-year rwDFS was the highest (87.3%) in HER2−/HR+,

followed by 79.9% in the HER2+ group, 71.1% in the triple-negative, and 68.7% in the status-unknown group (Fig. 1; supplemental online Table 2).

In MBC, 1-year rwPFS was the highest (58%) in HER2−/HR+, followed by 47% in HER2+, 40.2% in status unknown, and 21.4% in triple-negative patients (Fig. 1; supplemental online Table 2). Furthermore, 5-year rwPFS was 21.2% in HER2−/HR+ and 10.5% in HER2+, respectively. Median rwPFS was 1.4 years (95% CI, 1.0–1.7) in HER2−/HR+, 0.8 years (0.4–1.5) in HER2+, 0.6 years (0.3–1.02) in status unknown, and 0.3 years (0.2–0.5) in triple-negative patients. The poorest rwPFS was observed in triple-negative patients, even if the number of patients was small ($n = 33$), and results should be interpreted with caution (Fig. 1).

Overall Survival

Significant differences in OS among the four patient subgroups were detected in both EBC and MBC, with triple-negative patients showing worse survival than HER2+ or HER2−/HR+ patients (Fig. 2A, B). Median survival was not reached in any of the patient groups with EBC; however, 5-year survival rates were the highest for HER2−/HR+ (88%), followed by HER2+ (84.7%) and triple negative (74.9%), and the poorest were in the status-unknown group (69.2%; supplemental online Table 2).

The median OS was similar for metastatic HER2+ and HER2−/HR+ patient groups (2.0 years; 95% CI, 1.49–3.39 years and 1.9 years; 95% CI, 1.60–2.10 years) and markedly shorter for triple-negative patients (0.76 years; 95% CI, 0.35–1.37 years; Fig. 2B), even if patient numbers were low. To conclude, these results demonstrate that OS varies significantly between different breast cancer subgroups.

In a multivariable Cox regression model, factors significantly associated with mortality were subgroups HER2+ (hazard ratio [HR], 1.18), triple negative (HR, 1.85), and receptor status unknown (HR, 1.89) compared with HER2−/HR+ patients. Metastases increase the risk of death 9.7-fold and other malignancies 2.74-fold (Table 3). Including lymph node status to the model, LN positivity was associated with increased mortality (HR, 1.28), and the significance of subgroup status of HER2+ versus HER2−/HR+ disappeared (Table 3).

Real-World Distant Recurrence-Free Interval

The rwDRFI was analyzed to assess the timing of metastasis. A majority of the patients with available HER2 and HR status presented at index with EBC (95.7%) and 4.3% (232 out of 5,864) with metastatic disease. According to Kaplan-Meier estimates, 10 years after index, triple-negative patients developed metastasis (14.2%) more often than HER2+ (10.7%), HER2−/HR+ (7.5%), or those with status unknown (11.0%; Fig. 3; supplemental online Table 2). The differences in rwDRFI between breast cancer subgroups were statistically significant (Fig. 3).

Discussion

Significant advances have been made during the last decades in the treatment of patients with breast cancer; however, there is a growing need for data from real-world clinical treatment practices and outcomes to supplement the data received from interventional studies. The purpose of this retrospective, registry-based study was to evaluate treatment practices and outcomes in a real-life clinical setting, focusing on early and metastatic breast cancer in Finland. This study shows that even if net survival in patients with breast cancer in Finland is among the best three in Europe [7], there are large variations between different biological subgroups, pointing out patients with unmet medical need.

Data on breast cancer subgroup outcomes in real-life clinical practice have largely been missing in Finland and globally, especially for patients with metastatic breast cancer. This study brought new insight on metastasis status at diagnosis in Finland, where 4% of the breast cancer cases had distant metastases at the time of diagnosis. Furthermore, 6% of patients with known receptor status and 20% of patients with unknown receptor status had been diagnosed with another cancer before the diagnosis of breast cancer. In EBC, the rwDRFI differed between the subgroups, with 10-year metastasis probabilities varying from 14.2% in triple-negative, to 10.7% in HER2+, 7.5% in HER2−/HR+, and 11% in status-unknown patients. Comparable population-based studies reporting metastasis probabilities of different breast cancer subgroups are limited. One study showed that the risk of metastasis was significantly increased in HER2+ and triple-negative tumors [13]. Furthermore, substantial variation has been shown in another study in the cumulative incidence of local and distant recurrences among different breast cancers, with locally advanced, high grade, HER2+ and triple-negative tumors presenting particularly increased recurrence rates [9].This study also highlights the need for real-world clinical data to further our understanding of patient characteristics and outcomes in an uncontrolled and unselected patient population. For example, in long-term trastuzumab adjuvant trials, patients were required to have normal baseline hepatic, renal, and bone marrow functions, as well as no history of cardiac events [6,14,15], whereas in the current study, 31.9% of the HER2+ patients with EBC showed coexisting primary hypertension and 9.9% showed atrial fibrillation and flutter and would have been ineligible for the interventional adjuvant study. The age distribution also shows that patients included in the adjuvant trials with trastuzumab were considerably younger, that is approximately half of the trial patients were under 50 years of age [6,14,15], whereas in our study population, depending on the subgroup, 7%–25% of patients were under 50 years of age at diagnosis. The significant differences in patient characteristics is also reflected in the rwDFS and OS outcomes in this study, in which, for example, 5-year rwDFS in the HER2+ patients (76.2%) was of the same magnitude as 10-year rwDFS values of 69%–75% observed in clinical trials [6,14,16], even if the two settings are not head to head comparable.

In contrast, similar EBC OS outcomes have been observed in a population-based study determining the prognostic roles of different breast cancer subtypes in women with operable invasive breast cancer [17]. Data for 321,958 patients were extracted from the Surveillance, Epidemiology, and End Results (SEER) database during 2010–2015. In the SEER data, 5-year OS for the patients in the HR+/HER2− subgroup was 88.4%, in HR+/HER2+ was 88.2%, in HR−/HER2+ was 83.9%, and in

triple negative was 76.5%, and the following corresponding OS values for the patients with EBC in this study were in line with those: 88.0% for HR+/HER2−, 84.7% for HER2+, and 74.9% for triple negative.

Patient survival in this study was highly influenced by the breast cancer subtype, in which patients with triple negative or receptor status unknown each showed a 1.9-fold increased risk of death compared with HR+/HER2− patients; HER2+ patients, in constrast, presented a 1.2-fold increased risk. In the same model, metastasis (HR, 9.7) and other malignancies (HR, 2.7) increased the mortality risk the most. Moreover, LN status was highly associated with survival and diminished the impact of HER2+ status, likely because LN positivity status was more frequently observed in patients with HER2+ breast cancer.

Differences in treatments and the selection of what treatments to use may also explain differences in survival. The poorest outcomes were observed in those patients with EBC lacking a complete receptor status. Of these status-unknown patients, 40.6% received treatment and 46.1% underwent surgery, whereas the corresponding numbers were more than 90% in the other EBC subgroups. Notably, 20% of those with an unknown receptor status had another cancer diagnosis at the time of the breast cancer diagnosis. Plausible explanation for the outcomes may associate with ineligibility for treatments because of poor general health status. Similarly, 24% of HER2+ patients with EBC did not receive anti-HER2 therapy; they were on average 15 years older and presented more frequently with cardiovascular morbidities, compared with anti-HER2 treated HER2+ patients with EBC.

This study was subject to some registry-based limitations. All data may not be consistently recorded to EHR, and missing values cannot be imputed. For example, a complete receptor status was unavailable for 16% of the patients in this study. The majority of the status-unknown patients were diagnosed during the first 5 years of the study, demonstrating an improvement in the availability of receptor statuses in the EHR from 2010 onward. Furthermore, the proportion of triple-negative patients in this study was lower than reported elsewhere (6% vs. 15–20%) [18,19], even if only marginally lower than in one other Finnish registry-based study with 10.6% presenting with triple-negative EBC [20]. It is plausible that these patients are overrepresented in the unknown group. However, the proportions of HER2+ (14.2%) and HER2−/HR+ (79.8%) patients in this study are in line with the current literature strengthening external validity [21,22]. Additionally, although several different sources were used in the identification of metastatic patients, a possibility remains that not all were correctly captured. Also, the information regarding the site of metastasis could not be extracted from the EHRs.

Typically, OS is defined from treatment onset; however, here the index date was the first recorded breast cancer diagnosis for patients with EBC. In the MBC subgroup, the index date for OS was the first record of metastasis. As diagnosis, rather than onset of treatment, was considered index, depending on if diagnosis was recorded early or late in relation to the start of treatment, OS results may be slightly over- or underestimated. Furthermore, the proportion of untreated patients in the MBC subgroup varied from 11% to 44%, affecting survival. Treatment lines are usually defined for rwDFS analysis, which was not comprehensively possible in this study, because complex treatment patterns and reasons for medication change or cessation are not easily available through automated text mining of EHRs. Thus, rwDFS was based on metastasis or death. The difference in rwDFS compared with rwDRFI can be referred to the differing definitions, in which death was considered an event in rwDFS analyses and censoring event in the rwDRFI; that is, 5-year rwDFS in HER2+ was 76.2% (deaths, 15.3%), whereas rwDRFI 89.3% shows the metastasis-free proportion of patients.

Conclusion

This study provides unique data of the clinical outcomes in a real-world population in Finland and enables the comparison between different breast cancer subgroups. These results highlight the importance of assessing and understanding outcomes collected as part of standard of care in uncontrolled and unselected patient populations. In the recent years, registry-based studies have been published in which breast cancer treatment and outcomes have been described [17]. However, to the authors' knowledge, there is not a similar study published that has described early and metastatic breast cancer in different subgroups and reported the outcomes in these subgroups as in this publication. Although net survival of patients with breast cancer is high in Finland, the outcome results between different subgroups show significant variation, highlighting that there are still patients in demand of more effective treatment options. Overall, understanding the epidemiology of breast cancer, the prevalence of the biological subgroups, and the associated clinical characteristics is crucial in estimating the need for new treatment regimens.

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Disclosures

Heli Teerenhovi: Roche Oy (E); **Samuli Tuominen:** Medaffcon Oy (E); **Susanna Nurmi-Rantala**: Roche Oy (E); **Päivikki Hemmilä:** Medaffcon Oy (E). Antti Ellonen indicated no financial relationships.

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