BIOMARKERS

original reports abstract

Validity of 1% Hormonal Receptor Positivity Cutoff by the ASCO/College of American Pathologists Guidelines at the Georgia Cancer Center

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PURPOSE Treatment of breast cancer (BC) with borderline or low (1%-9%) estrogen and progesterone expression remains controversial, with recent data disputing ASCO/College of American Pathologists 2010 guidelines that lowered the threshold of receptor positivity from 10% to 1%. The objective of this retrospective study was to validate these guidelines at the Georgia Cancer Center with a high percentage of Black race.

METHODS All female patients with invasive BC diagnosed between 2005 and 2010 at the Georgia Cancer Center were chart reviewed up to an 11-year follow-up with data cutoff at 2016. We used Cox regression to explore survival among three hormonal status (HS) groups (< 1%, 1%-9%, and ≥ 10%) adjusting for all known BC clinicopathologic variables. Fisher's exact test was used to evaluate response to endocrine therapy (ET).

RESULTS Among 431 patients with mean age 59 years, 24.75% had HS < 1%, 17.5% HS 1%-9%, and 57.75% HS ≥ 10%. Race was 43.75% Black and 54% White. Disease stages were early (I-IIIA) in 84.4% and advanced (IIIB-IV) in 15.56%. Mortality in HS < 1% was significantly higher than that in HS ≥ 10% (hazard ratio [HR]: 1.8; 95% CI, 1.07 to 3.02), whereas no significant mortality difference between HS 1%-9% and HS ≥ 10% (HR: 1.05; 95% CI, 0.48 to 2.30) was observed. ET was protective, and treated patients had higher predicted survival than untreated patients in the 1%-9% group (HR: 0.10; 95% CI, 0.01 to 0.85). There was no significant mortality difference between ET-treated HS 1%-9% and ≥ 10% groups.

CONCLUSION One percent cutoff predicted superior survival on treatment with ET compared with the other groups, and HS as low as 1%-9% was equiprognostic to HS ≥ 10%. Whether other factors such as lymphovascular invasion, grade, and other parameters change the behavior of the 1%-9% HS group remains to be explored.

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INTRODUCTION

Over the past decade, breast cancer (BC) treatment has been continuously developing. With the advent of molecular biomarkers, individualized BC therapy has become of particular significance. Not only do these biomarkers have a prognostic value, but also they can be predictive of response to treatment. Hormone receptor status (HS) in BC is a universally accepted biomarker.[1] Patients with tumors expressing estrogen or progesterone receptors (ER/PR) tend to respond to endocrine therapy (ET) and have improved disease-specific survival and overall survival.[2,3]

The clinical significance of HS has rendered its analysis mandatory for all patients with BC. HS is typically tested by immunohistochemistry (IHC) through evaluation of protein expression.[4] Published in 2010, guidelines from ASCO and the College of American Pathologists (CAP) recommended considering ER and PR status as positive when 1% or more of the tumor cells' nuclei stain positive on IHC. However, this threshold for ER/PR positivity, lower than the previously accepted threshold of 10%, remained controversial, and recent data dispute these guidelines.[5-7]

Fujii et al[8] reported that patients whose tumors are ER/PR borderline or low positive, with positivity ranging between 1% and 9%, and who were human epidermal growth factor receptor 2–negative derived little benefit from adjuvant ET and that their tumors behaved similar to triple-negative BC (TNBC). A study by Iwamoto et al[9] examined borderline ER-positive and ER-positive cancers. This study showed that only a few tumors whose ER status ranged between 1% and 9% had molecular features similar to ER-positive tumors, whereas most tumors with ER between 1% and 9% showed ER-negative, basal-like molecular characteristics. Moreover, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that tamoxifen was ineffective against tumors with low ER expression.[10] There is a dearth of prospective studies

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Can the 1% threshold of estrogen and progesterone receptor (ER/PR) positivity in breast cancer adopted by ASCO/College of American Pathologists 2010 guidelines be validated to predict response to endocrine therapy in real life amid all controversy?

Knowledge Generated

A 10-year predictive model confirms survival benefit with hormonal therapy (hazard ratio: 0.10) in patients with breast cancer at the Georgia Cancer Center with the ER/PR expression as low as 1% in a population with the largest (n = 150) cohort of patients with borderline hormonal status disease (ER/PR 1%-9%). On the other hand, chemotherapy proved detrimental (hazard ratio: 1.77) for the borderline cohort.

Relevance

Our study proposes a model to marry the recent controversial findings and highlights the potential efficacy of immune therapy (and other treatments) in borderline hormonal status disease. These results are timely given the recent papers questioning the benefit of hormonal therapy in these patients.

investigating the optimal threshold cutoff for ER/PR positivity on the basis of the efficacy of ET, and results from retrospective studies need to be validated.

This study aimed to validate the 1% hormonal positivity cutoff recommended by the ASCO-CAP guidelines at the Georgia Cancer Center (GCC) in Augusta, Georgia, by analyzing its predictive value for response to therapy and to analyze prognosis among the different HS categories.

METHODS

In this retrospective study, charts were reviewed for all female patients with invasive BC diagnosed between 2005 and 2010 at GCC who had up to an 11-year follow-up, with data cutoff at 2016. The 3 HS categories were defined as $< 1\%$, 1%-9%, and $\geq 10\%$ of tumor cells' nuclei that stained positive on IHC. The Proportional Hazards Regression procedure, or Cox regression, was used to perform regression analysis of survival data among the three HS groups, adjusting for standard prognostic factors. We selected this model to assess these variables simultaneously in relation to survival. Hazard ratio (HR) and 95% CI were reported. The 1%-9% and $\geq 10\%$ groups were further explored using the same method to test survival differences with or without ET. Fisher's exact test was used to evaluate response to ET.

All statistical analyses were conducted at a significance level of .05 using SAS 9.4. Descriptive statistics were provided for all variables. Frequencies and column percentages were given for categorical variables. Mean, standard deviation, minimum, and maximum were provided for continuous variables. Cox regression was used to explore mortality rate differences among the three hormonal groups. We used a stepwise selection procedure with a select entry level ($P < .15$) and a select stay in the model level ($P < .05$) with the hormonal group forced into the model. Eleven independent variables were used for the stepwise selection procedure. Six variables were included in the final predictive model: hormonal group, age, stage, surgery, prior chemotherapy, and prior radiation. HRs and 95% CIs are presented in Table 2.

The study was not supported by any grant or funding institution. It was approved by the GCC Institutional Review Board under protocol number 893859.

RESULTS

Patient Demographics

Among the 431 patients included in this study, the mean age was 59 years; 43.75% were Black, and 54% were White. Most patients (84.4%) had early BC (stage I-IIIA), and 15.56% had advanced BC (stage IIIB-IV). 51.42% had low-grade disease (1-2), and 48.58% had high-grade disease (3). 24.75% were HS $< 1\%$, 17.5% were HS 1%-9%, and 57.75% were HS $\geq 10\%$.

Univariate Analysis: HS and Demographic/ Clinical Features

We examined demographic and clinical features by HS category. Table 1 shows the univariate analysis for the association between ER/PR percentage and demographic and clinical features. Eighty-two of 150 patients (54.67%) who were HS 1%-9% and 120 of 195 patients (60.91%) who were HS $\geq 10\%$ were White. Thirty-two of 84 patients (38.10%) who were HS $< 1\%$ were White, whereas 41.33%, 38.07%, and 58.33% who were HS 1%-9%, HS $\geq 10\%$, and HS $< 1\%$, respectively, were Black ($P = .0031$ for race).

Thirty-one of 136 patients (22.79%) who were HS 1%-9% and 71 of 188 patients (37.77%) who were HS $\geq 10\%$ drank alcohol; 24 of 57 patients (29.63%) who were HS $<$ 1% drank alcohol ($P = .0153$ for alcohol consumption).

TABLE 1. Univariate Analysis for Association Between Hormone Percentage and Demographic and Clinical Features

		ER and PR Percentage (N = 431), No. (%)			
Variable	**Levels**	**< 1%**	**1%-9%**	**≥ 10%**	***P*[a]**
ET	Yes	3 (3.57)	102 (68.00)	152 (77.16)	< .0001
	No	81 (96.43)	48 (32.00)	45 (22.84)	
CMI	0	20 (24.39)	47 (33.57)	52 (26.67)	.2285
	1	40 (48.78)	67 (47.86)	88 (45.13)	
	2	18 (21.95)	22 (15.71)	51 (26.15)	
	3	4 (4.88)	4 (2.86)	4 (2.05)	
Alcohol	Yes	24 (29.63)	31 (22.79)	71 (37.77)	.0153
	No	57 (70.37)	105 (77.21)	117 (62.23)	
Tobacco	Smoker	15 (18.52)	24 (17.52)	34 (17.99)	.3875
	Former smoker	11 (13.58)	19 (13.87)	40 (21.16)	
	Nonsmoker	55 (67.90)	94 (68.61)	115 (60.85)	
Response	Yes	58 (75.32)	125 (89.93)	154 (82.35)	.0172
	No	19 (24.68)	14 (10.07)	33 (17.65)	
Radiation	Yes	63 (75.00)	132 (88.00)	119 (60.41)	< .0001
	No	21 (25.00)	18 (12.00)	78 (39.59)	
Chemotherapy	Yes	62 (73.81)	71 (47.33)	68 (34.52)	< .0001
	No	22 (26.19)	79 (52.67)	129 (65.48)	
Surgery	Yes	70 (85.37)	136 (90.67)	176 (89.80)	.4351
	No	12 (14.63)	14 (9.33)	20 (10.20)	
Grade 1	High grade	66 (89.19)	43 (33.08)	54 (32.53)	< .0001
	Low grade	8 (10.81)	87 (66.92)	112 (67.47)	
Stage 1	Early stage 0-3A	61 (73.49)	129 (87.76)	170 (86.29)	.0098
	Late stage 3B-4	22 (26.51)	18 (12.24)	27 (13.71)	
Lymphovascular	Yes	43 (51.19)	26 (17.33)	36 (18.27)	< .0001
	No	41 (48.81)	124 (82.67)	161 (81.73)	
Race	White	32 (38.10)	82 (54.67)	120 (60.91)	.0031
	African American	49 (58.33)	62 (41.33)	75 (38.07)	
	Others	3 (3.57)	6 (4.00)	2 (1.02)	
Family history	Yes	28 (36.36)	51 (39.53)	70 (36.65)	.8483
	No	49 (63.64)	78 (60.47)	121 (63.35)	

Abbreviations: CMI, comorbidity index; ER, estrogen receptor; ET, endocrine therapy; PR, progesterone receptor.
[a]Fisher's *P* values are reported for ET, CMI, and race.

Forty-three of 130 patients (33.08%) who were HS 1%-9% and 54 of 166 patients (32.53%) who were HS ≥ 10% had grade 1 disease; 66 of 74 patients (89.19%) who were HS < 1% had grade 1 disease ($P < .0001$ for grade 1 disease). One hundred twenty-nine of 147 patients (87.76%) who were HS 1%-9% and 170 of 197 patients (86.29%) who were HS ≥ 10% had early-stage disease (0-3A), whereas 61 of 83 patients (73.49%) who were HS < 1% had early-stage disease (0-3A; $P = .0098$ for stage 1 disease). Twenty-six of 150 patients (17.33%) who were HS 1%-9% and 36 of 197 patients (18.27%) who were HS ≥ 10% had lymphovascular invasion (LVI); 43 of 84 patients (51.19%) who were HS < 1% had LVI ($P < .0001$ for LVI).

Associations between positive family history, surgery, tobacco use, and comorbidity index with HS was not statistically significant. Fifty-one of 129 patients (39.53%) who were HS 1%-9% had a positive family history of BC and 70 of 191 patients (36.65%) who were HS ≥ 10% had a positive family history. Twenty-eight of 77 patients (36.36%) who were HS < 1% had a positive family history of BC. One hundred thirty-six of 150 patients (90.67%) who were HS 1%-9% underwent surgery, and 176 of 196 patients (89.80%) who were HS ≥ 10% had surgery. Seventy of 82 patients (85.37%) who were HS < 1% had surgery. Twenty-four of 43 patients (17.52%) who were HS 1%-9% and 34 of 74 patients (17.99%) who were HS ≥ 10% used tobacco. Fifteen of 26 patients (18.52%)

who were HS < 1% used tobacco. The distribution of each comorbidity index category was similar among the different HS groups.

Seventy-one of 150 patients (47.33%) who were HS 1%-9% and 68 of 197 patients (34.52%) who were HS ≥ 10% received chemotherapy. Sixty-two of 84 patients (73.81%) who were HS < 1% received chemotherapy. Only 3 of 84 patients (3.57%) with HS < 1% received ET, whereas 102 of 150 patients (68%) and 152 of 197 patients (77.16%) who were HS 1%-9% and HS ≥ 10%, respectively, had ET ($P < .0001$ for ET and chemotherapy). One hundred thirty-two of 150 patients (88.00%) who were HS 1%-9% and 119 of 197 patients (60.41%) who were HS ≥ 10% received radiation therapy, and 63 of 84 patients (75.00%) who were HS < 1% received radiation therapy ($P < .0001$ for radiation therapy). One hundred twenty-five of 139 patients (89.93%) who were HS 1%-9% and 154 of 187 patients (82.35%) who were HS ≥ 10% had response to treatment; 58 of 77 patients (75.32%) who were HS < 1% had response to treatment ($P = .0172$ for response to treatment).

Cox Regression Analysis

Cox regression analysis was used to assess the association between variables and predict survival rates. Analysis of HRs for the different HS categories showed that patients with HS < 1% had an increased risk of death compared with those with HS ≥ 10% (HR: 1.77; 95% CI, 1.03 to 3.05). On the other hand, patients with HS 1%-9% had a protective effect compared with those with HS < 1% and ≥ 10% (HR: 0.39; 95% CI, 0.20 to 0.74 and HR: 0.68; 95% CI, 0.38 to 1.22, respectively). Patients who received chemotherapy had an increased risk compared with those who did not (HR: 1.77; 95% CI, 1.04 to 3.01). White race, surgery, radiation, and early-stage disease were protective (HR: 0.64, 0.46, 0.44, and 0.22, respectively; Table 2).

Predicted mortality for patients with HS < 1% was significantly higher than for those with HS ≥ 10% (HR: 1.8; 95% CI, 1.07 to 3.02), whereas predicted mortality for those with HS 1%-9% and HS ≥ 10% was not different (HR: 1.05; 95% CI, 0.48 to 2.30; Fig 1). Patients who received ET had a lower predicted mortality rate than untreated patients in the 1%-9% group (HR: 0.10; 95% CI, 0.01 to 0.85). Hundred percent of patients who received ET had no evidence of tumor at last follow-up compared with 87.5% of nontreated patients ($P = .048$). There was no significant difference in predicted mortality between ET-treated HS 1%-9% and HS ≥ 10% groups (Figs 2 and 3).

DISCUSSION

In this study, we classified women with BCs into 3 HS categories: those with < 1%, 1%-9%, and ≥ 10% of tumor cells' nuclei staining positive on IHC. Historically, the cutoff for ER positivity was 10% of nuclear staining. Among the first to challenge this cutoff was the CAP' consensus statement published in 1999.[11] Aiming to compare the role of IHC with that of ligand-binding assay in predicting clinical outcomes, Harvey et al[12] assessed the clinical utility of ER estimation by IHC in predicting responsiveness to ET. Not only was IHC superior to ligand-binding assay, but also the objective clinical benefit from ET was observed even in patients who stained weakly on IHC for ER, with as low as 1% positivity. This was confirmed by the ASCO-CAP consensus guidelines in 2010 (Data Supplement).

Although the new cutoff by ASCO-CAP can be viewed as an attempt to make the benefit of ET available to the widest number of patients, it was important to acknowledge that not all patient populations are similar and to validate the applicability of the borderline ER-positive subtype to our patient population in Georgia. According to the United States Census Bureau, around 32.6% of the population in Georgia is African American.[13] This explains the large proportion of African Americans in our patient population at GCC. However, there was comparable distribution of patients among White and African-American races for the 1%-9% and ≥ 10% subgroups (approximately 40% African Americans in each). This similar distribution among the subgroups helped remove race bias from our analysis. Among the 186 African-American women included in our study, 26.34% had TNBC. This compares with the population-based study from Georgia by Lund et al[14] where 29.5% of patients had TNBC. Our study population was, therefore, a representative sample of the population in Georgia.

Tumor HS classification can affect treatment decisions and predict response. ER-positive tumors can be treated with ET, including tamoxifen or aromatase inhibitors that target the ER pathway.[15] Borderline ER-positive tumors would have been labeled HS-negative using the earlier 10% cutoff. This raises concerns about the appropriate definition of ER-positive BC, which is particularly important for predicting response to ET. In fact, the ASCO-CAP panel

TABLE 2. Cox Regression Results

Label	Description	HR	95% CI
ER and PR	1%-9% *v* < 1%	0.39	0.20 to 0.74
	1%-9% *v* ≥ 10%	0.68	0.38 to 1.22
	< 1% *v* ≥ 10%	1.77	1.03 to 3.05
Race	White *v* Black	0.64	0.42 to 0.97
Surgery	Yes *v* no	0.46	0.25 to 0.88
Radiation	Yes *v* no	0.44	0.27 to 0.72
Stage	Early *v* late	0.22	0.13 to 0.38
Chemotherapy	Yes *v* no	1.77	1.04 to 3.01
Chemotherapy with LVI		1.491	0.48 to 4.627
Chemotherapy without LVI		1.744	0.323 to 9.422

Abbreviations: ER, estrogen receptor; HR, hazard ratio; LVI, lymphovascular invasion; PR, progesterone receptor.

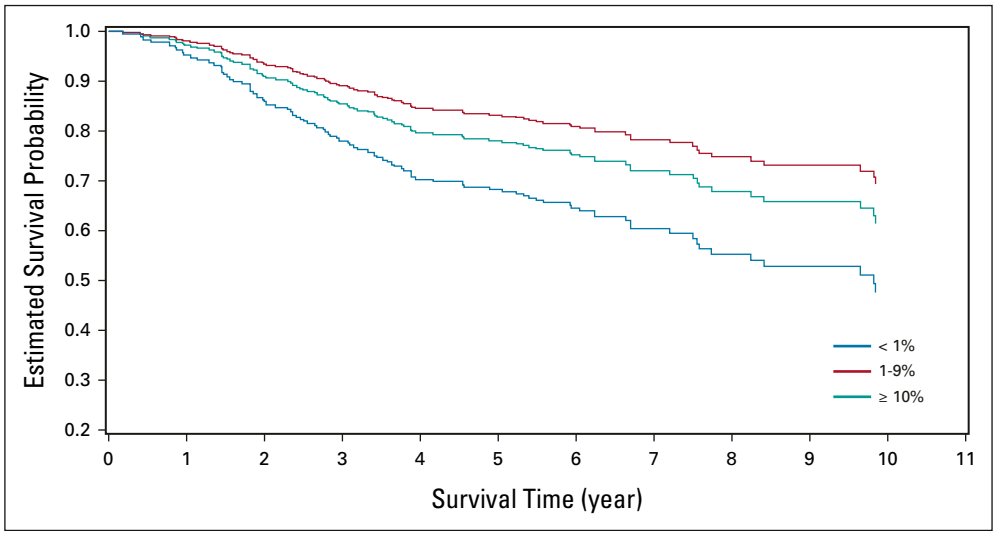

FIG 1. Survival probability for the three HS groups expressing ER/PR in < 1% versus 1%-9% versus ≥ 10% (after control age, race, stage, surgery, chemotherapy, and radiation). The Proportional Hazards Regression procedure, or Cox regression, was used to perform regression analysis of survival data among the three HS groups, adjusting for standard prognostic factors. ER, estrogen receptor; HS, hormonal status; PR, progesterone receptor.

acknowledged that there are limited data on the benefit of ET for tumors staining 1%-9% for ER.[16] Several studies reinforced the concern that a significant proportion of borderline ER-positive BC behaves more like TNBC.[5,9,15]

The 10-year predictive study reported here tested this hypothesis by evaluating the role of the 1% cutoff in predicting response to ET. Interestingly, patients who were 1%-9% HS and who received ET had the highest 10-year predictive survival probability for ET (87.5%). This was even greater than the 10-year predictive survival probability of 65% for patients in the HS ≥ 10% group. On the other hand, patients who were HS-negative or in the 1%-9% or ≥ 10% HS groups and who did not receive ET had the lowest estimated survival probability (approximately 50%). Although this agrees with the ASCO-CAP threshold in which patients with < 1% ER are expected to have the least response to ET, it was unexpected to obtain a greater probability of survival rate for ET among patients whose HS was 1%-9% compared with those with ≥ 10% HS. Interestingly, patients in the 1%-9% group who were treated with chemotherapy had HRs of 1.491 (95% CI, 0.48 to 4.627) and 1.744 (95% CI, 0.323 to 9.422) for those with and without LVI, respectively. This showed that chemotherapy was detrimental even after stratification for LVI and suggests that it is less likely that the superior predicted survival for the 1%-9% HS group was related to the benefit from chemotherapy. Also, univariate analysis of demographic variables showed no statistical significance among the three subgroups, which makes the possibility of different demographics contributing to this result in predicted behavior of borderline ER-positive disease unlikely.

Our results differ from some published studies in which patients with borderline HS disease had survival rates that were similar to TNBC and lower than HS-positive disease.[7,17,18] A recently published study by Benefield et al showed that borderline HS tumors more frequently had

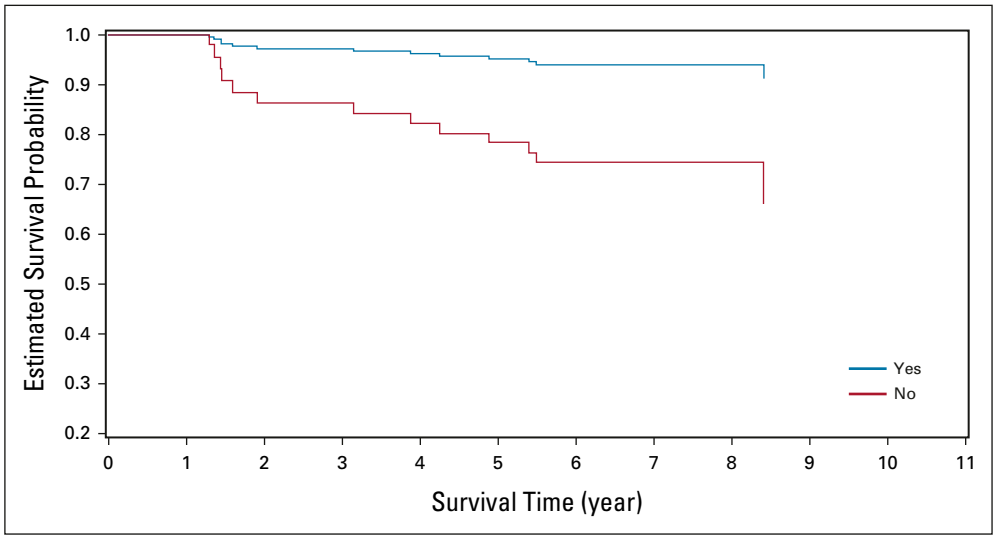

FIG 2. Survival probability according to receiving ET: predicted survival to ET in patients with borderline hormone status with estrogen and progesterone receptor expression of 1%-9% (hormone vs no hormone treatment in 1-9% HS, yes vs no). ET, endocrine therapy.

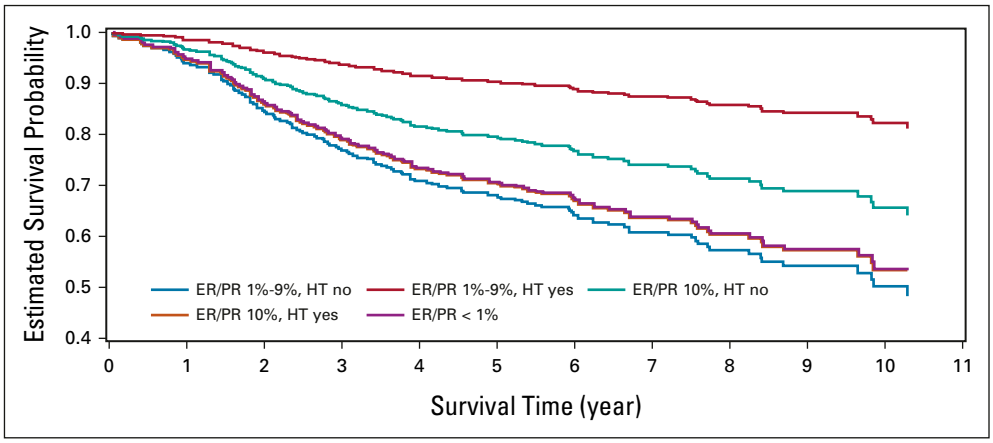

FIG 3. Survival probability according to receiving endocrine therapy for the three HS groups: predicted survival to endocrine therapy or HT in three HS groups expressing ER/PR in < 1% versus 1%-9% versus ≥ 10%. HT yes = treated, HT no = untreated. ER, estrogen receptor; HS, hormonal status; HT, hormone therapy; PR, progesterone receptor.

a basal-like molecular subtype. Compared with ER-positive disease, the borderline HS subgroup treated with ET had a poorer disease-free interval, yet without meeting statistical significance, compared with ER-positive disease. Black women with borderline ER tumors also had worse disease-free interval than women with ER-positive disease, which suggested that the borderline subgroup was heterogeneous.[18]

Chen et al[19] investigated differences in endocrine responsiveness, prognosis, and clinicopathologic characteristics between the borderline ER 1%-9% cohort and the ER-negative or ER-positive (≥ 10%) cohorts from six studies (n = 16,606). Patients with borderline ER expression had no significant survival benefit from ET but had an overall better prognosis than those with ER-negative cancer. Moreover, a recently published study by Villegas et al evaluated human epidermal growth factor receptor 2–negative BC with borderline 1%-9% HS compared with TNBC and HS-positive BC. It included a large cohort of patients with BC (n = 2,765) from neoadjuvant clinical trials. With basal-like gene expression signatures and clinical behavior similar to TNBC, borderline HS BC patients showed higher rates of pathologic complete response and lower survival compared with patients with HS-positive BC. Interestingly, the authors suggest that this group of patients should be treated similar to patients with TNBC.[17]

With superior predicted survival in response to ET despite lower HS positivity, we have shown that the 1%-9% HS group seems to behave similar to HS-positive disease in response to ET while remaining distinct at the same time. Therefore, we suggest that combining 1%-9% HS-positive and ≥ 10% HS-positive disease into one HS-positive group should be considered. Although the benefit of ET in ER-positive cases is indisputable, we believe that its application to patients with borderline ER-positive expression needs further study to better understand this subgroup. Interestingly, a retrospective study by Raghav et al evaluated outcomes and response to ET in patients in three subgroups: 0%, 1%-5%, and 6%-10% ER staining. There was a tendency toward survival advantage only in the 6%-10% ER/PR group,[20] indicating that the borderline ER-positive

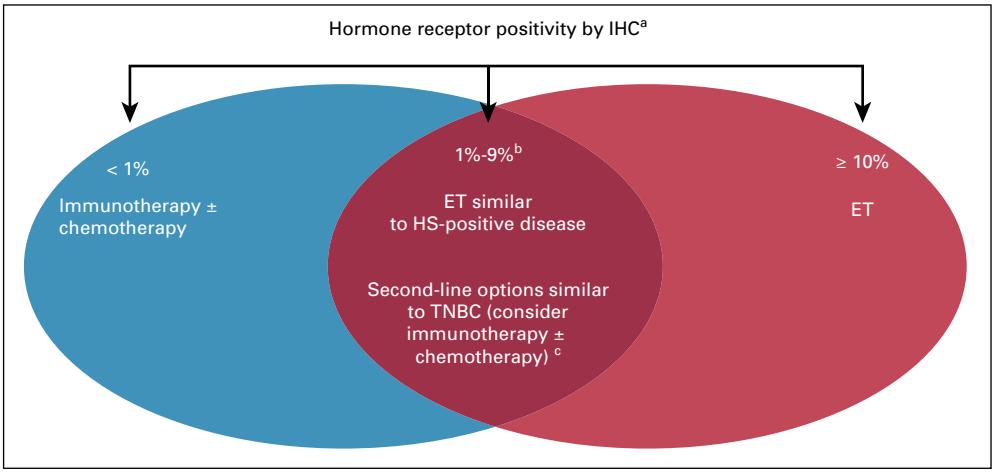

FIG 4. Treatment approach on the basis of hormone receptor positivity: a proposed hypothetical model for treatment considerations in patients with human epidermal growth factor receptor 2–negative breast cancer on the basis of their HS. Suggestions to consider immune therapy in the borderline HS-positive group may also apply for neoadjuvant setting. [a]Can consider molecular testing (eg, RNA sequencing) for further characterization of the tumor (estrogen receptor variants, G-protein coupled estrogen receptor). [b]Heterogeneous group and broad terminology have been divided in a few studies into smaller subgroups (eg, 1%-5% and 5%-9%). [c]Potential role for CDK4/6i and PIK3CA inhibitors. ET, endocrine therapy; HS, hormonal status; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

group is heterogeneous and that not all tumors belonging to this subgroup are alike (Data Supplement).

Patients with TNBC are not usually eligible for targeted treatment, including ET and trastuzumab, which leaves chemotherapy and/or immunotherapy as the alternatives.[18,20] Our 1%-9% subgroup had a superior predicted survival compared with the remaining groups, and chemotherapy was detrimental. We have shown that this subgroup is distinct from the ≥ 10% HS-positive group; its unique behavior suggests that the borderline ER-positive subgroup lies somewhere between TNBC and ER-positive disease. In addition to responding to ET, we suggest that this subgroup may have a biology like that of TNBC. Thus, we envision the possibility of using similar treatments, such as immunotherapy, for this group neoadjuvantly or after progression on ET (Fig 4 and Data Supplement). This is particularly important since breakthrough therapies in immuno-oncology for TNBC have been approved or have shown promising results in ongoing clinical trials.[21-24]

In conclusion, to our knowledge, this is the first and largest predictive model to validate the 1% hormonal positivity cutoff in response to the controversy raised in the literature, where HS 1%-9% disease behaved more like TNBC and derived little benefit from adjuvant ET. On the basis of our data, the 1% cutoff predicted superior survival on treatment with ET compared with the other groups and hormone receptor expression as low as 1%-9% was as prognostic as HS ≥ 10% expression. Both groups also had better survival than patients with TNBC. Chemotherapy was detrimental and should be avoided for HS ≥ 1%, even after stratification by LVI and regardless of other variables. Despite similarities in response and prognosis, the 1%-9% subgroup remains a unique group that lies between HS-positive and triple-negative subgroups. HS-positive disease is characterized by significant heterogeneity, which makes immunotherapy a potential therapeutic option on progression. Basic science and clinical research are needed to better understand the complex molecular mechanisms underlying steroid hormone receptors' effects on BC development, progression, and response to therapy. Until then, we urge clinicians to collect clinical data on a massive scale to analyze the predictive role of HS in response to ET. The goal is to provide BC patients with patient-centered care that can more accurately predict response to therapy and prognosis and that can render inaccurate the broad terms ER-positive BC and TNBC. Whether other factors, such as age, LVI, grade, and other parameters, change the behavior of the 1%-9% HS group remains to be explored in larger data sets.

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DATA SHARING STATEMENT

Clinicopathologic data are summarized in this article. No new data sets were generated or analyzed for this study.

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Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

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