Real-world overall survival and characteristics of patients with ER-zero and ER-low HER2-negative breast cancer treated as triple-negative breast cancer: a Swedish population-based cohort study

Balazs Acs,[a,b,*] Johan Hartman,[a,b] Demet Sönmez,[c] Henrik Lindman,[d,e] Anna L. V. Johansson,[f] and Irma Fredriksson[g,h,**]

[a]Dept of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden
[b]Dept of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden
[c]Center for Observational and Real-World Evidence, MSD, Stockholm, Sweden
[d]Dept of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
[e]Dept of Oncology, Uppsala University Hospital, Uppsala, Sweden
[f]Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[g]Dept of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[h]Dept of Breast-, Endocrine Tumors and Sarcoma, Karolinska Comprehensive Cancer Center, Karolinska University Hospital, Stockholm, Sweden

The Lancet Regional Health - Europe 2024;40: 100886

Published Online 19 March 2024
https://doi.org/10.1016/j.lanepe.2024.100886

Summary

Background Estrogen receptor-low (ER-low) HER2-negative breast cancer has similar pathological and molecular characteristics as triple-negative breast cancer (TNBC), and it is questionable whether it should be considered a separate entity. When the international guidelines lowered the cutoff for ER positivity to ≥1% in 2010, the ≥10% threshold was kept in Sweden. ER-low breast cancer (ER 1–9%) is thus in Sweden treated as TNBC. We aimed to describe patient and tumor characteristics, treatment patterns and overall survival in a Swedish population-based cohort of patients with ER-zero and ER-low HER2-negative breast cancer treated as TNBC.

Methods All TNBC cases diagnosed in Sweden 2008–2020 were included in a population-based cohort study. Patient, tumor and treatment characteristics were analyzed by ER-status (ER 0% vs 1–9%), and associations between subgroups compared using χ^2 test. Survival endpoint was overall survival (OS), and Kaplan–Meier curves were estimated. Cox proportional hazards models were used to estimate adjusted hazard ratios comparing ER-low to ER-zero.

Findings Of the 5655 tumors, 90.1% had an ER expression of 0%, while 9.9% were ER-low. ER-low tumors were grade III in 69.4% (80.8% in ER-zero tumors, p-value = 0.001), with a median Ki67 of 60% (63% in ER-zero tumors, p-value = 0.005). There were no significant differences in given chemotherapy (p = 0.546). A pathological complete response (pCR) was achieved in 28.1% of ER-low tumors (25.1% in ER-zero tumors). In the unadjusted analysis of OS, women with ER-low disease had a borderline but not significantly better OS than those with ER-zero disease (HR 0.84 (95% CI 0.71–1.00), p = 0.052). ER-status 1–9% vs 0% was not associated with OS in the multivariable analysis (HR 1.11 (0.90–1.36)). Distant disease-free survival did not differ by ER-status 0% vs 1–9% (HR 0.97 for ER-zero vs ER-low (0.62–1.53), p = 0.905). After preoperative treatment, the impact of pCR for OS did not significantly differ between ER-zero or ER-low disease.

Interpretation ER-low HER2-negative breast cancer has characteristics and prognosis similar to TNBC, when treated in the same way. Therefore, it seems reasonable to use a ≥10% threshold for ER positivity. This would provide patients with ER-low tumors the same treatment opportunities as patients with TNBC, within studies and within clinical routine.

Funding This work was financially supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in accordance with terms and conditions of a Master Collaboration Agreement between the company and Karolinska Institutet.

DOI of original article: https://doi.org/10.1016/j.lanepe.2024.100896
*Corresponding author. Department of Oncology and Pathology, Karolinska Institutet, R8:04, SE-171 76 Stockholm, Sweden.
**Corresponding author. Department of Breast-, Endocrine Tumors and Sarcoma, Karolinska University Hospital, Hotellet plan 2, SE-171 76, Stockholm, Sweden.
E-mail addresses: balazs.acs@ki.se (B. Acs), irma.fredriksson@ki.se (I. Fredriksson).

Keywords: Triple-negative breast cancer; Estrogen receptor-low; ER-low; Population-based; Prognosis; Real-world data

Research in context

Evidence before this study

Estrogen receptor-low (ER-low) HER2-negative breast cancer has been treated as ER positive breast cancer in accordance with the current international guidelines (ASCO Hormone Receptor–Positive Breast Cancer guideline 2018 and ESMO Early breast cancer: Clinical Practice Guidelines for diagnosis, treatment and follow-up 2019), and currently it is questionable whether it should be considered a separate entity (Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update 2020 and PubMed search [until date 09/2023] with term ER low breast cancer). When the international guidelines lowered the cutoff for ER positivity to ≥1% in 2010 (Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update 2010, Evidence quality: High, but limited data on endocrine therapy benefit for cancers with 1%–10% of cells staining ER positive), the ≥10% threshold was kept in Sweden. There is no current data on the overall survival (OS) and response to neoadjuvant therapy in ER-low breast cancer patients when treated as triple-negative breast cancer (TNBC).

Added value of this study

ER-low (ER 1–9%) breast cancer has in Sweden been treated as TNBC, constituting 10% of the TNBC population. This study showed that patients with ER-low breast cancer had a borderline, but not significantly better OS than those with ER-zero disease (current international TNBC definition). In the multivariable analysis, ER-status (ER-zero vs ER-low) was not significantly associated with prognosis.

Implications of all the available evidence

Using a ≥10% threshold for ER positivity seems reasonable based on real world outcomes. A change would provide patients with ER-low tumors the same treatment opportunities as patients with TNBC, within studies and within clinical routine.

Introduction

Triple-negative breast cancer (TNBC) constitutes around 10–20% of incident breast cancers[1] and is characterized by a distinctly aggressive biological behavior, with higher rates of recurrence and shorter overall survival in the metastatic setting compared to other subtypes of breast cancer.[2,3] Biologically, TNBC is a heterogenous disease that by gene expression profiling can be further grouped into at least four distinct molecular TNBC subtypes, each displaying unique ontologies and differential response to treatment.[4–6] Although a large proportion of TNBCs are of the basal-like intrinsic subtype,[4,7] approximately 20–30% are not, while a significant number of basal-like breast cancers express ER/PR or HER2.[8]

ER-low (ER 1–9%) HER2-negative breast cancer is uncommon, with a prevalence around 2% of all breast cancers.[9–11] ER-low HER2-negative breast cancers have similar pathological[11–15] and molecular characteristics as TNBC,[16] and it is questionable whether this group should be considered a separate entity. When the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) lowered the cutoffs for ER and PR positivity in breast cancer in 2010, from ≥10% to ≥1%,[17] the Swedish Breast Cancer Group considered the medical evidence for a change of cutoff yet too weak, and kept the ≥10% threshold. The Swedish TNBC population has thus encompassed a broader patient population than in international studies, including also ER-low HER2-negative breast cancer cases. ER-low HER2-negative cases has also in general been treated as TNBC, which is interesting now that the international community recognize limited data for benefit of endocrine therapy in the ER-low group.[18] It is of importance to investigate, in-depth, if patients classified as TNBC according to the Swedish broader definition, but not the international definition, those with ER-low breast cancer, have inherent different clinical characteristics and respond differently to given treatment.

We aimed to describe real-world patient and tumor characteristics, treatment patterns and outcome in a Swedish population-based cohort of patients with early TNBC defined as HER2-negative tumors with ER <10%, focusing on potential similarities and differences between patients with ER-zero and ER-low status.

Methods

Study cohort

We included all women diagnosed with TNBC in Sweden between January 2008 and December 2020 in a population-based cohort study, defined based on immunohistochemical (IHC) evaluation of ER (<10%), PR (<10%), HER2 (IHC 0–1+, or 2+ if negative after further verification through in situ hybridization). According to the Swedish guidelines, ER status is considered positive when ≥10% of tumor cells show

ER-specific staining in tumor nuclei detected by IHC. For ER evaluation, the vast majority of Swedish labs used Clone SP1.[19]

The cohort was identified through the Swedish National Breast Cancer Quality Register (NKBC) which contains detailed clinical data on patient and tumor characteristics, treatment and follow-up reported by all units handling breast cancer in Sweden. The completeness of the NKBC has been estimated to >99% by cross-validation to the Swedish Cancer Register,[20] a registry to which reporting of all newly diagnosed malignant neoplasms is mandatory for both clinicians and pathologists. Women with missing data on hormone receptor or HER2-status were not eligible for the study (7% of all invasive cancers in NKBC).

From the initial cohort of 8233 TNBC cases, we excluded patients that received anti-HER2 treatment due to false-positive preoperative biopsy or synchronous contralateral HER2-positive breast cancer (n = 113), and cases with synchronous or metachronous bilateral TNBC (n = 162) and thus the final cohort comprised a total of 7958 women with TNBC diagnosed in 2008–2020. Of the 7958 women, 5928 had data on % of hormone receptor staining by IHC and these were included in the comparative analysis between ER-zero and ER-low cases (Fig. 1). Pathological complete response (pCR) was defined as the absence of invasive carcinoma in both breast and lymph node tissue after neoadjuvant chemotherapy.

From the NKBC, we retrieved information on date and age at diagnosis, estrogen receptor status (0% or 1–9%), progesterone receptor (PR) status (<10% or ≥10%), HER2 status (0–1, 2+), Ki67 (continuous), Nottingham grade (I, II or III) and histological subtype. Information on clinical and pathological tumour size and stage, as well as nodal status and stage was also retrieved. TNM stage (0, I, II or III) was combined according to UICC. All tumour variables, except Ki67, were included as categorical variables in the analyses. Treatment information included surgery (breast conserving surgery, mastectomy, only axilla surgery), axillary surgery (none, sentinel node (SN) biopsy, sampling or axillary clearance), chemotherapy (yes/no and by neoadjuvant, adjuvant or both), radiotherapy (yes/no and by type of surgery) and endocrine therapy (yes/no), which were all treated as categorical variables.

Information on date and cause of death is regularly linked to the NKBC from the Swedish Cause of Death Register. Due to the NKBC data not being fully updated with cause-of death information at retrieval for the present study, overall survival (OS) was the chosen endpoint. During the studied years 2008–2018 however, 98.5% of the deaths in the TNBC population were due to breast cancer. Follow-up was from date of diagnosis to death, or end of study (December 31st, 2020), whichever came first.

Statistical methods

Descriptive frequencies of patient, tumor and treatment characteristics were calculated for all included patients, and for the comparative cohort by ER-status at diagnosis (ER 0% vs 1–9%) and presented as percentages. Differences between subgroups were compared using chi-square tests for categorical variables and Mann–Whitney U or Kruskal–Wallis test for continuous variables since our data were not normally distributed (according to Shapiro–Wilk and Kolmogorov–Smirnov tests).

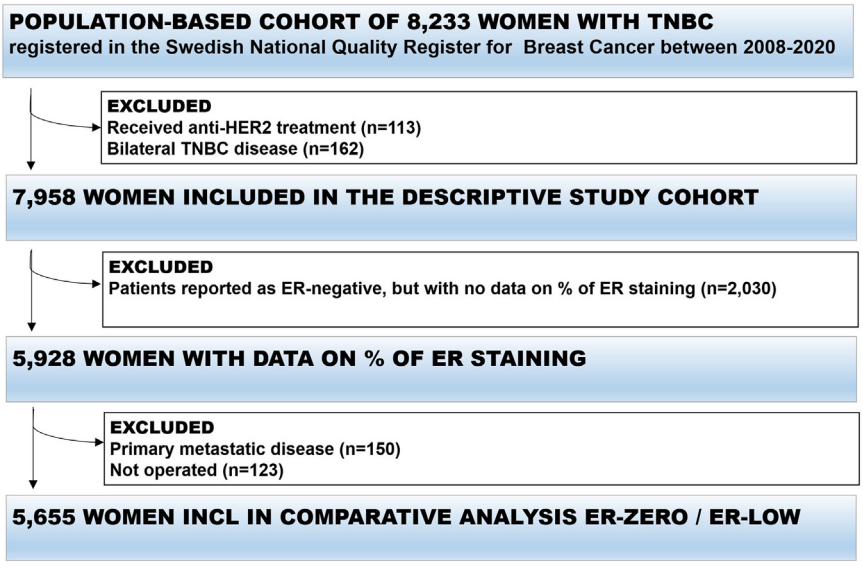

Fig. 1: Flowchart of inclusions and exclusions in the population-based cohort.

	ER 0%	ER 1–9%	Total	p-value
	N (%)	N (%)	N (%)	
Total	5095 (90.1)	560 (9.9)	5655 (100)	
Year of diagnosis				0.001
2008–2011	894 (17.5)	117 (20.9)	1011 (17.9)	
2012–2016	1871 (36.7)	239 (42.7)	2110 (37.3)	
2017–2020	2330 (45.7)	204 (36.4)	2534 (44.8)	
Age at diagnosis (yrs)				0.079
<40	463 (9.1)	61 (10.9)	524 (9.3)	
40–49	797 (15.6)	88 (15.7)	885 (15.6)	
50–64	1599 (31.4)	174 (31.1)	1773 (31.4)	
65–79	1610 (31.6)	189 (33.7)	1799 (31.8)	
≧80	626 (12.3)	48 (8.6)	674 (11.9)	
Mean (sd)	61.14 (15.14)	59.99 (14.72)	61.03 (15.11)	
Median (Q1, Q3)	62 (50,72)	62 (49,71)	62 (50,72)	0.162
T size (path)[a]				0.215
1–20 mm	2238 (56.6)	234 (54.5)	2472 (56.4)	
21–50 mm	1564 (39.6)	184 (42.9)	1748 (39.9)	
>50 mm	152 (3.8)	11 (2.6)	163 (3.7)	
Missing	34	0	34	
T stage (clin)[b]				0.246
T0	8 (0.7)	3 (2.3)	11 (0.9)	
T1	186 (16.9)	19 (14.5)	205 (16.6)	
T2	705 (64.0)	80 (61.1)	785 (63.7)	
T3	160 (14.5)	21 (16.0)	181 (14.7)	
T4	42 (3.8)	8 (6.1)	50 (4.1)	
Missing	4	0	4	
T stage (clin/path)[b]				0.227
T0	11 (0.2)	3 (0.5)	14 (0.2)	
T1	2425 (47.9)	253 (45.2)	2678 (47.3)	
T2	2269 (44.9)	264 (47.1)	2533 (44.8)	
T3	313 (6.2)	32 (5.7)	345 (6.1)	
T4	42 (0.8)	8 (1.4)	50 (0.9)	
Missing	35	0	35	
Lymph node status (path)[a]				0.685
Negative	2715 (70.9)	292 (69.7)	3007 (70.8)	
1–3 positive	794 (20.7)	95 (22.7)	889 (20.9)	
4–9 positive	201 (5.2)	22 (5.3)	223 (5.2)	
10+ positive	121 (3.2)	10 (2.4)	131 (3.1)	
Missing	157	10	167	
N stage (path)[c]				0.455
N0	3247 (64.8)	346 (62.2)	3593 (64.5)	
N1	1270 (25.3)	157 (28.2)	1427 (25.6)	
N2	321 (6.4)	32 (5.8)	353 (6.3)	
N3	174 (3.5)	21 (3.8)	195 (3.5)	
Missing	83	4	87	
TNM stage (clin/path)[c]				0.180
0	4 (0.08)	2 (0.4)	6 (0.1)	
I	1863 (38.4)	197 (36.1)	2060 (38.2)	
II	2400 (49.5)	284 (52.1)	2684 (49.8)	
III	582 (12.0)	62 (11.4)	644 (11.9)	
Missing	246	15	261	
Grade (NHG)				0.001
I	83 (1.9)	23 (4.8)	106 (2.2)	
II	851 (17.3)	124 (25.8)	975 (19.8)	

(Table 1 continues on next page)

	ER 0%	ER 1–9%	Total	p-value
	N (%)	N (%)	N (%)	
(Continued from previous page)				
III	3515 (80.8)	333 (69.4)	3849 (78.1)	
Missing	645	80	725	
Progesterone receptor				NA
Negative (<10%)	5092 (100)	533 (100)	5624 (100)	
Positive (≧10%)	0 (0)	0 (0)	0 (0)	
Missing (neg, but no %)	4	27	31	
Ki67				0.005
Mean (sd)	59.56 (25.5)	55.51 (27.4)	59.19 (25.7)	
Median (Q1, Q3)	63 (40, 80)	60 (30, 80)	62 (40, 80)	
Missing	694	119	813	
HER2-status by IHC				0.001
0–1+	2842 (86.4)	261 (78.1)	3103 (85.6)	
2+	449 (13.6)	73 (21.9)	522 (14.4)	
Missing[d]	1804	226	2030	
Histological subtype				<0.001
Ductal	4230 (83.5)	424 (76.0)	4654 (82.8)	
Lobular	83 (1.6)	38 (6.8)	121 (2.2)	
Mixed/other	752 (14.8)	96 (17.2)	848 (15.1)	
Missing	30	2	32	

[a]Only given for patients with primary surgery. [b]Clinical tumor size in patients with neoadjuvant treatment. [c]cT and cN/pN were used for patients with neoadjuvant treatment. [d]IHC result missing, but ISH negative.

Table 1: **Patient- and tumor characteristics in a population-based cohort of 5655 women with ER-negative or ER-low primary breast cancer diagnosed between 2008 and 2020.**

Survival proportions for overall survival were estimated with the Kaplan–Meier method by ER-status. The log rank test was performed to compare the survival proportions by subgroups. In a sub-cohort (cases diagnosed within the Stockholm-Gotland region) data was valid also for analysis of distant-disease free survival (DDFS). Univariable and multivariable Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) comparing ER-low to ER-zero. In the multivariable models, the HRs were adjusted for ER-status, histological subtype, stage, grade, age and year of diagnosis (model 1). In a second model the HRs were also adjusted for chemotherapy (model 2). The proportional hazards assumption was tested using the scaled Schoenfeld residuals. The proportional hazard assumption was met.

For statistical analysis, SPSS 22 (IBM, Armonk, USA) and MedCalc 13.3.3.0 software (MedCalc Software, Ostend, Belgium) were used. All statistical tests were two-sided with a significance level of 5%.

Role of the funding source

This work was financially supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in accordance with terms and conditions of a Master Collaboration Agreement between the company and Karolinska Institutet. The funding source was not involved in study design, data collection, analysis or interpretation of data, writing of the report or decision to submit the article for publication.

Results

Population and treatment characteristics

Median follow-up time in the full cohort was 4.4 years with an interquartile range of 5.01 years.

Descriptive data on patient and tumor characteristics of the 7958 women in the full cohort are shown in Table S1. Preoperative treatment got more common over time. Distant metastasis at diagnosis (defined as within 3 months of diagnosis) were present in 2.5% (n = 197). Further 1.8% (n = 140) had no surgery. Of those treated with a curative intent (primary surgery or preoperative treatment), a majority presented with T1-T2 disease and node-negativity at diagnosis. Treatment characteristics in primary operated vs preoperatively treated are shown in Table S2, and treatment trends in Table S3. Chemotherapy was given to 77.9% of the patients, increasing from 73.0% of the patients in the beginning of the study period to 83.2% in 2017–2020. Given chemotherapy consisted of anthracyclins and taxanes in combination (70.0%), anthracyclines alone (27.4%) or taxanes alone (2.6%), with the addition of postneoadjuvant capecitabine in 35 patients (34 ER-zero/1 ER-low). Endocrine therapy was given to 3.6% of the patients (n = 232).

	ER 0%	ER 1–9%	Total	p-value
	N (%)	N (%)	N (%)	
Total	5095 (90.1)	560 (9.9)	5655 (100)	
Surgery				0.614
BCS	2790 (54.8)	309 (55.2)	3099 (54.8)	
Mastectomy	2285 (44.9)	248 (44.3)	2533 (44.8)	
Only axilla surgery	15 (0.3)	3 (0.5)	18 (0.3)	
Missing	5	0	5	
Axillary surgery				0.191
None	157 (3.1)	10 (1.8)	167 (3.0)	
SN biopsy	3074 (60.4)	330 (59.0)	3404 (60.3)	
Sampling	118 (2.3)	17 (3.0)	135 (2.4)	
Axillary clearance	1739 (34.2)	202 (36.1)	1941 (34.4)	
Missing	7	1	8	
Chemotherapy				0.546
No	937 (21.1)	111 (22.3)	1048 (21.2)	
Yes	3499 (78.9)	387 (77.7)	3886 (78.8)	
Neoadjuvant only	734 (21.0)	90 (23.3)	824 (21.2)	
Neoadj and postneoadj	345 (9.9)	36 (9.3)	381 (9.8)	
Adjuvant	2420 (69.2)	261 (67.4)	2681 (69.0)	
Missing	659	62	721	
Radiotherapy				0.713
No	1114 (25.6)	121 (24.8)	1235 (25.5)	
Yes	3246 (74.4)	367 (75.2)	3613 (74.5)	
After BCS	2320 (71.5)	258 (70.3)	2578 (71.3)	
After mastectomy	906 (27.9)	106 (28.9)	1012 (28.0)	
After axilla surg only	13 (0.4)	2 (0.5)	15 (0.4)	
Surgery data missing	7 (0.2)	1 (0.3)	8 (0.2)	
Missing	735	72	807	
Endocrine therapy				0.006
No	4213 (96.7)	459 (94.3)	4672 (96.4)	
Yes	145 (3.3)	28 (5.7)	173 (3.6)	
Missing	737	73	810	

Table 2: **Treatment characteristics in a population-based cohort of 5655 women with ER-negative or ER-low primary breast cancer diagnosed between 2008 and 2020.**

Comparison cohort ER-zero vs ER-low; population and treatment characteristics

Of the 8233 patients defined to have TNBC according to the Swedish definition, 5928 had data on % of ER staining by IHC (Fig. 1). Those with data on % of ER staining were representative of the full descriptive cohort except regarding year of diagnosis (Table 1 and Table S1). Reporting of % of ER staining increased over time (Figure S1). There was no significant difference in proportion of ER-low tumors between the six healthcare regions in Sweden (Figure S2). Of the 5655 included women, 5095 (90.1%) had tumors with an ER-expression of 0%, while 560 had tumors that were ER-low (9.9%). The proportion of ER-low was somewhat higher, 11.6% in 2008–2011 and 11.3% in 2012–2016, than during the latter part of the studied period (8.1% in 2017–2020), p = 0.001 (Table 1). The median follow-up time was equal in ER-zero and ER-low disease (4.3 years vs 4.8 years).

There was no significant difference in age distribution between patients with ER-zero vs ER-low tumors (Table 1). Grade III tumors were significantly more common in ER-zero tumors than ER-low tumors (80.8% vs 69.4%, p = 0.001). Mean and median Ki67 were also somewhat higher in ER-zero than in ER-low tumors (p = 0.005). ER-low tumors were more often HER2-IHC 2+ than ER-zero tumors (21.9% vs 13.6%, p = 0.001). ER-low tumors were significantly more often of lobular histopathology (6.8% vs 1.6%, p < 0.001).

There were no significant differences in given treatment between women with ER-zero vs ER-low disease with regard to surgery, chemotherapy or radiotherapy (Table 2). Of the 1205 women that had neoadjuvant treatment, 1199 had data to assess response to treatment. Pathological complete response was achieved in 25.1% of ER-zero tumors (269/1071) and in 28.1% of ER-low tumors (36/128), p = 0.953 (Fig. 2). Endocrine treatment was

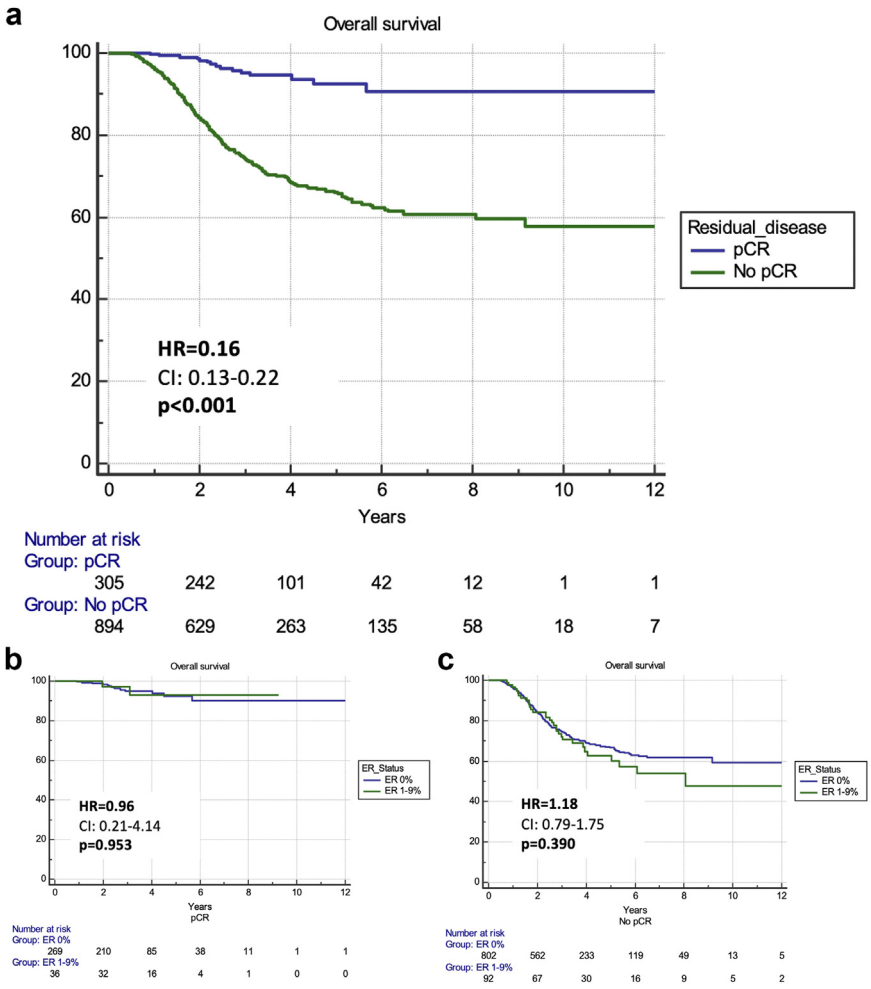

Fig. 2: Overall survival by response to neoadjuvant treatment in the full cohort (n = 1199) (a) and by ER-status (n = 1110). Women with pCR (b) and no pCR (c). Univariate, unadjusted HR and log rank test p values are shown.

given to 5.7% of the women with ER-low tumors while the corresponding proportion in ER-zero patients was 3.3% (p = 0.006) (Table 2). Excluding GnRH-treatment only, the proportion given endocrine treatment was 4.9% (ER-low, n = 24) and 2.6% (ER-zero, n = 113).

Survival analysis by ER-status (ER-zero vs ER-low)

With respect to overall survival, women with ER-low disease had a borderline significant but not significantly better OS than those with ER-zero disease (HR 0.84, 95% CI 0.71–1.00, p = 0.052) (Fig. 3a). In women given chemotherapy there was no difference in OS (HR 1.06, 95% CI 0.82–1.36, p = 0.667) (Fig. 3b), while in women not given chemotherapy those with ER-low tumors had a statistically significantly better OS than those with ER-zero disease (HR 0.65, 95% CI 0.52–0.82, p = 0.002) (Fig. 3c).

There was no significant difference in OS by ER-status (ER-zero vs ER-low) and age group (Figure S3). After preoperative treatment, the impact of a pCR on OS did not differ between women with ER-zero vs ER-low disease (Fig. 2). There was no difference in DDFS between those with ER-zero vs ER-low disease (HR 0.97, 95% CI 0.62–1.53) (Figure S4).

Multivariable survival analysis

In the multivariable analysis adjusting for potential confounders (model 1) and mediator (model 2), there was no association between ER-status and OS (HR 1.13, 95% CI 0.91–1.39, model 1) after adjustment for stage, age, grade and year of diagnosis (Table 3). Further adjustment for chemotherapy did not change the association (HR 1.11, 0.90–1.36, model 2).

Sensitivity analysis

In a sensitivity analysis, we excluded the 173 women that had received endocrine therapy and those with missing data on endocrine treatment (n = 724), leaving

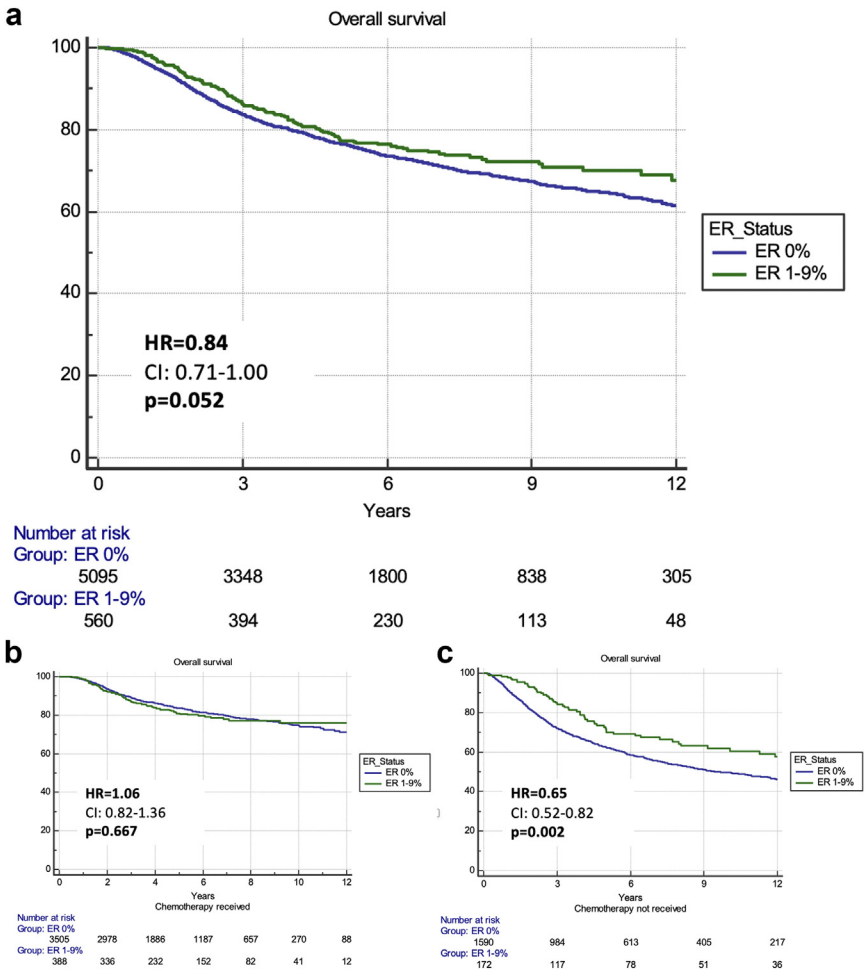

Fig. 3: Overall survival by ER status (n = 5655) (a), and by chemotherapy (b) or not (c). Univariate, unadjusted HR and log rank test p values are shown.

4758 women not treated with endocrine therapy in the analysis. OS did not differ by ER-status (ER-low vs ER-zero HR 0.88 (95% CI 0.72–1.07, p = 0.217) (Figure S5). This was true also in the multivariable analysis (HR 1.12 (95% CI 0.89–1.42) (Table S5).

Discussion

When the international community changed the cut-offs for ER- and PR-positivity in breast cancer in 2010, Sweden kept the ≥10% threshold. The Swedish somewhat broader TNBC population has thus encompassed ER-low HER2-negative breast cancer cases, in general also treated as TNBC. We studied patient- and tumor characteristics, treatment patterns and overall survival in a nationwide population-based study focusing on potential similarities and differences between women with ER-zero and ER-low disease. Patient- and tumor characteristics were similar, as were treatment characteristics. In accordance with the Swedish treatment guidelines, very few received endocrine treatment. ER-low disease had a borderline, but not significantly better OS than ER-zero disease, while in the multivariable analysis ER-status was not associated with prognosis. After preoperative treatment, the proportions of women achieving a pCR within the two groups were comparable, and the impact of pCR on OS did not differ significantly between ER-zero or ER-low disease.

The proportion of ER-low was somewhat higher in the first years of the studied period (2008–2016) than during the latter part (2017–2020), highlighting the test validity and reproducibility issues of IHC at low levels of ER expression and underlining the importance of second reviews and digital quantitative analysis to confirm or adjudicate an ER-low initial result.[18]

We found patient- and tumor characteristics in women with ER-zero and ER-low tumors to be very

Variables in model	Patients (N)	Events (N)	Model 1		Model 2	
			HR (95% CI)	95% CI	HR (95% CI)	95% CI
ER status						
ER-low (ER 1–9%)	468	101	**ref.**		**ref.**	
ER-negative (ER 0%)	4260	1018	1.13	0.91–1.39	1.11	0.90–1.36
Histological subtype						
Ductal	3928	951	**ref.**		**ref.**	
Lobular	100	35	1.10	0.77–1.58	1.04	0.72–1.48
Mixed	700	133	0.83	0.69–1.00	0.83	0.69–1.00
Grade (NHG)						
I	99	16	**ref.**		**ref.**	
II	938	197	1.23	0.74–2.06	1.36	0.81–2.28
III	3691	906	1.47	0.89–2.42	1.76	1.07–2.90
TNM stage (clin/path)[a]						
I	1950	258	**ref.**		**ref.**	
II	2252	557	1.85	1.59–2.15	1.96	1.68–2.28
III	526	304	5.25	4.41–6.25	5.79	4.86–6.90
Chemotherapy						
No	1547	636	Not incl		**ref.**	
Yes	3181	483	Not incl		0.50	0.43–0.58
Age						
<40	378	55	**ref.**		**ref.**	
40–49	705	118	1.14	0.83–1.57	1.11	0.80–1.53
50–64	1487	214	1.04	0.78–1.41	1.01	0.75–1.36
65–79	1596	391	2.02	1.52–2.68	1.80	1.35–2.39
≧80	562	341	5.49	4.11–7.32	3.33	2.44–4.53
Year of diagnosis						
2008–2011	906	331	**ref.**		**ref.**	
2012–2016	1667	461	1.02	0.87–1.18	1.28	1.09–1.51
2017–2020	2155	327	1.06	0.90–1.26	1.38	1.15–1.66

Model 1: adjusted for ER-status, histological subtype, grade, stage, age and year of diagnosis. **Model 2**: adjusted for ER-status, histological subtype, grade, stage, age, year of diagnosis and chemotherapy. [a]cT and cN/pN were used for patients with neoadjuvant treatment.

Table 3: **Multivariable Cox regression analysis of prognostic factors associated with overall survival in a poulation-based cohort of 4728 women with ER-negative or ER-low primary breast cancer diagnosed between 2008 and 2020.**

similar. Those with ER-low tumors had a somewhat higher proportion of lobular carcinomas, a somewhat lower proportion of grade III and highly proliferating tumors which is in line with previous publications.[11–13,16,21] Molecular evidence supports that ER-low HER2-negative breast cancers are as heterogenous as ER-negative tumors. Just like in TNBC, a major proportion of ER-low HER2-negative tumors are of the basal-like molecular phenotype, while some exhibit HER2-enriched, Luminal A/B or normal-like phenotypes.[16] On a gene expression level, studies have shown TNBC and ER-low breast cancer to cluster together, although also HER2-positive tumors were included within these studies.[22,23] Furthermore, the degree of tumor infiltrating lymphocytes (TILs) in ER-negative and ER-low tumors seem to be the same with a high infiltration indicating that both groups are equally immunogenic.[10,24] Up to 15–20% of women with TNBC harbor a BRCA mutation,[25,26] and the incidence of BRCA 1/2 mutations seems to be at the same level in women with ER-low tumors.[27]

We found the prognosis of ER-low breast cancer not to significantly differ from that of ER-zero disease in multivariable analysis, which is line with previous publications including ER-low HER2-negative tumors only.[11–13,16,21,28,29] Approximately 50–60% of patients achieve pCR with modern regimes of neoadjuvant chemotherapy,[30] and previous publications have shown no significant differences in pCR rates between women with ER-low HER2-negative tumors and women with TNBC.[16,28,29] In this population-based cohort study the pCR levels were much lower, but the importance of pCR for overall survival did not differ among those ER-zero and those ER-low.

The main strength of this study was the nationwide population-based design and the large cohort size including both ER-zero and ER-low HER2-negative patients treated as TNBC with detailed real-world

individual information and long-term follow-up enabling estimation of survival at 10 years. Swedish registry data include high-quality information with essentially complete follow-up. Sweden has a tax funded healthcare system, including a national breast cancer screening program inviting women up to age 74, hence our results should be generalizable to similar populations. A number of limitations should be acknowledged. Although being a population-based study covering 99.8% of all Swedish breast cancers diagnosed during a 13-year period, ER-low disease is rare, limiting the study power. The cases were diagnosed and treated during a long period, why treatment changes over time are likely to have impacted outcomes. There was no central review to confirm ER expression levels, but the vast majority of cases had primarily evaluation by breast-dedicated pathologists and with limited variability among departments.[19]

To conclude, ER-low breast cancer has clinical characteristics and prognosis similar to ER-zero breast cancer when treated as TNBC which is underlined by this population-based nation-wide cohort study. However, these findings may not reflect the complexity of tumor biology between these subtypes. Although an absolute majority of ER-low tumors are non-luminal, and despite strong evidence from retrospective meta-analyses showing no benefit of endocrine treatment in ER-poor tumors (ER 1–9%)[31,32] the 1% cutoff for ER-positivity has been kept within international guidelines. In addition to endocrine therapy having significant side-effects and an association with decreased health-related quality-of-life,[33] an ER-low status may contribute to refraining from other essential treatment options. Using a ≥10% threshold for ER positivity therefore seems reasonable based on real world outcomes. A change would provide women with ER-low tumors the same treatment opportunities as women with TNBC, within studies and within clinical routine.

Contributors

IF, DS, JH and HL conceptualized the study. All authors contributed to study design. IF supervised the study and was responsible for data acquisition. BA, IF and AJ performed the quality control of data and algorithms. BA and IF performed the statistical analysis. All authors took part in data analysis and interpretation. IF and BA wrote the original draft. All authors participated in manuscript review and editing, agreed on the content of the manuscript, and approved the final version.

Data sharing statement

The data are not publicly available due to restrictions by Swedish and European law, in order to protect patient privacy. Data are available from the register holder of the Swedish National Breast Cancer Quality Register (NKBC) for researchers with relevant ethical approvals and who meet the criteria for access to confidential data.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden (approval diary number 2022-00757-01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of interests

B.A is supported by The Swedish Society for Medical Research (Svenska Sällskapet för Medicinsk Forskning) postdoctoral grant. J.H has obtained speaker's honoraria or advisory board remunerations from Roche, Novartis, AstraZeneca, Pfizer, Eli Lilly, MSD and Gilead and has received institutional research support from Novartis, Pfizer, MSD, AstraZeneca outside the current work. J.H is scientific advisor to the National Board of Health and Welfare (Socialstyrelsen). J.H. is a co-founder and shareholder of Stratipath AB. J.H has two pending patent applications through Stratipath on AI-software medical device (filed 2021 and 2023). D.S. is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and owns stocks and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. H.L. reports personal fees from Novartis, AstraZeneca, Daiichi Sankyo, Pierre Fabre, MSD outside the current work. H.L. is scientific advisor to Lilly, MSD, Daiichi Sankyo, Pierre Fabre, Seagen, Astra Zeneca, Gilead. A.L.V.J. has no disclosures to declare. I.F. has received an institutional research support from MSD for this project in accordance with terms and conditions of a Master Collaboration Agreement between the company and Karolinska Institutet, as well as research grants from the Swedish Breast cancer Association and the Swedish Cancer Association unrelated to the current work.

Acknowledgements

The authors would like to thank Emmanouil Sifakis for his valuable comments on the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100886.

References

1 Zhang X. Molecular classification of breast cancer. *Arch Pathol Lab Med*. 2022;147(1):46–51.
2 Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Res Treat*. 2009;115(2):423–428.
3 Li X, Yang J, Peng L, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. *Breast Cancer Res Treat*. 2017;161(2):279–287.
4 Lehmann BD, Jovanovic B, Chen X, et al. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. *PLoS One*. 2016;11(6):e0157368.
5 Burstein MD, Tsimelzon A, Poage GM, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res*. 2015;21(7):1688–1698.
6 Masuda H, Baggerly KA, Wang Y, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. *Clin Cancer Res*. 2013;19(19):5533–5540.
7 Cheang MC, Martin M, Nielsen TO, et al. Defining breast cancer intrinsic subtypes by quantitative receptor expression. *Oncol*. 2015;20(5):474–482.
8 Bertucci F, Finetti P, Cervera N, et al. How basal are triple-negative breast cancers? *Int J Cancer*. 2008;123(1):236–240.
9 Yi M, Huo L, Koenig KB, et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. *Ann Oncol*. 2014;25(5):1004–1011.
10 Poon IK, Tsang JY, Li J, Chan SK, Shea KH, Tse GM. The significance of highlighting the oestrogen receptor low category in breast cancer. *Br J Cancer*. 2020;123(8):1223–1227.
11 Schrodi S, Braun M, Andrulat A, et al. Outcome of breast cancer patients with low hormone receptor positivity: analysis of a 15-year population-based cohort. *Ann Oncol*. 2021;32(11):1410–1424.
12 Raghav KP, Hernandez-Aya LF, Lei X, et al. Impact of low estrogen/progesterone receptor expression on survival outcomes in breast cancers previously classified as triple negative breast cancers. *Cancer*. 2012;118(6):1498–1506.
13 Balduzzi A, Bagnardi V, Rotmensz N, et al. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. *Clin Breast Cancer*. 2014;14(4):258–264.
14 Moldoveanu D, Hoskin TL, Day CN, Schulze AK, Goetz MP, Boughey JC. Clinical behavior, management, and treatment

response of estrogen receptor low (1-10%) breast cancer. *Ann Surg Oncol*. 2023;30(11):6475–6483.
15 Yoder R, Kimler BF, Staley JM, et al. Impact of low versus negative estrogen/progesterone receptor status on clinico-pathologic characteristics and survival outcomes in HER2-negative breast cancer. *NPJ Breast Cancer*. 2022;8(1):80.
16 Villegas SL, Nekljudova V, Pfarr N, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors–an analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer*. 2021;148:159–170.
17 Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784–2795.
18 Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American society of clinical oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med*. 2020;144(5):545–563.
19 Acs B, Fredriksson I, Ronnlund C, et al. Variability in breast cancer biomarker assessment and the effect on oncological treatment decisions: a nationwide 5-year population-based study. *Cancers*. 2021;13(5).
20 Lofgren L, Eloranta S, Krawiec K, et al. Validation of data quality in the Swedish national register for breast cancer. *BMC Public Health*. 2019;19(1):495.
21 Bari S, Boulware D, Li J, et al. A real-world data retrospective cohort study of low estrogen receptor-positive early breast cancer: natural history and treatment outcomes. Dove Med Press *Breast Cancer*. 2022;14:199–210.
22 Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30(7):729–734.
23 Deyarmin B, Kane JL, Valente AL, et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. *Ann Surg Oncol*. 2013;20(1):87–93.
24 Voorwerk L, Sanders J, Keusters MS, et al. Immune landscape of breast tumors with low and intermediate estrogen receptor expression. *NPJ Breast Cancer*. 2023;9(1):39.
25 Engel C, Rhiem K, Hahnen E, et al. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer*. 2018;18(1):265.
26 Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin Epidemiol*. 2019;11:543–561.
27 Sanford RA, Song J, Gutierrez-Barrera AM, et al. High incidence of germline BRCA mutation in patients with ER low-positive/PR low-positive/HER-2 neu negative tumors. *Cancer*. 2015;121(19):3422–3427.
28 Dieci MV, Griguolo G, Bottosso M, et al. Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. *NPJ Breast Cancer*. 2021;7(1):101.
29 Fujii T, Kogawa T, Dong W, et al. Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer. *Ann Oncol*. 2017;28(10):2420–2428.
30 Lee JS, Yost SE, Yuan Y. Neoadjuvant treatment for triple negative breast cancer: recent progresses and challenges. *Cancers*. 2020;12(6).
31 Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771–784.
32 Chen T, Zhang N, Moran MS, Su P, Haffty BG, Yang Q. Borderline ER-positive primary breast cancer gains No significant survival benefit from endocrine therapy: a systematic review and meta-analysis. *Clin Breast Cancer*. 2018;18(1):1–8.
33 Andreu Y, Soto-Rubio A, Ramos-Campos M, Escriche-Saura A, Martinez M, Gavila J. Impact of hormone therapy side effects on health-related quality of life, distress, and well-being of breast cancer survivors. *Sci Rep*. 2022;12(1):18673.