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Racial differences in estrogen receptor staining levels and implications for treatment and survival among estrogen receptor positive, HER2-negative invasive breast cancers

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Abstract

Background—African American women (AAW) die more frequently from estrogen receptor (ER) positive breast cancer than European American women (EAW). We investigated the relationship between race, percent ER staining, treatment, and clinical outcomes.

Methods—Percent ER staining (weakly ER+: 1–10%, moderately ER+: 11–50%, strongly ER+: > 50%) was abstracted from pathology reports for 1573 women with ER+/HER2− invasive breast cancer treated at a single cancer center in Detroit, MI from 2010 to 2017. Clinical outcomes and tumor characteristics were obtained from the Metropolitan Detroit Cancer Surveillance System. Associations of ER levels with demographic and clinical characteristics were evaluated using logistic regression. Overall and breast cancer-specific (BCS) survival were evaluated using Cox proportional hazards models.

Results—AAW were more likely to have tumors with lower ER staining levels than EAW (weakly ER+: Odds ratio (OR) 2.19, $p = 0.019$; moderately ER+: OR 2.80, $p = 0.005$). Women with weakly compared to strongly ER+ tumors were less likely to receive endocrine therapy (ET) regardless of race (OR 0.79, $p < 0.001$). Mortality was predicted by both AA race (Overall hazard ratio (HR) = 1.72, $p < 0.001$; BCS HR 1.45, $p = 0.08$) and low (1–50%) ER (Overall HR 1.57, $p = 0.083$; BCS HR 2.11, $p = 0.017$) adjusting for clinic-pathologic characteristics. ET was associated

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with improved BCS survival in all women (1–50%: HR 0.11, $p < 0.001$; > 50%: HR 0.24, $p < 0.001$).

Conclusion—The biology of ER+/HER2− tumors varies by race, although this does not appear to account for racial differences in survival. Although ET substantially reduces mortality among women with weakly ER+ tumors, these women are less likely to be treated with ET and have poorer outcomes.

Keywords

Gene expression; Pathology; Clinical outcomes; Racial disparities

Introduction

Breast cancer incidence among African American women (AAW) in the USA has increased in recent years, with AAW now equally likely to be diagnosed with breast cancer compared to European American women (EAW) [1]. Disparities in breast cancer mortality, however, continue to widen, where AAW are 1.4 times as likely to die from breast cancer compared to EAW [2]. Despite the fact that women with estrogen receptor positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer have the highest 5-year survival rates compared to other breast cancer subtypes [3], recent studies have shown that AAW are nearly twice as likely to die from ER+/HER2− disease than EAW even when accounting for clinical and tumor characteristics associated with poor prognosis [4–6]. It has been hypothesized that this disparity is partially driven by the reductions in treatment course because of toxicity or under-dosing, but there is also evidence for racial differences in tumor biology among ER+/HER2− breast tumors [7–9].

In 2010, the American Society of Clinical Oncology and the College of American Pathologists recommended that tumors should be classified as ER+ if they show as little as 1% ER staining of tumor cells by immunohistochemistry [10], and this threshold for ER positivity is the current standard for oncology practice in the USA [11]. While women with tumors across the ER+ spectrum benefit from endocrine therapy and have better survival compared to women with ER-negative tumors [12–14], there is evidence for heterogeneity in tumor biology among the ER+ group. Tumors with 1–10% ER staining show molecular properties more similar to triple negative breast cancers, a subtype that is twice as common among AAs compared to EAW [15], than to strongly ER+ tumors [16]. Specifically, there is an increased prevalence of the basal-like subtype among weakly ER+ tumors compared to strongly ER+ tumors, corresponding to reduced overall survival rates in the weakly compared to strongly ER+ groups [16]. We also recently showed that AAW are 75% more likely to have higher predicted risk of distant recurrence than EAW using the 21-gene recurrence score (RS) assay, OncotypeDx [17], which is used as a clinical decision-making tool to guide the recommendation for adjuvant chemotherapy [17–20] and is highly correlated with ER expression levels [21–25]. However, it is unclear whether these molecular differences by ER expression levels translate into differences in clinical outcomes.

Clinical decision-making with respect to treatment recommendations for women with ER+/HER2− breast cancer is also likely to be impacted by the percentage of tumor cells that stain

positive for ER. This happens directly through the correlation between ER expression and the 21-gene RS assay, where low ER expression correlates with high RS and increased recommendations for chemotherapy [21–25]. However, only a relatively small proportion of women with ER+/HER2− breast cancer meet NCCN guidelines for and receive 21-gene RS testing, and utilizing ER protein expression levels when evaluating treatments and prognosis is more broadly applicable. There is evidence that women with weakly ER+ tumors are less likely to be prescribed adjuvant endocrine therapy compared to women with strongly ER+ breast cancer [26], despite the fact that evidence-based guidelines recommend endocrine therapy for all patients with ER+ breast cancer [27]. This is possibly due to clinicians' perceptions that weakly ER+ tumors have low anticipated benefit from endocrine therapy relative to the side effects of such therapy and their impact on quality of life. Establishing whether ER staining levels influence receipt of endocrine therapy is important given that endocrine therapy impacts survival for all levels of ER staining. The main goal of this analysis was to evaluate the hypothesis that differences in ER expression partially explain racial disparities in survival among all women treated for ER+/HER2− breast cancer at a single cancer center in Detroit, MI. To do this, we first estimated racial differences in ER protein expression levels and then evaluated the impact of race and clinical characteristics on treatment and survival in our cohort.

Methods

Study population

Using the Metropolitan Detroit Cancer Surveillance System (MDCSS) database, we identified 1652 women who (1) were diagnosed with and underwent surgery for ER+/HER2− invasive breast cancer from 2010 to 2017 at the Karmanos Cancer Institute (KCI) in Detroit, MI and (2) identified as AA or EA. 2010 is the first year for which HER2 status data were available in MDCSS. MDCSS is a founding member of the Surveillance, Epidemiology, and End Results (SEER) Program [28], and has been continuously collecting population-based cancer data since 1973. This study was granted concurrence of exemption by the Wayne State University Institutional Review Board (IRB).

Estrogen receptor staining levels

ER staining levels, measured as the percentage of cells staining positive for ER by immunohistochemistry, were abstracted from KCI pathology reports and entered into a de-identified database. ER staining was categorized as weakly ER+ (1–10%), moderately ER+ (11–50%), and strongly ER+ (> 50%). Two records where percent ER staining was reported as a range were excluded because the range fell within more than one ER category (> 1% and 30–60%). The threshold for strongly ER+ tumors was set at 50% by fitting a two-component mixture model of Weibull distributions to the percent ER variable using the "mixtools" R package (https://cran.r-project.org/). Percent ER staining was not reported for 77 women, and we restricted our dataset to include only those women with known ER percent staining ($n = 1573$).

Clinical and demographic variables

Clinical, treatment, and outcomes data were obtained via linkage with the MDCSS registry, including stage, grade, age at diagnosis, race/ethnicity, node status, histology, tumor size, 21-gene recurrence score (RS), ER and PR status, surgery type, systemic therapy type, radiation, vital status at last contact, cause of death, and date of last contact. Treatment data for KCI patients in MDCSS are abstracted directly from KC medical records by MDCSS staff. For those women who had treatment data recorded in MDCSS ($n = 1614$, 99.3%), first course of treatment was defined as receipt of therapy for a cancer diagnosis before disease progression or recurrence and included type of surgery (breast-conserving versus mastectomy), adjuvant chemotherapy, endocrine therapy, and radiation therapy.

Statistical analysis

Univariable associations between demographics, clinical characteristics, tumor characteristics, and race were examined using χ^2 tests and Wilcoxon rank sum tests for categorical and continuous variables, respectively. Because 21-gene RS scores were not available for the majority of women in the cohort, this variable was not included in subsequent analyses. Multinomial logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for predictors of ER staining levels, where the reference outcome category was > 50% ER staining. Binomial logistic regression was used to evaluate associations between demographic/tumor characteristics and receiving endocrine therapy. Cox proportional hazards regression was used to estimate associations with overall survival and breast cancer-specific (BCS) survival. For all regression models, covariates were included based on a priori evidence for being related to the outcome and main exposure of interest. Adjusted survival curves were generated by applying the “survfit” function of the R package *survival* to the previously fitted Cox proportional hazards models, where we specified a new data frame consisting of the median values for each of the variables in the original Cox model (race, age at diagnosis, grade, node status, stage, chemotherapy) with indicators for hormone therapy status. All data were analyzed using R statistical software (https://cran.r-project.org/). All statistical tests were two-sided, with a p-value of < 0.05 considered to be statistically significant.

Results

Racial differences in ER+/HER2− tumor characteristics

Overall, weakly ER+ (1–10%), moderately ER+ (11–50%), and strongly ER+(> 50%) staining levels accounted for 3.2%, 2.7%, and 94.1% of tumors, respectively; however, this differed by race, with weakly and moderately ER+ staining accounting for 1% each of tumors in EAW and 4% and 3%, respectively, in AAW ($p < 0.001$). Low ER staining levels were associated with younger age at diagnosis ($p < 0.001$), AA race ($p < 0.001$), ductal histology ($p = 0.008$), higher grade ($p < 0.001$), and 21-gene RS high risk category ($p < 0.001$) (Table 1). AAW were more than twice as likely to have weakly ER+ tumors (OR 2.40, 95% CI 1.28–4.49, $p = 6.4 \times 10^{-3}$) and moderately ER+ tumors (OR 2.79, 95% CI 1.40–5.58, $p = 3.7 \times 10^{-3}$) than EAW. AAW were also more likely to be diagnosed at an older age ($p = 0.002$), had higher 21-gene RS scores among the 38% of women who received the test ($p = 0.016$), and were more likely to have tumors with higher grade ($p =$

0.013) and larger size ($p = 0.001$) (Table S1). Race remained significantly associated with ER staining level (1–10%: adjusted OR 2.19, $p = 0.019$; 11–50%: adjusted OR 2.80, $p = 0.005$) after adjustment for age, tumor size, grade, and stage (Table 2). Further adjustment for histology did not appreciably change the effect estimates, and histology was not associated with ER staining levels in the multivariable model.

We next evaluated whether racial differences in tumor characteristics persisted when accounting for ER staining level (Table S2). Tumor size was only significantly associated with race among the > 50% ER staining group (AA: 20 mm, EA: 18 mm $p = 0.048$). In contrast to the overall analysis, we identified a marginally significant association between race and node involvement among weakly ER+ tumors, where AAW were more likely to be node positive than EAW (54% vs. 21%, respectively; $p = 0.057$). Similarly, while not statistically significant, AAW with moderately ER+ tumors were more likely to be node positive than EAW. This association remained marginally significant when adjusting for tumor size with AAW fourfold more likely to be node positive than EAW (adjusted OR 3.94, 95% CI 0.92–16.87, $p = 0.065$). While not statistically significant, AAW with moderately ER+ tumors were approximately twofold more likely to be node positive than EAW adjusting for tumor size (OR 2.09, $p = 0.42$). No difference in node status was seen among strongly ER+ tumors, and no other differences by ER staining level were observed for associations between race and tumor characteristics.

ER staining levels, race, and treatment

We next evaluated the impact of ER staining levels on whether a woman received endocrine therapy and if this differed for AAW compared to EAW, noting that there is potential for therapy misclassification due to unknown therapy information (Tables 1, 3). Adjusted for age at diagnosis, tumor size, node involvement, grade, stage, and receiving chemotherapy, women with weakly ER+ tumors were 20% less likely to receive endocrine therapy compared to those with strongly ER+ tumors (OR 0.79, 95% CI 0.72–0.86, $p < 0.001$) (Table 3). The association between weakly ER+ status and receiving endocrine therapy did not differ for AAW compared to EAW (AA: OR 0.77, white OR 0.83, p-interaction = 0.33).

ER staining levels, race, and survival

We next evaluated the impact of race and ER staining levels on overall and BCS mortality. Given the small sample sizes and numbers of deaths in the weakly and moderately ER+ groups, we combined the 1–10% and 11–50% ER staining groups (1–50% n = 90, events $n = 16$). We adjusted for tumor characteristics as well as treatment to be able to evaluate the effect of endocrine therapy on mortality. AAW were significantly more likely to die from any cause (hazard ratio (HR) = 1.75, 95% CI 1.32–3.32, $p < 0.001$) and marginally significantly more likely to die from breast cancer (HR 1.48, 95% CI 0.99–2.21, $p = 0.054$) compared to EAW when adjusting for tumor characteristics and treatment (Table 4). When ER staining level was added to the models, the association between race and overall and BCS mortality did not change appreciably (overall HR 1.72, BCS HR 1.45). Having a weakly ER+tumor, however, was itself significantly associated with BCS mortality and marginally significantly associated with overall mortality (overall HR 1.57, $p = 0.083$; BCS HR 2.11, $p = 0.017$). Endocrine therapy was significantly associated with substantial

reductions in overall and BCS mortality (Full model overall HR 0.35, $p < 0.001$; Full model BCS HR 0.23, $p < 0.001$). Given that endocrine therapy was one of the strongest predictors of mortality in our cohort, we performed a sensitivity analysis to evaluate the effects of race on mortality only among women who received endocrine therapy (Table S3). Race remained significantly associated with overall mortality when adjusting for ER staining level (HR 1.72, $p = 0.001$). While we had limited power for the breast cancer-specific mortality analyses due to a reduction in the number of breast cancer deaths, we observed a 22% increase in death in AAW compared to EAW, although this was not statistically significant.

To directly evaluate the effect of endocrine therapy among women with low versus high ER staining levels, we next stratified our survival analyses by ER staining level (Fig. 1, Table S4). Endocrine therapy was significantly associated with reduced overall and BCS mortality for both the 1–50% ER staining group (Overall HR 0.17, $p = 0.001$; BCS HR 0.11, $p < 0.001$) and the > 50% ER staining group (Overall HR 0.41, $p < 0.001$; > 50% BCS HR 0.24, $p < 0.001$) (Table S4). There was a marginally significant interaction between ER staining level and endocrine therapy for overall survival ($p = 0.074$), where the effect estimate for endocrine therapy was strongest for the lower ER staining group. Importantly, while survival for women in the 1–50% ER group who did not receive endocrine therapy was poor, survival for women who did receive endocrine therapy was comparable for women in the 1–50% and the > 50% ER group (Fig. 1). Interestingly, the effect of race on overall survival appeared to vary by ER staining level, although these results should be interpreted with caution given the small sample sizes. AAW with 1–50% ER staining were threefold more likely to die from their breast cancer compared to EAW (HR 3.11, $p = 0.067$), in contrast to AAW with > 50% staining who were only 70% more likely to die from their breast cancer compared to EAW (HR 1.70, $p < 0.001$). There was no significant interaction between ER staining level and race for either overall mortality ($p = 0.53$) or BCS mortality ($p = 0.37$). While not statistically significant, mortality was also higher for AAW compared to EAW for those with 1–50% ER staining (HR 2.03, $p = 0.26$) and > 50% staining (HR 1.36, $p = 0.17$).

Discussion

This is the first report to show that AAW are more likely to have weakly ER+ breast cancer compared to EAW. We also provide additional evidence for differences in tumor biology by ER staining level. Specifically, lower levels of ER staining were associated with higher grade, primarily ductal histology, and higher predicted risk of recurrence. This is consistent with previous reports showing that weakly ER+ breast cancers are more likely to be classified as basal-like [16, 29]. It follows that the ER level-race association could be reflecting a higher proportion of basal-like tumors in AAW compared to EAW [30], but future molecular tumor-based studies are needed to confirm this. AAW with weakly ER+ breast cancer were also more than four times as likely to have node-positive tumors and have threefold higher risk of death compared to EAW. These two phenomena are likely related as nodal status is one of the best predictors of metastasis and survival [31, 32]. Interestingly, it appears that the proportion of AAW with node involvement is relatively constant across ER staining levels, in contrast to EAW, where the proportion of women with node involvement decreases for lower ER staining categories. This suggests that there may be racial differences in tumor biology beyond ER staining level alone.

Given that the observed ~ 70% increase in mortality among AAW compared to EAW was not substantially impacted when adjusting for ER staining level, these data do not support our original hypothesis that differences in ER expression levels partially explain racial disparities in survival. There was, however, a strong relationship between both race and ER staining level and survival. The literature on the relationship between quantitative ER staining and survival is sparse, although there is evidence that ten-year survival is substantially worse for weakly ER+ tumors than strongly ER+ tumors in a dose-dependent manner [33, 34]. A study of more than 1200 AAW and EAW showed overall that only women with strongly ER+ tumors (≥ 40%) had a survival advantage compared to ER− tumors in a dose–response manner, where women with the highest level of ER staining had the best survival [35]. This remained true among EAW, but for AAW, any level of ER staining, from 1 to 100%, was consistently associated with a 40% reduction in breast cancer-specific mortality. A separate study identified ER staining intensity as a significant prognostic factor, though only among non-Hispanic white women and percent ER staining was not associated with survival [36]. A set of genes co-expressed with *ESR1* has also been significantly inversely associated with distant relapse and survival in both endocrine- and chemo-endocrine-treated cohorts, specifically using the genomic sensitivity to ET (SET) index [37]. Here we showed that while low ER staining appears to be associated with worse overall and breast cancer-specific survival, this association does not account for the worse survival among AAW with ER+/HER2− breast cancer. Indeed, there may be an interaction between race and ER staining levels, although this should be investigated in future studies to both increase the weakly ER+ sample size and to validate this initial finding. Further, the differences in survival that we observed for AAW and EAW could be reflecting differing rates of compliance with endocrine therapy between the two groups, which could not be evaluated in this study. Taken together, these data strongly suggest that not only AAW are disproportionately affected by this low ER+ subtype, but also clinical outcomes among this group are worse for AAW than EAW.

Women with weakly ER+ tumors were also 20% less likely to receive endocrine therapy, and importantly, our data suggest that women in the 1–50% ER staining group who receive endocrine therapy have survival comparable to women in the strongly ER+ group who receive endocrine therapy. These data are consistent with the literature suggesting that oncologists are less likely to prescribe endocrine therapy to women with weakly ER+ tumors due to a perception of low benefit in this group. Importantly, we show here that AAW are not less likely to receive endocrine therapy than EAW when accounting for ER staining level. Evidence-based guidelines recommend endocrine therapy for all patients with ER+ breast cancer regardless of ER/PR staining level, with the stipulation that physicians might wish to discuss the risks and benefits of endocrine therapy with patients in the 1–10% category [27]. These recommendations are based largely on evidence from a few studies showing that response to tamoxifen was observed among patients with as little as 1% ER tumor staining [13, 14]. In contrast to these recommendations, we showed that women with weakly ER+ breast cancer are less likely to be prescribed endocrine therapy, which is consistent with the limited literature on this topic [26] and may be in part due to inadequate evidence regarding the degree of benefit associated with adjuvant endocrine therapy for women specifically with weakly ER+ cancers [38]. Importantly, we provide compelling evidence that endocrine

therapy is beneficial among weakly and moderately ER+ breast cancer as well as strongly ER+ cancers. While we did not observe racial differences in the receipt of endocrine therapy, it is important to note that AAW would be less likely to receive beneficial endocrine therapy because they are disproportionately affected by weakly ER+ breast cancer.

A major strength of our study is the use of data from the population-based MDCSS registry because invasive breast cancer cases are pathologically verified, follow-up data are high quality and highly complete, and standardized data entry is continuously monitored for accuracy. However, our analyses were limited to the Karmanos Cancer Institute because we required medical record review, and this hospital-based cohort may not be generalizable to the US population. Future studies that incorporate data from the larger MDCSS catchment area would increase generalizability. A second limitation is that data on chemotherapy or endocrine therapy is collected primarily at hospitals, radiation facilities, and laboratories, rather than physician offices where patients may undergo these treatments.

The physiological impact of hormone activity in the tumor may be determined by the strength of the signaling within the receptor-positive cells, which in turn may be determined by the expression level of the receptor and as well a host of downstream effectors such as hormone receptor co-regulators. Strong hormone signaling in even a small fraction of the tumor cells could produce paracrine effects profoundly affecting tumor growth. Further studies of the molecular characteristics of weakly ER+ tumors, specifically with respect to hormone signaling and dependence, will be important in understanding the mechanisms of hormone sensitivity in these tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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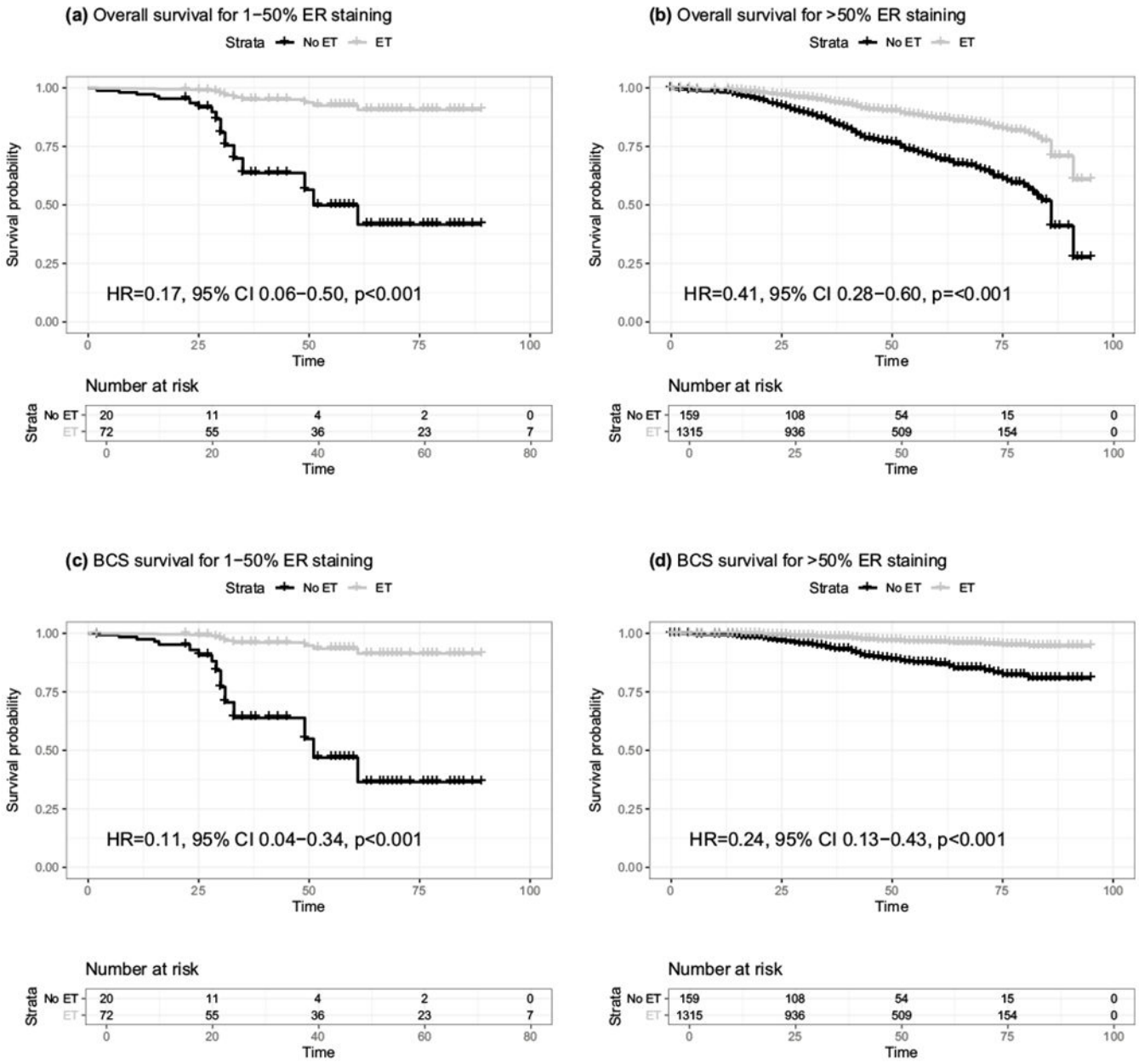

Fig. 1.

Overall and breast cancer-specific mortality curves by receipt of endocrine therapy and ER staining level. Survival curves adjusted for race, age at diagnosis, grade, node status, stage, and chemotherapy are shown for **a** overall survival for 1–50% ER staining, **b** overall survival for > 50% ER staining, **c** breast cancer-specific (BCS) survival for 1–50% ER staining, and **d** BCS survival for > 50% ER staining. Black lines represent survival curves among women who did not receive endocrine therapy and grey lines represent survival curves among women who did receive endocrine therapy. Censored events are indicated by vertical dashes along the survival curves

Table 1

Associations between ER staining level and demographic, tumor, and clinical characteristics of 1573 women with ER+/HER2− invasive breast cancer

	1–10%		11–50%		> 50%		*p*-value*
	N = 50		N = 43		*N* = 1480		
	n	%	*n*	%	*n*	%	
Demographics							
Race							< 0.001
White	14	29%	11	26%	722	49%	
African American	35	71%	32	74%	753	51%	
Age at diagnosis (years)							< 0.001
Median, IQR	53	22	52	24.5	60	17.5	
Clinical/tumor characteristics							
Histology							0.008
Ductal	41	83%	35	81%	974	66%	
Ductal + Lobular	1	2%	0	0%	120	8%	
Lobular	0	0%	4	9%	209	14%	
Other	7	14%	4	9%	170	11%	
Grade							< 0.001
1	0	0%	7	16%	333	23%	
2	8	16%	9	20%	795	55%	
3	40	83%	27	62%	299	20%	
Stage							0.48
Local	19	38%	20	46%	677	45%	
Regional	13	26%	14	32%	415	28%	
Distant	4	8%	3	6%	61	4%	
Unknown	14	28%	6	13%	327	22%	
Node involvement							0.23
No	27	55%	28	65%	769	52%	
Yes	22	44%	15	34%	706	47%	
21-gene RS risk category[a]							< 0.001
Low	1	25%	3	18%	332	58%	

	1–10%		11–50%		> 50%		*p*-value*
	N = 50		N = 43		*N* = 1480		
	n	%	*n*	%	*n*	%	
Intermediate	1	25%	2	12%	182	31%	
High	2	50%	11	68%	56	9%	
Tumor size (mm)							0.15
Median, IQR	31.11	23.58	28.48	14.66	24.92	21.50	
Treatment-related factors							
Received 21-gene RS testing							< 0.001
No	46	92%	27	63%	910	61%	
Yes	4	8%	16	37%	570	39%	
Received chemotherapy							< 0.001
No	12	24%	15	34%	933	63%	
Yes	37	75%	28	65%	541	36%	
Received endocrine therapy							< 0.001
No	16	32%	4	9%	159	10%	
Yes	33	67%	39	90%	1315	89%	
Underwent surgery							0.027
No	40	80%	39	90%	1349	91%	
Yes	10	20%	4	9%	131	8%	
Survival characteristics							
Vital status							0.028
Alive	35	71%	37	86%	1258	85%	
Dead	14	28%	6	13%	217	14%	
Months of active follow-up							0.31
Median, IQR[a]	36	26	43	27	41	24	

[a] Among 592 women who received OncotypeDx testing

IQR Interquartile range

* *p*-values: χ^2 tests for categorical variables, Wilcoxon rank sum tests for continuous variables, log-rank test for follow-up time

Table 2

Associations between race and ER staining level in a multivariable model adjusted for age, tumor size, grade, and stage among 1,573 women with ER+/HER2− invasive breast cancer

Predictors in multivariable model	1–10% vs. > 50%		11–50% < vs. > 50%	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Race (AAW vs. EAW)	2.19 (1.14–4.23)	0.019	2.80 (1.37–5.71)	0.005
Age at diagnosis (years)	0.98 (0.96–1.00)	0.078	0.95 (0.93–0.98)	< 0.001
Tumor size (mm)	1.00 (0.99–1.01)	0.96	1.00 (0.98–1.01)	0.92
Grade (1 vs 3)	_[a]	_[a]	0.23 (0.09–0.59)	0.002
Grade (2 vs 3)	0.08 (0.04–0.17)	< 0.001	0.13 (0.06–0.28)	< 0.001
Stage (Regional vs. Local)	0.52 (0.23–1.21)	0.13	0.69 (0.31–1.51)	0.35
Stage (Distant vs. Local)	1.49 (0.43–5.12)	0.53	1.23 (0.32–4.77)	0.77
Stage (Unknown vs. Local)	1.01 (0.47–2.16)	0.98	0.41 (0.15–1.14)	0.089

[a]No tumors were grade 1 with 1–10% ER staining

Table 3

Overall and race-specific associations between ER staining levels and receipt of endocrine therapy in multivariable models adjusted for age, tumor size, node involvement, grade, stage, and chemotherapy among women with ER+/HER2− invasive breast cancer

Predictors in multivariable model[a]	Overall (*n* = 1573)			AAW (*n* = 855)			EAW (*n* = 762)		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Race (AAW vs EAW)	0.99	0.96–1.03	0.68	–	–	–	–	–	–
ER level (1–10% vs. > 50%)	0.79	0.72–0.86	< 0.001	0.77	0.68–0.86	< 0.001	0.83	0.71–0.98	0.027
ER level (11–50% vs. > 50%)	0.97	0.88–1.07	0.51	0.97	0.87–1.09	0.65	0.95	0.79–1.14	0.89

[a]Adjusted for age at diagnosis, tumor size, node involvement, grade, stage, and chemotherapy

Table 4

Associations between race and mortality before and after adjusting for ER staining levels in multivariable models among 1573 women with ER+/HER2− invasive breast cancer

	Overall mortality[a]						Breast cancer-specific mortality[b]					
	Model 1[c]			Model 1 + adjustment for % ER			Model 2[d]			Model 2 + adjustment for % ER		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Race (AAW vs. EAW)	1.75	1.32–3.32	< 0.001	1.72	1.29–2.30	< 0.001	1.48	0.99–2.21	0.054	1.45	0.96–2.20	0.080
Age at diagnosis (years)	1.03	1.01–1.04	< 0.001	1.03	1.02–1.04	< 0.001	1.01	0.99–1.02	0.43	1.01	0.99–1.02	0.20
Grade (2 vs 1)	1.75	1.13–2.72	0.012	1.70	1.10–2.64	0.018	4.26	1.53–11.8	0.54	3.85	1.38–10.8	0.0010
Grade (3 vs 1)	2.29	1.44–3.67	< 0.001	2.07	1.28–3.34	0.003	6.54	2.32–18.5	< 0.001	5.36	1.88–15.3	0.0017
Node involvement (yes vs no)	2.23	1.41–3.54	< 0.001	2.74	1.70–4.42	< 0.001	1.43	0.66–3.10	0.36	2.22	0.95–5.17	0.061
Stage (regional vs. local)	0.89	0.55–1.45	0.65	0.78	0.47–1.28	< 0.001	1.71	0.75–3.91	0.20	1.35	0.56–3.25	0.50
Stage (distant vs. local)	9.21	5.40–15.7	< 0.001	8.59	5.01–14.7	0.32	31.8	13.4–72.5	< 0.001	27.5	11.4–66.3	< 0.001
Stage (unknown vs. local)	2.66	1.37–5.16	0.004	2.77	1.38–5.56	0.004	3.61	1.18–11.0	0.024	4.38	1.35–14.2	0.014
ET (yes vs. no)	0.30	0.22–0.41	< 0.001	0.35	0.25–0.49	< 0.001	0.18	0.12–0.28	< 0.001	0.23	0.14–0.38	< 0.001
Chemo (yes vs. no)	0.84	0.61–1.16	0.29	0.85	0.61–1.20	0.36	1.02	0.66–1.59	0.92	1.00	0.62–1.62	0.99
ER (1–50% vs. > 50%)				1.57	0.94–2.58	0.083				2.11	1.14–3.87	0.017

[a] Total number of deaths = 228

[b] Total number of deaths due to breast cancer = 110

[c] Model 1 evaluates the effect of race on overall mortality adjusting for age, grade, node involvement, stage, endocrine therapy, and chemotherapy

[d] Model 2 evaluates the effect of race on breast cancer-specific mortality adjusting for age, grade, node involvement, stage, endocrine therapy, and chemotherapy