Original Study

Characterizing Clinicopathologic Features of Estrogen Receptor-Positive/Progesterone Receptor-Negative Breast Cancers

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Abstract

Approximately 12% of breast cancers have an estrogen receptor-positive/progesterone receptor-negative (ER+/PR-) phenotype. The prognosis of ER+/PR- tumors is intermediate to that between ER+/PR+ and ER-/PR- tumors. A near-maximal ER expression is needed to compensate for the altered ER signaling in ER/PR- tumors.

Background: While most estrogen receptor-positive (ER+) breast cancers express progesterone receptor (PR), a small subset of tumors exhibits an ER+/PR- phenotype despite the fact that PR is an ER-dependent gene product. Previous studies have shown that these tumors are generally associated with a worse clinical outcome when compared to the ER+/PR+ breast cancers, indicating that they are clinically and probably genetically different entities. **Methods:** We characterized the clinicopathologic features of ER+/PR- tumors from the Surveillance, Epidemiology and End Results (SEER) database and the authors' institutional cohort. **Results:** ER+/PR- tumors, constituting 12% of all breast cancers in both cohorts, less frequently occurred in Caucasians, were more likely to be of a higher histologic grade and presented with a higher stage when compared to ER+/PR+ tumors. Conversely, ER+/PR- neoplasms were more frequently seen in Caucasians, less likely to be of a higher histologic grade and less frequently presented with an advanced clinical stage when compared to ER-/PR- tumors. Further, the ER+/PR- tumors were associated with a disease-specific survival intermediate to that between ER+/PR+ and ER-/PR- tumors. An ER H-score of ≥270 was associated with a significantly superior relapse-free survival in the ER+/PR- tumors, suggesting that a near-maximal ER expression is needed to compensate for the altered ER signaling in these tumors. Pathologic stage and HER2 status were independent prognostic factors in the ER+/PR- tumors. These findings may provide additional insights in directing clinical decision making for individualized systemic therapy in the pursuit of precision medicine.

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Introduction

Breast cancer is the most common cancer in women globally, with over 2 million cases diagnosed annually, and is also the most frequent cause of cancer deaths in most regions of the world.[1] In the United States, breast cancer accounts for 31% of all female cancers, with a continued slowly increased incidence rate up by 0.5% annually, and an estimated 287,850 new cases and 43,250 deaths in 2022, respectively.[2]

Estrogen receptor (ER) signaling is essential for normal mammary gland development, and drives the majority of breast cancers as approximately 78% of invasive breast cancers are ER+, and this rate is projected to increase 0.75% per year.[3] The independent predictive and prognostic values of ER have been well established as ER-targeted endocrine therapies have significantly improved the clinical outcomes in patients with these cancers, and the therapeutic effects are correlated with the expression levels of the ER protein in tumor cells.[4-6]

Progesterone receptor (PR) is an ER-dependent gene product, thus is theoretically a surrogate marker for a functional ER pathway.[7] However, ER+ breast cancers are not always PR+, and 10-15% of tumors reportedly exhibit an ER+/PR- phenotype.[8,9] There have been controversies on its independent predictive and prognostic values. Some studies have demonstrated that PR is independently associated with disease-free and overall survivals in the adjuvant setting and in patients with ER+ metastatic disease,[10-12] while others have argued that PR is not a strong factor

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for predicting endocrine response nor for survival outcome, thus adding neither diagnostic information nor having a therapeutic impact.[13-15] Given that the ER+/PR- phenotype suggests a blockade of the functional ER signaling, it is not surprising that these tumors show a more aggressive biological behavior than that of ER+/PR+ breast cancers.[8-10,16] Thus, tumors with the two different phenotypes are clinically and probably genetically different entities.

While the clinical practice decisions in endocrine therapy are primarily based on the ER status of the tumors, different strategies may be required for patients with ER+/PR- breast cancer to ensure optimal treatment and maximum benefits, as endocrine therapies have been shown to be less effective for tumors with this phenotype when compared to the ER+/PR+ tumors.[8-10,17,18] Nonetheless, while the clinical significance of evaluating PR expression remains controversial, it is generally accepted that PR status may further stratify ER-positive tumors into different prognostic categories, although the thresholds of PR for this purpose have not been well studied.

In this study, we sought to further characterize the clinicopathologic features and prognostic outcomes of ER+/PR- breast cancers using the Surveillance, Epidemiology, and End Results (SEER) database and the authors' institutional cohort. Further, the levels of ER expression in ER+/PR- tumors on the survival outcome was also studied.

Materials and Methods

This study was performed after the approval of the institutional review board of the University of Alabama at Birmingham. A search to identify breast cancer patients was conducted in the SEER database which retrospectively collects data from population-based cancer registries covering approximately 34.6% of the US population. SEER program statistical analysis software packages were used to identify the patients. The patients were included in the study when meeting the following criteria: female older than 18 years age and diagnosed with invasive breast cancer between 2010 and 2015. A search of the tumor registry at the authors' institution was also performed to identify female patients diagnosed with invasive breast cancer between 1998 and 2018. The patients' demographic information (age at diagnosis and race), the pathologic characteristics of the primary tumor (histologic type and grade, TNM status, ER, PR and HER2 status), and survival outcomes were collected from both cohorts. All patients included in the authors' cohort received standard of care treatment at the time of diagnosis. The median follow-up time was 53 months and 1881 days (63 months) for the SEER and authors' cohorts, respectively.

Of the 627 ER+/PR- breast cancers identified in the authors' cohort, 140 had HER2 amplification and/or overexpression, and 67 patients received HER2-targeted therapy at the authors' institution. Most patients who did not receive HER2-directed therapy were diagnosed early in the study period (prior to 2010).

Hormonal receptor (ER and PR) and HER2 overexpression or gene amplification status were assessed by following the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guideline Recommendations as previously described.[19] While the cutoff value for ER and PR positivity at the authors' institution was 10% prior to the 2010 ASCO/CAP Guideline Recommendations and revised to 1% thereafter, the cases with an 1-10% ER and PR expression prior to 2010 were re-reviewed and regarded as ER+ and/or PR+ in the analyses in order to maintain the same cutoff values in the study period. In addition, semiquantitative analysis of ER expression in ER+PR- tumors was performed using an H-score as calculated by multiplying the intensity (0, 1+, 2+, and 3+) by the percentage of tumor cell nuclei stained, giving a range of 0 to 300, as previously described.[20]

The categorical data were evaluated by Chi-square testing, while continuous data were analyzed by an independent t-test. Distant recurrence-free survival (RFS; from the date of diagnosis to the date of distant recurrence) and disease-specific survival (DSS; from the date of diagnosis to the date of death from the disease) were determined by Kaplan-Meier analysis. Patients who survived or were lost to follow-up were considered as censored data in the analyses. The Cox proportional hazards regression model was utilized to identify significant factors for survival. A P value of less than .05 was considered statistically significant. All data were analyzed using IBM SPSS Statistics (Version 26) predictive analytics software.

Results

Clinicopathologic characteristics of breast cancers stratified by ER and PR status

There are a total of 36279 patients from the SEER database meeting the inclusion criteria and thus were included in the study for further analyses. Most of the patients were Caucasians (28431; 78.4%), followed by African Americans (4375; 12.1%) and others. The ER+/PR+, ER+/PR-, ER-/PR+ and ER-PR- cases were 26006 (71.68%), 4172 (11.5%), 347 (0.96%) and 5754 (15.86%), respectively (Table 1). Approximately 14% of ER+ tumors (4127/30178) had an ER+/PR- phenotype, an incidence rate similar to that observed in the National Cancer Database.[8] The ER-/PR+ tumors were not further analyzed given their low incidence rate and beyond the scope of the study.

When compared to ER+/PR+ breast cancers, the patients with ER+/PR- tumors were significantly older and less frequently Caucasians (80.3% vs. 76.6%). Further, the ER+PR- tumors were more likely to be HER2-positive (28.2% vs 12.0%), of higher histologic grades (Grades II & III 86.0% vs. 75.7%), and to present with a higher pathologic tumor stage (mean size 83.4 vs. 58.7 mm) and nodal stage (N1/2/3 47.4% vs. 41.1%). Thus, it is not surprising that ER+PR- tumors more frequently presented with advanced clinical stages (stage II/III/IV 66.3% vs. 38.5%).

We next compared ER+/PR- and ER-PR- tumors. To that end, the patients with ER+/PR- tumors were significantly older and more frequently Caucasians (76.6% vs. 71.0%). The ER-PR- tumors were more likely to be HER2-positive (36.9% vs. 28.2%), of higher histologic grades (Grades II and III 98.0% vs. 86.0%), and to present with a higher pathologic tumor stage (mean size 121.7 mm vs. 83.4 mm) and nodal stage (N1/2/3 52.9% vs. 47.4%). Again, these tumors were more likely to present with advanced clinical stages (Stage II/III/IV 71.0% vs. 66.3%).

The clinicopathologic features of the 5309 patients from the authors' institutional cohort are summarized in Table 2, of which the ER+/PR+, ER+/PR-, ER-/PR+ and ER-/PR- tumors were 3582 (67.47%), 627 (11.81%), 144 (2.71%) and 956 (18%),

Table 1 Clinicopathologic features of the patients from the SEER cohort.

Clinicopathologic factor	Phenotype (N)				P value	
	ER+/PR+ (26006)	ER+/PR- (4172)	ER-/PR+ (347)	ER-/PR- (5754)	ER+/PR- vs. ER+/PR+	ER+/PR- vs. ER-/PR-
Age (median) (range)						
	61 (18-85+)	62 (20-85+)	57 (20-85+)	58 (22-85+)	< 0.0001	< 0.0001
Race						
Caucasian	20893	3195	259	4084	< 0.0001	< 0.0001
African American	2659	588	48	1080		
Other	2265	360	37	556		
Unknown	189	29	3	34		
Histologic type						
Ductal	19572	3229	312	5283	0.798	< 0.0001
Lobular	3448	579	10	122		
Ductal & lobular	2462	240	8	113		
Other	524	127	17	236		
Histologic grade						
I	6307	582	10	114	< 0.0001	< 0.0001
II	13531	1722	77	1202		
III	6168	1868	260	4438		
HER2 status						
Positive	3116	1175	128	2121	< 0.0001	< 0.0001
Negative	22890	2997	219	3633		
Mean tumor size (mm) (range)						
	58.7 (1-999)	83.4 (1-999)	136.6 (1-999)	121.7 (1-999)	< 0.0001	< 0.0001
Pathologic nodal stage						
N0	15311	2195	159	2708	< 0.0001	< 0.0001
N1	7207	1235	123	1870		
N2	2101	401	32	591		
N3	1387	341	33	585		
Clinical stage						
I	15981	1408	81	1517	< 0.0001	< 0.0001
II	5538	1196	105	1402		
III	2532	1078	107	1817		
IV	1955	490	54	864		

respectively. Approximately 15% of ER+ tumors (627/4209) had an ER+/PR- phenotype. Interestingly, the proportions of ER-/PR+ and ER-/PR- tumors in our cohort were significantly higher than those of the SEER database (both $P < 0.0001$), likely reflecting the racial and ethnic differences in the Southern United States.[20]

Analyses of the patients in this latter cohort revealed largely similar observations. When compared to ER+PR+ tumors, the patients with ER+/PR- tumors were less frequently Caucasians (82.8% vs. 73.0%), while no significant difference for median age between the two groups was identified. Once again, the ER+PR- tumors were more likely to be HER2-positive (22.5% vs. 12.1%), of higher histologic grades (Grades II & III 82.9% vs. 73.6%), and to present with a higher pathologic tumor stage (mean size 24.4 mm vs. 20 mm) and nodal stage (N1/2/3 35.9% vs. 30.7%). Accordingly, these tumors were more likely to present wih advanced clinical stages (Stage II/III/IV 61.6% vs. 30.0%, $P < 0.0001$). Comparing to those with ER-/PR- tumors, the patients with ER+PR- carcinomas were significantly older at the time of presentation and more frequently Caucasians (73.0% vs. 64.9%). Once again, The ER-PR- tumors were more likely to be HER2-positive (25.4% vs. 22.5%), of higher histologic grades (Grade II/III 98.6% vs. 82.9%), and to present with a higher pathologic tumor stage (mean size 30.5 mm vs. 24.4 mm) but of similar nodal stage (N1/2/3 34.9% vs. 35.9%, $P = 0.9$), and thus expectedly more advanced clinical stages (Stage II/III/IV 69.4% vs. 61.6%).

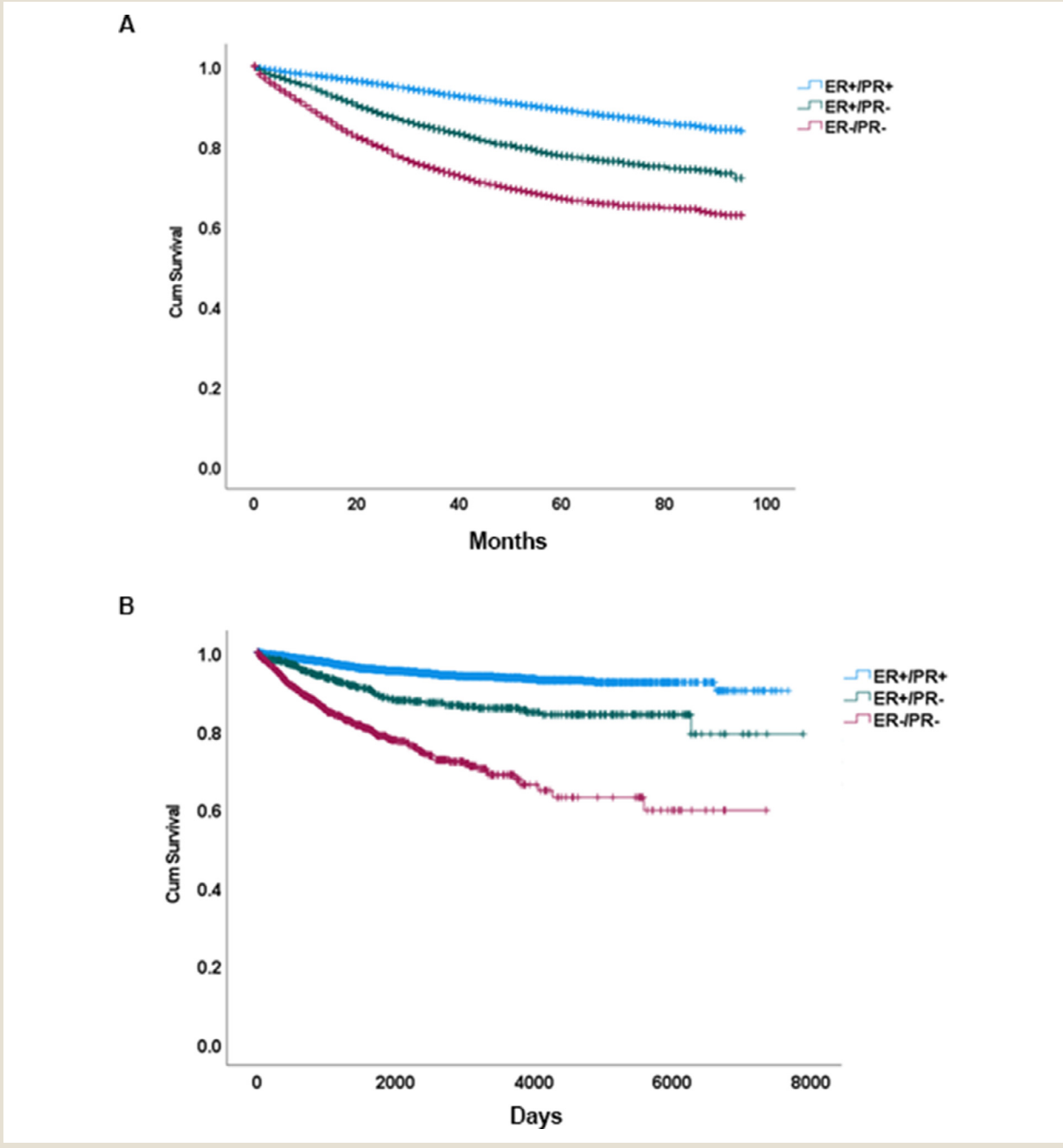
Table 2 Clinicopathologic features of the patients from the authors' cohort.

Clinicopathologic factor	Phenotype (N)				P value	
	ER+/PR+ (3582)	ER+/PR- (627)	ER-/PR+ (144)	ER-/PR- (956)	ER+/PR- vs. ER+/PR+	ER+/PR- vs. ER-/PR-
Age (median) (range)						
	58 (18-99)	58 (20-98)	54.5 (24-93)	54 (22-95)	0.743	< 0.0001
Race						
Caucasian	2866	458	86	620	< 0.0001	< 0.0001
African American	669	158	56	324		
Other	41	11	2	11		
Unknown	6	0	0	1		
Histologic type						
Ductal	2602	466	121	856	0.921	< 0.0001
Lobular	385	68	15	80		
Ductal & lobular	565	79	7	16		
Other	30	14	1	4		
Histologic grade						
I	919	101	3	13	< 0.0001	< 0.0001
II	1839	290	31	167		
III	799	230	110	776		
Unknown	25	6	0	0		
HER2 status						
Positive	433	141	38	243	< 0.0001	< 0.0001
Negative	3083	465	103	701		
Equivocal	56	16	3	7		
Unknown	10	5	0	5		
Mean tumor size (mm) (range)						
	22 (1-170)	24.4 (1-275)	34.5 (3-150)	30.5 (1-205)	0.002	< 0.0001
Pathologic nodal stage						
N0	2320	369	79	551	< 0.0001	< 0.0001
N1	812	149	43	228		
N2	189	54	7	62		
N3	100	22	10	44		
Unknown	161	33	5	71		
Clinical stage						
I	2508	241	43	293	< 0.0001	< 0.0001
II	717	233	50	317		
III	159	105	40	232		
IV	189	48	11	111		
Unknown	9	0	0	3		

Clinical outcomes stratified by ER/PR profiles

We next turned to analyze the clinical outcomes of the patients stratified by ER/PR profiles of their tumors. To that end, a significantly inferior DSS was seen in patients with ER+/PR- tumors when compared to those with ER+/PR+ tumors [hazard ratio (HR) 2.732, 95% confidence interval (CI) (2.471 - 3.022), $P<0.0001$] in the SEER cohort. Further, the former was associated with a significantly prolonged DSS when compared to those with ER-/PR- tumors [HR 0.6331, 95% CI (0.5845 - 0.6857), $P<0.0001$], in keeping with the previous studies.[8-10,17,18,20] Similar observations were obtained in the authors' institutional cohort [ER+/PR- vs. ER+/PR+: HR 2.917, 95% CI (2.077 - 4.098), $P<0.0001$;

Figure 1 Disease-specific survival of breast cancers stratified by ER and PR status in the SEER database (A) and the authors' cohort (B).



ER+/PR- vs. ER-/PR-: HR 0.4311, 95% CI (0.3411 - 0.5447), $P<0.0001$] (Figure 1).

Factors associated with survival outcomes for ER+/PR- breast cancers

Univariate and multivariate analyses were performed to identify significant prognostic factors for DSS in the subset of patients with ER+/PR- tumors. To that end, an older age, being African American, high histologic grade, a negative HER2 status, higher pathologic tumor and nodal stages were independently associated with a worse DSS in the SEER cohort (Table 3). Similar observations were obtained in the authors' institutional cohort, except for the age and race of the patients, probably attributed to their relatively smaller sample size. Interestingly, a positive HER2 status was a worse prognosticator in the univariate analysis but not an independent factor after controlling for other variables in this cohort (Table 4).

Table 3 Univariate and multivariate analyses for disease specific survival in the patients with ER+/PR- breast cancer from the SEER cohort.

Clinicopathologic factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (> 60 vs ≤ 60)	1.129 (0.986 - 1.293)	0.079	1.445(1.255 - 1.664)	< 0.0001
Race (African American vs. Caucasian)	1.467 (1.231 - 1.748)	< 0.0001	1.282 (1.073 - 1.532	0.006
Histologic type (lobular vs. ductal)	0.881 (0.717 - 1.082)	0.228	0.926 (0.743 - 1.155)	0.496
Histologic grade (III vs. I/II)	2.141 (1.863 - 2.461)	< 0.0001	1.664 (1.430 - 1.935)	< 0.0001
Tumor size (2.0-5.0 cm vs. ≤ 2.0 cm)	2.660 (2.191 - 3.229)	< 0.0001	2.014 (1.649 - 2.460)	< 0.0001
Tumor size (>5.0 cm vs. ≤ 2.0 cm)	7.068 (5.871 - 8.510)	< 0.0001	4.704 (3.860 - 5.733)	< 0.0001
HER2 (positive vs. negative)	0.934 (0.801 - 1.088)	0.381	0.764 (0.653 - 0.894)	0.001
Lymph node status (positive vs. negative)	3.497 (3.001 - 4.074)	< 0.0001	1.445 (1.255 - 1.664)	< 0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval

Table 4 Univariate and multivariate analyses for disease specific survival in the patients with ER+/PR- breast cancer from the authors' cohort.

Clinicopathologic factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (> 60 vs ≤ 60)	0.389 (0.171 - 0.885)	0.024	0.515 (0.222 - 1.192)	0.121
Race (African American vs. Caucasian)	0.942 (0.445 - 1.993)	0.875	0.567 (0.260 - 1.241)	0.156
Histologic type (lobular vs. ductal)	0.694 (0.213 - 2.257)	0.543	1.153 (0.311 - 4.271)	0.831
Histologic grade (III vs. I/II)	3.221 (1.655 - 6.270)	0.001	2.538 (1.200 - 5.368)	0.015
Tumor size (2.0-5.0 cm vs. ≤ 2.0 cm)	3.755 (1.830 - 7.705)	< 0.0001	2.647 (1.262 - 5.551)	0.010
Tumor size (>5.0 cm vs. ≤ 2.0 cm)	4.197 (1.457 - 12.084)	0.008	3.111 (1.041 - 9.297)	0.042
HER2 (positive vs. negative)	2.004 (1.051 - 3.821)	0.035	1.322 (0.663 - 2.636)	0.427
Lymph node status (positive vs. negative)	5.141 (2.504 - 10.556)	< 0.0001	3.995 (1.930 - 8.267)	< 0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval

Given that the effects of ER-targeted therapies are correlated with the ER levels in the tumor cells of ER+ breast cancers,[21,22] we next explored if the level of ER expression was prognostically significant in the subset of tumors with an ER+PR- phenotype. Logistic regression and survival analyses for RFS and DSS were performed in the authors' institutional cohort using consecutive cutoffs of ER H-scores with increment by 10. To that end, an ER H-score of 270 yielded an optimal cutoff with a significant difference for RFS [HR1.737, 95% CI (1.083 - 2.787), P=0.0221] and a marginal significance for DSS [HR 1.701, 95% CI (0.9586 - 3.017), P=0.0694] (Figure 2). Interestingly, the patients with a tumor showing an ER H-score < 270 were significantly younger. These tumors were more frequently HER2-positive (24.3% vs. 14.3%; P=0.015), of higher histologic grades (Grade II/III 85% vs. 73.5%; P<0.0001), presented with both higher pathologic tumor and nodal stages (P=0.008 and 0.002, respectively), and thus were at more advanced clinical stages (Stage II/III/IV 62.3% vs. 40.7%; P=0.001), as illustrated in Table 5.

We further included the ER H-score in the survival analyses to ascertain if the level of ER expression is of prognostic significance in ER+/PR- tumors. To that end, the level of ER expression was only significantly correlated with RFS, but not DSS, whereas patient age, histologic grade, HER2 status, and pathologic tumor and nodal stages were associated with both RFS and DSS by univariate analyses (Table 6). In multivariate analysis, tumor size and nodal status were independently correlated with both RFS and DSS, while the significance of HER2 status was only seen in DSS (Table 7).

Discussion

In this study, we found that approximately 12% of breast cancers were ER+/PR-. This is in keeping with the 10-15% reported incidence range of this subtype in previous population-based studies.[8,9] Furthermore, up to 15% of ER+ tumors had an ER+/PR- phenotype.

ER+/PR- breast cancers demonstrate different clinicopathologic features when compared to other subtypes. Reflecting the racial and ethnic differences, there were significantly more African American patients having an ER+/PR- tumor when compared to those with an ER+/PR+ tumor, while there were significantly more Caucasians with an ER+/PR- tumor than those with an ER-/PR- tumor in both cohorts. The patients with ER+/PR- tumors were significantly older than those with ER+/PR+ and ER-/PR- tumors in the SEER cohort, consistent with an analysis using an early (1990-2012) SEER database.[9] Similarly, a higher proportion of elderly patients (older than 70 years) were found to have ER+PR− tumors than the patients in the other age groups in a study using the National Cancer Database.[8] Moreover, the significant association of younger age and the ER-/PR- subtype has been observed in most published cohorts.[23-25] The discrepancies in the survival outcomes

Table 5 Clinicopathologic features of ER+PR- breast cancers stratified by ER H-score.

Clinicopathologic factor	ER H-score (N)		P value
	ER < 270 (300)	ER ≥ 270 (230)	
Age (median) (range)			
	57.4 (20 - 98)	62.0 (28-96)	< 0.0001
Race			
Caucasian	207	173	0.325
African American	79	54	
Other	14	3	
Histologic type			
Ductal	228	165	0.152
Lobular	65	63	
Other	7	2	
Histologic grade			
I	34	58	< 0.0001
II	128	122	
III	127	47	
Unknown	11	3	
HER2 status			
Positive	73	33	0.015
Negative	200	173	
Equivocal	6	7	
Unknown	21	17	
Mean tumor size (mm) (range)			
	26.5 (0.4 - 275)	21.1 (1 - 100)	0.008
Pathologic nodal stage			
N0	174	160	0.002
N1	76	37	
N2	24	15	
N3	4	12	
Unknown	22	6	
Clinical stage			
I	105	119	0.001
II	129	76	
III	34	27	
IV	24	7	
Unknown	8	1	

Table 6 Univariate analysis for survival outcomes in the patients with ER+/PR- breast cancer.

Clinicopathologic factor	Relapse-free survival		Disease-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
ER H-score (≥ 270 vs. < 270)	0.562 (0.341 - 0.926)	0.024	0.592 (0.322 - 1.086)	0.090
Age (> 60 vs ≤ 60)	0.598 (0.363 - 0.985)	0.044	0.419 (0.212 - 0.827)	0.012
Race (African American vs. Caucasian)	0.789 (0.469 - 1.327)	0.371	0.606 (0.326 - 1.126)	0.113
Histologic type (lobular vs. ductal)	1.007 (0.574 - 1.765)	0.981	0.745 (0.347 - 1.602)	0.451
Histologic grade (III vs. I/II)	2.298 (1.412 - 3.742)	0.001	2.744 (1.512 - 4.980)	0.001
Tumor size (2.0-5.0 cm vs. ≤ 2.0 cm)	2.217 (1.161 - 4.234)	0.016	2.765 (1.283 - 5.961)	0.009
Tumor size (>5.0 cm vs. ≤ 2.0 cm)	5.781 (2.806 -11.911)	< 0.0001	5.443 (2.188 - 13.538)	< 0.0001
HER2 (positive vs. negative)	1.679 (1.002 - 2.813)	0.049	2.808 (1.546 - 5.101)	0.001
Lymph node status (positive vs. negative)	7.168 (3.744 - 13.724)	< 0.0001	4.628 (2.255 - 9.500)	< 0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval

Figure 2 Relapse-free survival (A) and disease-specific survival (B) of ER+/PR- breast cancers stratified by ER H-score.

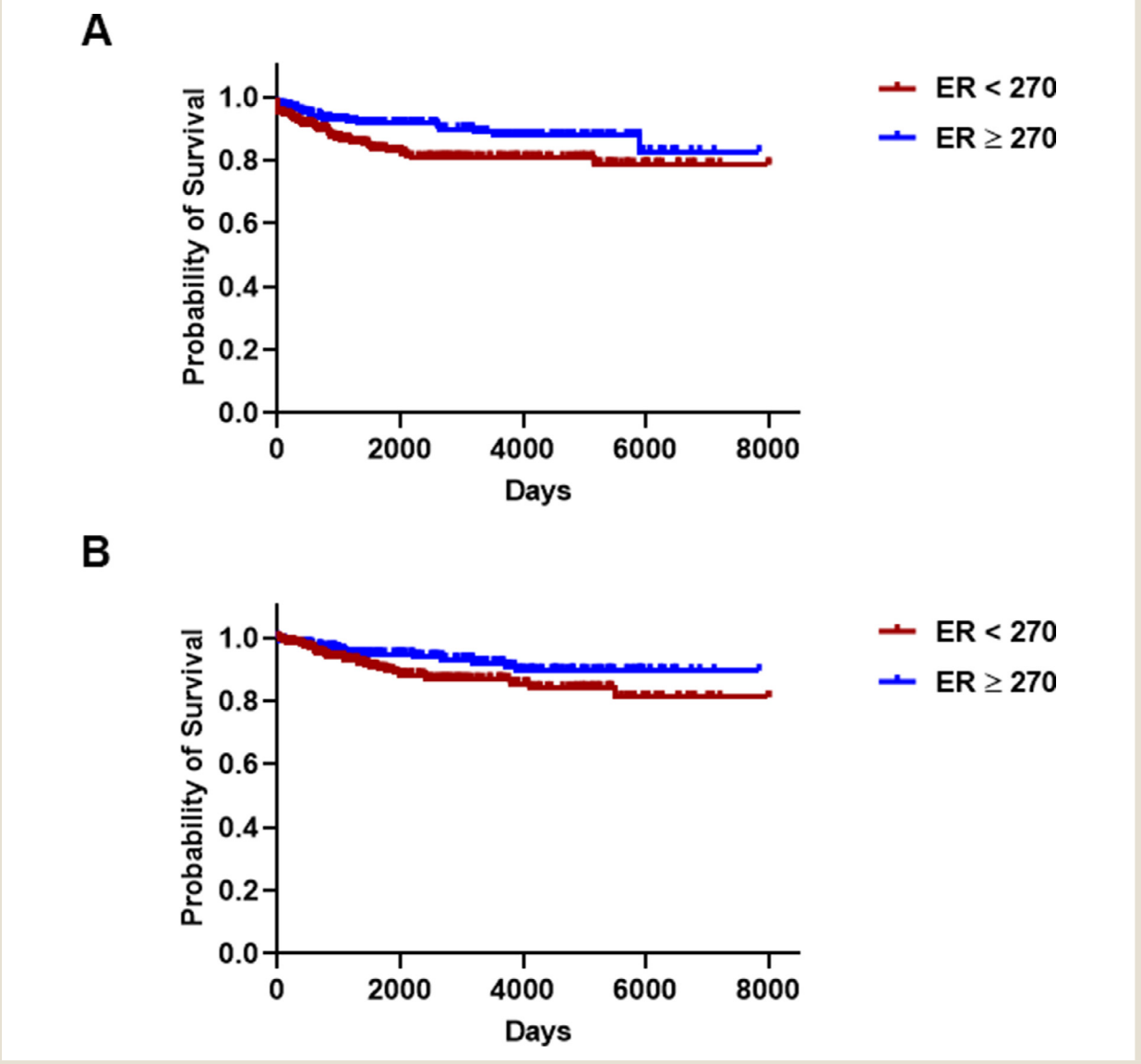


Table 7 Multivariant analysis for survival outcomes in the patients with ER+/PR- breast cancer.

Clinicopathologic factor	Relapse-free survival		Disease-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
ER H-score (≥ 270 vs. < 270)	1.013 (0.580 - 1.769)	0.963	1.290 (0.660 - 2.523)	0.456
Age (> 60 vs ≤ 60)	0.754 (0.437 - 1.298)	0.308	0.583 (0.278 - 1.225)	0.154
Race (African American vs. Caucasian)	1.325 (0.754 - 2.329)	0.328	0.926 (0.481 - 1.781)	0.818
Histologic type (lobular vs. ductal)	1.098 (0.590 - 2.044)	0.767	0.984 (0.418 - 2.319)	0.971
Histologic grade (III vs. I/II)	1.679 (0.957 - 2.943)	0.071	1.772 (0.919 - 3.417)	0.088
Tumor size (2.0-5.0 cm vs. ≤ 2.0 cm)	1.582 (0.803 - 3.116)	0.185	2.032 (0.899 - 4.594)	0.088
Tumor size (>5.0 cm vs. ≤ 2.0 cm)	2.886 (1.299 -6.412)	0.009	3.233 (1.154 - 9.054)	0.026
HER2 (positive vs. negative)	1.203 (0.701 - 2.066)	0.503	2.056 (1.109 - 3.812)	0.022
Lymph node status (positive vs. negative)	5.778 (2.951 - 11.311)	< 0.0001	3.392 (1.587 - 7.249)	0.002

Abbreviations: HR, hazard ratio; CI, confidence interval

in the age and race between the SEER database and the authors' cohort are of further interest. It is noteworthy that in the patients with an ER+/PR- tumor, the median age in the SEER database is significantly older than that of our cohort (62 vs. 58 years), and the proportion of African Americans is significantly higher in our database (25.6% vs.15.5%, $P<0.0001$). These findings are likely a reflection of larger African American patient population in the southern states from which our cohort derived. The relationship between age and racial disparity may also reflect the intrinsic nature of the tumor subtypes and thus is worth further investigation.[24,26]

When compared to the ER+/PR+ tumors, the ER+/PR- subtype was significantly associated with more frequent HER2 positivity and higher histologic grades, thus more likely to be of Luminal B intrinsic subtype. Of note, the frequency of Luminal B tumors in African American patients is reportedly higher when compared to that in Caucasians.[27,28] Reversed observations were found when comparing the ER+/PR- and ER-/PR- tumors in both cohorts, the latter of which are predominantly of HER2-enriched and basal-like subtypes. As these are largely reproducible findings in most large cohort studies, it is not surprising that the clinical outcomes of the ER+/PR- tumors are intermediate between the ER+/PR+ and ER-/PR- subtypes, even though the HER2 status was not available in early (prior to 2010) national databases. It is noteworthy that a recent Korean cohort study of 6980 patients demonstrated comparable prognostic outcomes between ER+/PR-/HER2- and ER-/PR-/HER2- (triple-negative) breast cancers.[18] This is in contrast to our recent cohort consisting of exclusively Caucasian and African American patients, in which ER+/PR-/HER2- tumors, even when limited to those of Grade III and ER-low (H-score ≤ 10), were associated with a significantly better RFS when compared to triple-negative breast cancers.[19] Thus, similar large-scaled studies in patients with different genetic backgrounds may be needed to draw further conclusions.

The biology of PR loss in breast cancer is of further interest given that PR is primarily regulated by ER at the transcriptional level. The predictive value of PR has long been attributed to its ER-dependent activity; therefore, the absence of PR has been thought to be a hallmark for a nonfunctional ER and thus resistance to endocrine therapy. However, previous studies have shown that ER+/PR- breast cancers may be specifically resistant to selective ER modulator (SERM) therapy (i.e., tamoxifen), but less resistant to aromatase inhibitors, agents blocking the synthesis of estrogen, thus conflicting with the nonfunctional ER theory.[29] Increased growth factor signaling (i.e., HER2 and other members of the epidermal growth factor receptor family) has been found to be associated both with the ER+/PR- phenotype and with SERM resistance functions.[16,30] The significant association of HER2 overexpression/amplification with the ER+/PR- phenotype, when compared to ER+/PR+ tumors, was also found in the current study. It has been postulated that the enhanced cross talk between ER and growth factor signaling pathways may downregulate PR expression while activating other ER functions.[16] Moreover, differential sensitivity to endocrine agents has been linked to bypassing resistance pathways. An interesting finding in this regard is that tamoxifen and fulvestrant (a selective ER degrader) up-regulate ERα expression, while aromatase inhibitors induce ERβ expression, which may contribute to the superior antiestrogen effect of the latter.[31] Nonetheless, ER+/PR- breast cancers may rely on more than one mechanism for its aggressiveness and resistance to endocrine therapies, thus further understanding the biology driving its oncogenic process is crucial for the development of better therapeutic strategies.

We have performed further analyses to identify significant prognostic factors in the subset of patients with ER+/PR- tumors. In the previous analysis using the early (1990-2012) SEER database, similar observations were obtained on the significance of age and HER2 status, although the HER2 information was missing during most of the data collection period (prior to 2010).[9] While race/ethnicity and tumor grade were also significant prognostic factors in the early cohort, non-Caucasian/non-African American was used as the reference race, and Grade IV was used as reference grade which is nonstandard and not utilized in modern pathology practice.[32,33]

It has been well established that the prognostic outcomes of all ER+ breast cancers are significantly correlated with the expression levels of the ER protein in tumor cells.[19,34-36] We thus sought to investigate if this remains true in the subset of ER+/PR- tumors, a study not previously conducted. To that end, an ER H-score of ≥ 270 was associated with a significantly superior RFS in the ER+/PR- tumors, suggesting that a near-maximal ER expression is needed to compensate for the altered ER signaling in these tumors. Molecular studies examining the crosstalk between ER and growth factor signaling as well as dissecting differentially expressed genes downstream of ER signaling in the two groups may provide further insight into the mechanisms of endocrine resistance in ER+/PR- breast cancers. Moreover, the cutoff changes for ER and PR from 10% to 1% in the study period and arbitrary thresholds for endocrine therapy used in practice for ER-low positive tumors might have an impact in the treatment decision-making and clinical outcomes in this small subset of patients.

It is of further interest that HER2 positivity is a favorable factor for clinical outcome in the patients with ER+/PR- tumors in the SEER cohort, whereas it is a worse prognosticator in the authors' cohort, although a statistical significance was not reached in the multivariant analysis. The patients in the SEER database included in this study were from 2010 to 2015 and thus more likely received HER2-targeted therapy for HER2+ diseases. These patients also had a relatively shorter follow up. This contrasts with our cohort derived from 1998-2018. Further, only a subset of patients with ER+/PR-/HER2+ breast cancer (67/140; 48%) in our cohort received HER2-targeted therapy at the authors' institution. Thus, the fact that over 50% patients with HER2-positive disease did not receive HER2-targeted therapy likely biased the results toward unfavorable survival outcomes. Moreover, most of those who did not receive anti-HER2 therapy were diagnosed before 2010 and had a much longer follow up, thus likely represented the natural course of ER+/PR-/HER2+ disease without HER2-targeted therapy. A disadvantage of national databases is that detailed treatment information is not available.

Conclusions

In summary, we have characterized the clinicopathologic features and prognostic outcomes of ER+/PR- breast cancers using a

population-based national database and our institutional cohort. While the results from the former have a greater statistical power given its sample size, the latter is superior in minimizing potential incomplete or inaccurate data more often in national tumor registries, available treatment information, and a longer clinical follow up. Nonetheless, analyses of the two cohorts resulted in similar observations for the clinicopathologic features and clinical outcomes for this subtype of breast cancer. The ER+/PR- tumors should be regarded clinically as distinct from ER+PR+ and ER-/PR- diseases. Furthermore, a near-maximal ER expression is needed to make up the altered ER signaling in the ER+/PR- tumors as indicated by the responsiveness to endocrine therapies. These findings may provide additional insights in directing clinical decision making for individualized systemic therapy in the pursuit of precision medicine.

Clinical Practice Points

- While most estrogen receptor-positive (ER+) breast cancers express progesterone receptor (PR), 12% of breast cancers have an ER+/PR- phenotype, despite the fact that PR is an ER-dependent gene product.
- The prognosis of ER+/PR- tumors is intermediate to that between ER+/PR+ and ER-/PR- tumors from the Surveillance, Epidemiology and End Results (SEER) database and the authors' institutional cohort.
- A near-maximal ER expression (H-score of $\geq$270) is needed to compensate for the altered ER signaling in ER+/PR- tumors.
- Pathologic stage and HER2 status were independent prognostic factors in the ER+/PR- tumors.
- These findings may provide novel insights in directing clinical decision making for individualized systemic therapy in the pursuit of precision medicine.

Disclosure

The authors declare no conflict of interest.

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