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Troester, M. A., Sun, X., Allott, E. H., Geradts, J., Cohen, S. M., Tse, C-K., ... Perou, C. M. (2018). Racial Differences in PAM50 Subtypes in the Carolina Breast Cancer Study. Journal of the National Cancer Institute, 110(2), 176-182. https://doi.org/10.1093/jnci/djx135

Published in:
Journal of the National Cancer Institute

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Racial Differences in Subtype and PAM50 Biomarker Status in the Carolina Breast Cancer Study

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Word count: 2555

ABSTRACT

Importance: African American breast cancer patients have lower relative frequency of hormone receptor (HR)-positive/HER2-negative disease and higher subtype-specific mortality. However, few population-based studies have RNA-based subtyping data, and racial differences among HR-positive/HER2-negative tumors are not well understood.

Objective: To classify invasive breast cancers according to PAM50 subtype and two risk of recurrence scores (ROR-P and ROR-PT). To compare relative frequency of Luminal A, Luminal B, Her2-enriched, and Basal-like subtypes and ROR scores (low/medium/high) by race (blacks vs. whites) and age (≤50 years vs. >50 years), overall and among HR-positive/HER2-negative cases.

Design: This study samples from the Carolina Breast Cancer Study (CBCS) Phase 3, a cohort of invasive cases diagnosed between 2008-2013 in 44 North Carolina Counties, (2008-2013).

Setting: Population-based sampling of cases identified through Rapid Case Ascertainment and the North Carolina Central Cancer Registry.

Participants: Approximately 1000 participants with invasive breast cancer.

Exposure: Race (black vs. white) and age (<50 vs. ≥50 years old) were primary exposures. Main outcome: PAM50 subtype and two risk of recurrence scores (ROR-P and ROR-PT).

Results: Black women of all ages had significantly higher relative frequency of Basal-like and significantly lower frequency of Luminal A breast cancer. Frequency of Luminal B and HER2-enriched breast cancer did not vary by race or age. Among clinically HR-positive, HER2-negative cases, Luminal A subtype comprised only half of the cases among black women, and was significantly less common than among white women (51% vs 60% in whites, $p<0.05$). Black women with HR-positive/HER2-negative disease also had significantly higher ROR scores

(ROR-P medium or high 82% vs. 66% in whites, p=0.01; ROR-PT medium or high 85% vs. 69% in whites, p<0.01).

Conclusions and Relevance: Multi-gene assays highlight disparities in frequency of aggressive, poorer prognosis tumor subtypes and implicate differences in tumor biology as an important contributor to mortality disparities among HR-positive/HER2-negative patients.

INTRODUCTION

Breast cancer incidence is higher in young black women (<40 years old) compared to young white women, and while 2010 Surveillence Epidemiology and End Results data showed that across all ages white women had higher incidence[1], recent data from the American Cancer Society suggest that overall incidence rates have converged[2]. This convergence could compound breast cancer mortality disparities. Hazard rates among black women vary by subtype, but are 20-150% higher relative to white women[3,4]. Differences are particularly pronounced among hormone receptor (HR)-positive, HER2-negative patients [4,5]. Interventions to reduce these disparities require improved understanding of how tumor-level and patient-level factors interact, but detailed molecular characterization of tumors in population-based studies is uncommon.

The Carolina Breast Cancer Study Phase 3 (CBCS3, 2008-2013) was initiated to disentangle the role of health service and tumor biological factors in breast cancer disparities [6-8]. Research from earlier phases of the Carolina Breast Cancer Study (CBCS1 and 2, 1993-2001) found higher prevalence of Basal-like breast cancer and lower prevalence of Luminal A breast cancer among young (<50 years old) black women[9], findings that been confirmed in other studies [4,10-12]. Decreased ER-positive disease among young black women could arise from lower screening utilization[13] and from differences in risk factor profiles[14]. These factors could further lead to differences in genomic characteristics even within clinically homogeneous groups. Of particular interest is whether there are biological differences in tumors of black and white women with hormone receptor (HR)-positive, HER2-negative disease. Few studies have utilized genomic data to characterize racial differences in clinically homogenous groups[15], and population-based studies of these differences have not been previously reported.

To elucidate differences in tumor aggressiveness by race, we used RNA-based methods to accurately determine the molecular subtypes of invasive breast cancers from over 1000

women participating in the population-based CBCS3, with roughly equal numbers of black and white women. We identified PAM50-based intrinsic subtype, and classified patients for a risk of relapse (ROR) score based on proliferation (ROR-P) or a combination of proliferation and tumor size (ROR-PT)[16]. We also compared Oncotype DX scores by race for a subset of patients who underwent clinical genomic testing. Our findings show significant racial differences in the relative frequency of molecular subtype and further indicate that differences in tumor genomics persist even within clinically homogeneous subgroups of HR-positive, HER2-negative patients.

METHODS

Study population. The Carolina Breast Cancer Study (CBCS3) is the third phase (2008-2013) of a population-based study conducted in North Carolina (NC) beginning in 1993[7,17]. The study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill and informed consent was obtained from each participant. Cases of invasive breast cancer between 20-74 years of age were identified using rapid case ascertainment in cooperation with the NC Central Cancer Registry, with African American (AA) and young cases (aged 20-49 years) oversampled using randomized recruitment [17]. Tumor size, stage, node status, estrogen receptor (ER), progesterone receptor (PR), HER2, and Oncotype DX data were abstracted from medical records, and tumor grade was centrally assigned for each case in Phases 1 and 3 by a single pathologist (JG) using the Nottingham breast cancer grading system [18].

Molecular and clinical subtyping. Paraffin-embedded tumor blocks were requested from participating pathology laboratories for each case. The study pathologist (JG) reviewed H&Es for each tumor, selected a representative tumor block, and circled tumor areas for coring. Ten 10-uM sections were cut from blocks after coring (for future immunohistochemistry) and an additional H&E section was obtained and reviewed for tumor cellularity. Only cores with both

top and bottom tumor cellularity by manual review were selected for RNA analyses. Nanostring assays were performed using two separate 1.0-mm cores. RNA was isolated from cores using Qiagen RNeasy FFPE kit and protocol, with 95% of samples producing quantifiable RNA. A random sample of all available cores was selected for each batch of RNA analyses. In total, 1122 samples from 1,042 cases from CBCS Phase 3 were analyzed for the PAM50 assay, including 9 patients with more than one tumor block and 52 patients with duplicate RNA samples. All assays were performed in the Rapid Adoption Molecular (RAM) laboratory at UNC, a Clinical Laboratory Improvement Amendments (CLIA)-approved facility.

To classify samples, the NanoStringNorm package in Bioconductor was first used to eliminate samples that did not have sufficient Nanostring data quality (39 of 1122, 3%). The PAM50 predictor[16] was used to categorize breast tumors as Luminal A, Luminal B, HER2-enriched, Basal-like, normal-like and to calculate the risk of relapse (ROR) score with proliferation (ROR-P) and with tumor size included (ROR-PT). Briefly, each sample was classified based upon the subtype centroid with the highest Pearson correlation. Duplicate samples were treated independently during classification; after classification, the sample with the highest PAM50 confidence score was selected for inclusion in patient-level analyses. After excluding patients with missing clinical data and patients with race other than black or white, 980 patients were included in the final analysis. Compared to cases not analyzed, included samples were more likely to be older than 50 years (33% vs. 51%, Chi-square p=0.0247) and have tumor of grade 2 (15% vs. 34%; Chi-square p=0.0143).

Statistical analysis. Biomarker variables, including PAM50-based ROR-P and ROR-PT and Oncotype DX, were used both continuously and categorically. The cutoff points to define low/medium/high levels were 11.8 and 52.9 for ROR-P; 17.6 and 64.7 for ROR-PT; 18 and 30

for Oncotype DX. Racial differences by categorical variables, such as clinical characteristics and subtype, were assessed with Pearson Chi-square tests. Two-way ANOVA was used to assess statistical differences for continuous variables. All statistical tests were two sided with α=0.05, all analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). P-values were not corrected for multiple comparisons because tumor characteristics are not independent.

RESULTS

Prevalence and tumor characteristics for breast cancer subtypes. Differences in molecular subtype were most pronounced for Basal-like and Luminal A breast cancer. As shown in Table 1, the proportion of Basal-like breast cancer as measured by RNA profiling was 25% overall (n=249 cases)**,** but was higher in black women. 36% and 31% of younger ($\leq$ 50 years) and older (>50 years) black women, respectively, had Basal-like breast cancer. Basal-like breast cancer comprised only 15-18% of cases among white women. The higher proportion of Basal-like tumors in black women appeared to be offset by a decrease in the relative frequency of Luminal A breast cancer. Luminal A breast cancer had lowest frequency among young black women (26%, n=63), followed by older black women (34%, n=86), young white (43%, n=103) and older white (52%, n=125) women. Luminal B prevalence was relatively stable across all four age-and race-defined groups, at approximately 20%. There was a suggestion that HER2-enriched tumors may be more frequent among young black women (15%, n=37) compared to all other groups (9-11%), however this small difference was not statistically significant.

Mortality disparities are greatest among HR-positive, HER2-negative cancers, so racial differences in clinical, histopathologic and biomarker data are important for this group. Table 2 shows that tumor size and grade varied significantly by race and age. Compared to older white women, younger black women had more than twice the odds of a large tumor, and both younger and older black women had twice the odds of having a high grade tumor. Stage and node status

were not significantly different by race or age, although younger black women had higher odds of being node positive. Table 3 shows racial differences in biomarker levels and class distributions, including PAM50 subtype, ROR-P and ROR-PT, and Oncotype DX. ROR-P is a risk of recurrence score based on proliferation genes and ROR-PT incorporates proliferation gene expression along with tumor size. The three PAM50 tests are research versions of the FDA-approved test (ProSigna). While PAM50 subtype did not significantly differ across all race and age strata shown in Table 3, there were significant differences in the percentage of Luminal A breast tumors between black and white women with HR-positive/HER2-negative disease. Both older and younger black women were more likely to have non-Luminal A subtype, but the association was attenuated and borderline significant in older black women. Considering black women vs. white women, regardless of age, only about half of black women (51%) had Luminal A subtype compared to 60% of white women ($p<0.05$). The ROR-P and ROR-PT scores both differed by race and age, with black women having significantly higher prevalence of medium and high risk tumors for both scores (OR>2.5 for both scores in both younger and older black women). On a continuous scale, average scores for ROR-P and ROR-PT also differed by race and age ($p<0.01$). In contrast, Oncotype DX did not differ by race or age, either considered categorically ($p=0.89$) or as a continuous variable ($p=0.54$), although Oncotype DX data was available only for a subset of women based upon clinical indication for testing (typically low grade, lower stage, and node negative cases). When restricting the dataset to only those cases where Oncotype DX data was available, the ROR-P scores remained higher and statistically significant for both older and younger black women (relative to older white women). ROR-PT scores were significantly different comparing younger black women to older white women, and although ORs were imprecise, the ROR-PT scores remained significantly elevated in older black women.

DISCUSSION

Using RNA expression data, this analysis more accurately classified molecular subtype in a population-based sample of black and white women. The results show that the racial disparity in frequency of Basal-like breast cancer is greater than previously estimated[9], affecting both younger and older black women. The higher relative frequency of Basal-like breast cancer in black women is offset by a decreased frequency of Luminal A breast cancers. Furthermore, even among clinically homogeneous HR-positive/HER2-negative cases, black women are more likely to have aggressive molecular subtypes (Luminal B, HER2-enriched, or Basal-like) and high risk of recurrence (ROR) scores.

The potential of genomic biomarkers to guide clinical decision making has had the largest impact among HR-positive/HER2-negative cases. Although clinically indistinguishable by standard tests, outcomes vary widely and racial disparities are pronounced in this group[4,5]. Several commercial genomic tests are available clinically, and relative to standard clinical markers or immunohistochemical surrogates[19,20]. At least one study has shown that RNA-based subtyping more accurately predicts recurrence and survival[21]. Based on our current analysis, admixture of all four tumor subtypes occurs in this clinically homogeneous group, with HR-positive/HER2- black women having higher prevalence of non-Luminal A (Basal-like, HER2-enriched, and Luminal B) cancer relative to white women with the same clinical profile. The ROR-P and ROR-PT scores that track proliferation and proliferation plus tumor size, respectively, were higher in black women of all ages relative to white women. Oncotype DX scores did not vary by significantly by race, but these data were only collected in a subset of cases that tended to have less aggressive pathology findings. While previous studies have evaluated uptake of Oncotype DX by race[8,22,23], we were unable to identify any other study that

has compared quantitative of categorical Oncotype DX scores by race among HR-positive/HER2-negative cases.

The distribution of PAM50 subtype detected in our analysis differs from a previous population-based analysis conducted in the Life After Cancer Epidemiology (LACE) and Pathways studies[24], and suggests a poorer prognostic profile. In LACE/Pathways, roughly half of the tumors were Luminal A, whereas only 38% were Luminal A in CBCS3. Prevalence of Luminal B (both studies approximately 20%) and HER2 tumors were similar (13% in LACE/Pathways, 12% in CBCS3), but CBCS3 had a much higher frequency of basal-like breast cancer (9.8% in LACE/Pathways vs. 25% in CBCS3). The differences between these two studies may reflect national geographic trends; a recent Report to the Nation has emphasized geographic variation in incidence of triple negative breast cancer, with highest incidence in the southeastern United States[25]. However the most compelling differences between LACE/Pathways and CBCS are in race and age composition; namely, LACE/Pathways was predominantly (>75%) older women and fewer than 10% were black. A strength of the CBCS3 for disparities research is oversampling of young women (<50) and black women.

Our findings should be interpreted in light of some limitations. First, the clinical relevance of our biomarker findings merits confirmation because we used a research version of the PAM50 and not the clinically-approved assay. However, our assay was applied to a random sampling of a population-based study and performed in a CLIA-approved laboratory, so we expect this limitation did not substantially alter our findings. Second, clinical Oncotype DX scores were missing for about 60% of HR-positive/HER2-negative patients in our study, limiting statistical power to detect small differences by race and age. The high rate of missingness also limits the validity of comparisons with the ROR-P score as Oncotype DX data were more likely to be obtained in patients with low stage, low grade, and negative node status. However,

sensitivity analyses restricted to just cases with Oncotype DX data available still showed significant differences by race and age for ROR-P and ROR-PT. Third, we lacked statistical power to assess race- and age-associated differences in the prevalence of HER2-enriched and Luminal B breast cancer.

Despite limitations, these data clearly show that even within more homogeneous clinical subgroups there are important biological differences between black and white women's tumors. A persistent high priority research question is how tumor-level factors balance with patient-level variables (such as access to care and treatment adherence) in progression of HR-positive/HER2-breast cancers. CBCS3 recruitment ended in 2013 and survival data is not mature for analyses of how subtype mediates survival disparities, but future work will leverage the biological data collected herein, together with detailed treatment data, to elucidate how multiple causes work together to produce poorer outcomes in HR-positive/HER2-negative black women.

ACKNOWLEDGEMENTS

MAT, XS, EHA, C-KT, WRR, KAH, KER-H, HSE, JG, AFO, LAC, CMP contributed to data collection, analysis, and review of manuscript. LT, MM, SC, EK, YL, and ZH contributed to data collection and review of manuscript. MAT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Funding was provided by the National Institutes of Health, National Cancer Institute P50-CA058223, U54-CA156733, and U01-CA179715.

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Table 1. Molecular subtype by race and age, Carolina Breast Cancer Study Phase 3, 2008-2013.

	All cases	**Black, ≤ 50 y**	**Black, > 50 y**	**White, ≤ 50 y**	**White, > 50 y**
	N=980	N=244	N=256	N=240	N=240
	N (%)	N (%)	N (%)	N (%)	N (%)
Basal-like[a]	249 (25)	89 (36)	80 (31)	44 (18)	36 (15)
HER2-Enriched	114 (12)	37 (15)	29 (11)	22 (9)	26 (11)
Luminal A	377 (38)	63 (26)	86 (34)	103 (43)	125 (52)
Luminal B	194 (20)	47 (19)	49 (19)	57 (24)	41 (17)
Normal-like	46 (5)	8 (3)	12 (5)	14 (6)	12 (5)

[a]Chi-square p-value<0.0001, comparing Basal-like to Non-basal-like.

[b]Chi-square p-value<0.0001, comparing Luminal A to Non-luminal A.

Table 2. Relative frequency of clinical features, HR-positive, HER2-negative cases, CBCS3, 2008-2013[a].

	All cases N (%)	**AA, ≤ 50 y** N (%)	**AA, > 50 y** N (%)	**White, ≤ 50 y** N (%)	**White, > 50 y** N (%)
Tumor Size					
<2 cm	265 (54)	40 (42)	59 (54)	71 (55)	95 (64)
≥2 cm	216 (45)	55 (58)	50 (46)	58 (45)	53 (36)
Missing	11	1	3	1	6
			X^2 p=0.009		
≥2 cm vs. <2 cm OR (95% CI)		**2.47 (1.45-4.18)**	**1.51 (0.92-2.52)**	**1.46 (0.90-2.37)**	**Ref**
Grade					
I, II	342 (72)	59 (63)	71 (66)	93 (72)	119 (81)
III	136 (28)	35 (37)	37 (34)	36 (28)	28 (19)
Missing	14	2	4	1	7
			X^2 p=0.008		
III vs. I,II OR (95% CI)		**2.52 (1.40-4.53)**	**2.22 (1.25-3.93)**	**1.65 (0.94-2.89)**	**Ref**
Stage					
I, II	403 (84)	78 (82)	94 (86)	106 (82)	125 (84)
III, IV	79 (16)	17 (18)	15 (14)	24 (18)	23 (16)
Missing	10	1	3	0	6
			X^2 p=0.755		
III,IV vs. I,II OR (95% CI)		**1.19 (0.50-2.36)**	**0.87 (0.43-1.75)**	**2.23 (0.66-2.31)**	**Ref**
Node					
Negative	277 (57)	47 (49)	64 (59)	72 (55)	94 (64)
Positive	205 (43)	48 (51)	45 (41)	58 (45)	54 (36)
Missing	10	1	3	0	6
			X^2 p=0.172		
Pos vs. Neg OR (95% CI)		**1.78 (1.05-3.00)**	**1.22 (0.74-2.03)**	**1.40 (0.87-2.27)**	**Ref**

[a] Chi-square p-values exclude participants with missing data.

Table 3. Relative frequency of biomarker class, HR-positive, HER2-negative cases, CBCS3, 2008-2013[a].

	All cases N (%)	**AA, ≤ 50 y N (%)**	**AA, > 50 y N (%)**	**White, ≤ 50 y N (%)**	**White, > 50 y N (%)**
PAM50 subtype					
Basal-like	26 (5)	7 (7)	7 (6)	8 (6)	4 (3)
Her2-Enriched	26 (5)	7 (7)	7 (6)	4 (3)	8 (5)
Luminal A	276 (56)	44 (46)	62 (55)	67 (52)	103 (67)
Luminal B	135 (27)	33 (34)	30 (27)	42 (32)	30 (19)
Normal-like	29 (6)	5 (5)	6 (5)	9 (7)	9 (6)
			X^2 p=0.129		
Lum A vs. Other OR (95% CI)		**2.39 (1.41-4.03)**	**1.63 (0.99-2.69)**	**1.90 (1.17-3.07)**	**Ref**
ROR-P					
Mean (SE)	29.07 (1.03)	35.34 (2.35)	32.70 (1.99)	28.54 (2.14)	22.98 (1.71)
			ANOVA p=0.542		
Low	133 (27)	18 (19)	19 (17)	39 (30)	57 (37)
Medium	269 (55)	52 (54)	75 (67)	62 (48)	80 (52)
High	90 (18)	26 (27)	18 (16)	29 (22)	17 (11)
			X^2 p<0.0001		
Med/Hi vs. Low OR (95% CI)		**2.55 (1.39-4.68)**	**2.88 (1.59-5.20)**	**1.37 (0.83-2.25)**	**Ref**
ROR-PT					
Mean (SE)	36.71 (1.10)	45.10 (2.52)	40.62 (2.14)	36.29 (2.20)	28.76 (1.83)
			ANOVA p<0.001		
Low	117 (24)	15 (16)	16 (15)	36 (28)	50 (34)
Medium	296 (62)	59 (62)	76 (70)	75 (58)	86 (59)
High	67 (14)	21 (22)	17 (16)	18 (14)	11 (7)
Missing	12	1	3	1	7
			X^2 p<0.001		
Med/Hi vs. Low OR (95% CI)		**2.75 (1.44-5.26)**	**3.00 (1.60-5.63)**	**1.33 (0.80-2.23)**	**Ref**
Oncotype DX					
Mean (SE)	18.85 (0.65)	19.12 (1.17)	20.07 (1.45)	17.49 (1.03)	19.05 (1.17)
			ANOVA p<.001		
Low	92 (48)	11 (44)	20 (44)	29 (53)	32 (48)
Medium	80 (42)	11 (44)	19 (42)	23 (42)	27 (41)
High	19 (10)	3 (12)	6 (13)	3 (5)	7 (11)
Missing	301	71	67	75	88
			X^2 p=0.893		
Med/Hi vs. Low OR (95% CI)		**1.20 (0.48-3.02)**	**1.18 (0.55-2.52)**	**0.84 (0.41-1.73)**	**Ref**

[a] Chi-square p-values exclude participants with missing data.