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Breast Tumor Microenvironment in Black Women: A Distinct Signature of CD8+ T-Cell Exhaustion

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Abstract

Background: Blacks tend to have a stronger inflammatory immune response than Whites. We hypothesized that racial differences in host immunity also manifest in the tumor microenvironment, constituting part of a distinct aggressive tumor biology underlying higher mortality in Black women. **Methods:** Pathological and gene expression profiling approaches were used for characterizing infiltrating immune cells in breast tumor microenvironment from 1315 patients from the Women's Circle of Health Study. Racial differences in tumor immune phenotypes were compared, with results validated in a publicly accessible dataset. Prognostic associations of immune phenotypes were assessed in 3 independent cohorts. **Results:** We found marked and consistent differences in tumor immune responses between Black and White patients. Not only did tumors from Blacks display a stronger overall immune presence but also the composition and quality of immune infiltrates differed, regardless of tumor subtypes. Black patients had a stronger CD4+ and B-cell response, and further, a more exhausted CD8+ T-cell profile. A signature indicating a higher ratio of exhausted CD8+ T cells to total CD8+ T cells (ExCD8-r) was consistently associated with poorer survival, particularly among hormone receptor–positive patients. Among hormone receptor–negative patients, combinations of the absolute fraction of CD8+ T cells and ExCD8-r signature identified the CD8^low^ExCD8-r^high^ subgroup, the most prevalent among Blacks, with the worst survival. **Conclusions:** Our findings of a distinct exhausted CD8+ T-cell signature in Black breast cancer patients indicate an immunobiological basis for their more aggressive disease and a rationale for the use of immune checkpoint inhibitors targeting the exhaustion phenotype.

In the United States, breast cancer mortality rates are the highest in African American or Black women ([1]). Findings from the last decade suggest that tumor biology may play a role in these racial disparities ([2-5]). Whereas previous research has focused on the tumor itself, less attention was paid to immune infiltrates in the tumor microenvironment (TME), increasingly recognized for their roles in carcinogenesis and as a target of cancer immunotherapy ([6]).

Multiple lines of evidence indicate possible racial differences in immune responses to tumors. Systemic immune responses, measured by circulating cytokine levels ([7]) and transcriptomic profiles of cultured immune cells, differ across ancestral populations ([8-10]). Further genetic analysis attributed these differences, in part, to immune adaptation to ancestral environments of early human populations ([7,9,10]). Two earlier studies also showed differential gene expression in immune-related

Table 1. Descriptive characteristics of patients used for pathological and molecular analysis of tumor-infiltrating lymphocytes[a]

Patient characteristics	Patients with pathological TIL data (n = 1315)			Patients with molecular TIL data (n = 367)		
	Black (n = 920)	White (n = 395)	P	Black (n = 190)	White (n = 177)	P
Age at diagnosis, mean (SD), y	53.3 (10.6)	52.6 (10.3)	.29	53.4 (10.5)	54.8 (13.4)	.29
Tumor grade, No. (%)			.63			.63
I	106 (12.1)	98 (26.0)		11 (5.9)	15 (8.6)	
II	341 (38.9)	165 (43.8)		51 (27.6)	46 (26.3)	
III	430 (49.0)	114 (30.2)		123 (66.5)	114 (65.1)	
ER status, No. (%)			<.001			.34
Positive	630 (68.7)	322 (82.8)		85 (44.7)	88 (49.7)	
Negative	287 (31.3)	67 (17.2)		105 (55.3)	89 (50.3)	
PR status, No. (%)			<.001			.29
Positive	567 (63.5)	280 (74.5)		64 (33.7)	69 (39.0)	
Negative	326 (36.5)	96 (25.5)		126 (66.3)	108 (61.0)	
HER2 status, No. (%)			.46			.09
Positive	170 (19.1)	67 (17.3)		61 (32.1)	72 (40.7)	
Negative	722 (80.9)	320 (82.7)		129 (67.9)	105 (59.3)	
IHC subtype, No. (%)			<.001			.16
Luminal (ER+ or PR+ and HER2-)	526 (59.6)	270 (72.8)		54 (28.4)	38 (21.5)	
HER2+	166 (18.8)	59 (15.9)		61 (32.1)	72 (40.7)	
Triple-negative (ER-, PR- and HER2-)	191 (21.6)	42 (11.3)		75 (39.5)	67 (37.9)	

[a]Pathologic TIL analysis was performed on all tumors from the Women's Circle of Health Study (WCHS); molecular TIL analysis was performed on tumors from a subset of WCHS patients, supplemented with additional tumors from the Roswell Park Pathology Network Shared Resource. Patients were selected based on matching by race, age, and tumor subtype, oversampling patients with HER2+ and triple-negative breast cancer (TNBC) for Black–White comparisons. ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor 2; TIL = tumor-infiltrating lymphocytes.

pathways in prostate and breast cancers from Black and European American orWhite patients (11,12). Because the sample sizes in these studies were limited and methods predated the advent of advanced profiling of immune infiltrates, it remains to be established whether immune responses in breast cancer differ by race.

Two recent studies based on The Cancer Genome Atlas (TCGA) data showed only modest racial differences in tumor immune gene expression between Black and White patients after accounting for breast cancer subtypes (13,14). Despite being an invaluable public resource used for many important studies of immune infiltration in TME, TCGA tumor tissues were collected and processed primarily for sequencing of tumor cells but not necessarily immune cells, which might preside outside of tumor foci (15). Moreover, the design of TCGA, with no matching of patients by race, was not optimal for racial comparisons. To overcome these limitations and to systematically investigate breast TME between Black and White patients, we profiled immune infiltrates using pathological and molecular methods in tumors from the Women's Circle of Health Study (WCHS), which was established specifically to investigate breast cancer racial disparities, with results validated in publicly accessible data.

Methods

Patient Population

Tumor tissues and data for this study were derived from WCHS as previously described (16) and in the Supplementary Methods (available online). Clinicopathological data were obtained from pathology reports, supplemented with data obtained from the New Jersey State Cancer Registry, which actively maintains updated information on deaths and causes of deaths through various follow-up sources. All study participants provided consent for the use of their data and specimens for research. The studies were approved by the institutional review boards at participating institutions.

Pathological Tumor-Infiltrating Lymphocytes (TIL) Assessment

As part of the protocol of receiving unstained slides and tumor blocks in WCHS, hematoxylin and eosin sections were prepared and reviewed for histopathologic scoring of stromal TILs by a board-certified breast pathologist (TK) blinded to patient characteristics, following the recommendations by the International TILs Working Group (17). TIL data were available from 1315 WCHS patients with invasive cancer (920 Blacks and 395 Whites). Descriptive characteristics of this patient population are summarized in Table 1.

Gene Expression Profiling of Breast TME

The NanoString PanCancer Immune Panel was used to quantify immune cell subsets in the breast TME from WCHS patients, complemented with samples from the Roswell Park Pathology Network Shared Resource. Tissue samples from 190 Black breast cancer patients were frequency matched to 177 White patients by age at diagnosis and tumor subtypes. Women with HER2-positive and triple-negative breast cancer were oversampled to allow comparisons between White and Black women by subtype. Patient characteristics are summarized in Table 1. Two 10-micron curls were cut from a formalin-fixed parafin-embedded block for RNA extraction.

Normalized and transformed gene expression data were used to estimate the absolute fractions (ie, relative to all types of cells in the bulk tissue) of 10 major immune cell subsets derived from the literature where consensus could be reached across multiple algorithms (18) (total T cells, CD4+ T cells, CD8+ T cells, regulatory T cells, B cells, macrophages, neutrophils, mast cells, dendritic cells, and natural killer cells). The relative fractions of each immune cell type (ie, relative to all infiltrating immune cells) were calculated as the ratio of the absolute fraction to CD3+ cells. In a subset of patients with both pathological
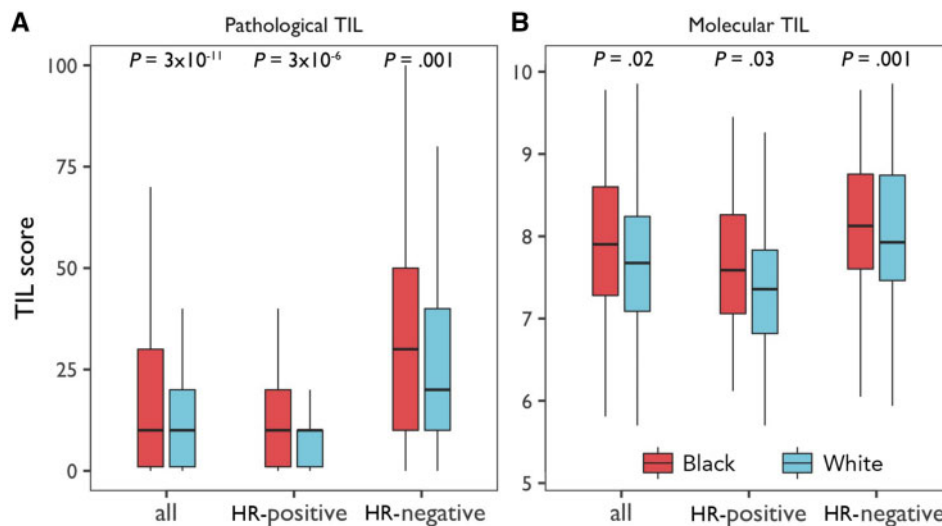
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Figure 1. Pathological and molecular estimates of tumor-infiltrating lymphocytes in Black and White breast cancer patients in the Women's Circle of Health Study. **A)** Boxplots of pathological tumor-infiltrating lymphocytes (TIL) scores by race, with and without stratification by tumor hormone receptor (HR) status. The bar in the middle of a box indicates the subgroup median, and the lower and upper edges indicate the first and third quartiles, respectively. The extended lines indicate the range in each subgroup. P values were derived from 2-sided Wilcoxon test between Black and White patients. **B)** Boxplots of molecular TIL scores estimated based on immune panel gene expression data, with and without stratification by tumor hormone receptor status.

and molecular TIL scores, the correlations between the 2 were moderate to strong (Supplementary Figure 1, available online; $r = 0.65; P < 2.2 \times 10^{-16}$).

Publicly Accessible Datasets

We used 2 publicly accessible datasets: TCGA breast cancer subset (n = 1080, including 180 Blacks and 714 Whites) (19) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC; n = 1904 Whites only) (20). TCGA was used as a validation cohort for racial differences in immune infiltrates identified in WCHS, and TCGA and METABRIC were used for survival analysis of tumor immune phenotypes. In addition, genomic estimates of immune receptor repertoire were obtained from TCGA (21). Patient selection and inclusion of the studies are depicted in a CONSORT flow diagram (Supplementary Figure 2, available online).

Statistical Analysis

Comparisons of tumor-immune phenotypes between tumors from Black and White patients were conducted using Wilcoxon tests. Multivariable linear regression models were used to derive standardized residuals for race after controlling for hormone receptor status (estrogen receptor and progesterone receptor). Analyses of all-cause mortality with tumor immune phenotypes were conducted using Cox proportional hazards regression, with hazard ratios (HR) and 95% confidence intervals (CI) adjusted for clinical prognostic variables and the assumption of proportionality verified by time-independent Schoenfeld residuals. Analyses of disease-specific mortality were conducted by treating other causes of death as competing risk. The mean follow-up time (range) of TCGA, WCHS, and METABRIC was 27 (0-287) months, 72 (9-153) months, and 115 (0-355) months, respectively. All analyses were 2-sided and performed using R 3.6.1. Multiple comparison error was controlled for using the Bonferroni method, with a family-wise error rate of .05.

Results

Pathological TIL Scores

Among WCHS patients, TIL scores were higher in hormone receptor–negative than hormone receptor–positive tumors; no associations with HER2 status were found after adjusting for hormone receptor status (Supplementary Figure 3, available online). In comparisons by race overall and by hormone receptor subtype, tumors from Black women had higher pathological TIL scores than those from White women (all $P \leq .001$) (Figure 1, A), with similar associations noted in molecular estimates of TILs in a subset of the patients (all $P \leq .03$) (Figure 1, B).

Higher pathological TIL scores in Black patients in WCHS were associated with all-cause and disease-specific mortality (Supplementary Table 3, available online). Patients with lymphocyte-predominant breast cancer (TIL score ≥50%) had a statistically significantly lower hazard of all-cause mortality (HR = 0.38, 95% CI = 0.19 to 0.76), in comparison to those with lymphocyte-depleted breast cancer (TIL score <10%).

Molecular Estimates of Immune Infiltrates in Breast TME

Consistent with the results of pathological TIL assessment, no associations between HER2 status and the absolute or relative fractions of any immune cell subsets were found after adjusting for hormone receptor status (Supplementary Figure 4, available online). Thus, we relied on hormone receptor status to assess the tumor influences on immune estimates in TME, which is also supported by previous studies demonstrating 2 major etiological subtypes of breast cancer proximated by hormone receptor status (22). Hormone receptor–negative cancers had statistically significantly higher absolute fractions of all immune cell subsets than hormone receptor–positive cancers, except for mast cells, which differed in an opposite direction (Supplementary Figure 4, available online). In contrast, similar comparisons of the relative fractions of immune cells revealed no differences in any of the immune cells except mast cells.
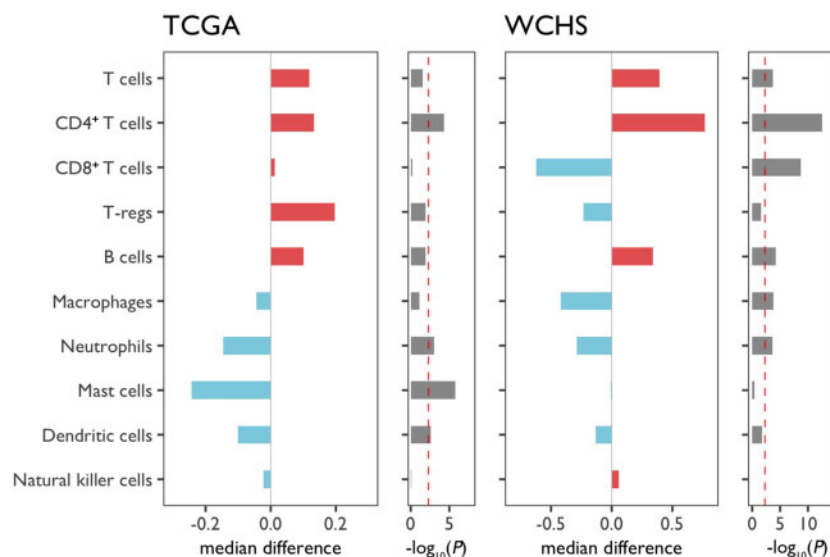
Figure 2. Racial differences in the relative fractions of immune cells between Black and White breast cancer patients. Relative fractions of the 10 major immune cell subsets plus CD4$^+$ to CD8$^+$ T-cell ratios were centered to an overall mean of 0 before subgroup medians were calculated for Whites and Blacks. The differences in subgroup medians are plotted in bar graphs, with **red** indicating higher immune cell estimates in Blacks, and **blue** indicating higher estimates in Whites. P values from 2-sided Wilcoxon test were log$_{10}$-transformed, negated, and plotted as bar graphs along the median differences. The **red reference line** indicates a cutoff of statistical significance level after adjusting for multiple testing [-log$_{10}$(0.05/11) = 2.3]. Patient populations from Women's Circle of Health Study (WCHS) and The Cancer Genome Atlas (TCGA) were included for cross-validation.

Because the relative fractions were not strongly confounded by tumor hormone receptor status, they were used in subsequent analyses unless otherwise specified.

As shown in Figure 2 and Supplementary Figure 5 (available online), in contrast to lower fractions of neutrophils and dendritic cells in Blacks, the most statistically significant and consistent racial differences in immune infiltrates were higher fractions of CD4$^+$ T cells in Black patients compared with White patients in both WCHS and TCGA. The racial differences in immune cell subsets remained after adjusting for or stratifying by tumor hormone receptor status (Supplementary Figures 6 and 7, available online). In a validation study of CD4$^+$ T cells using immunohistochemical (IHC) staining and WCHS tissue microarrays, there was a moderate-to-strong correlation between IHC and molecular scores of CD4$^+$ T cells ($r = 0.59$; $P < 2.2 \times 10^{-16}$); higher IHC scores of CD4 were also observed in Black than in White patients, although the differences were restricted to hormone receptor–negative cancer subtype (Supplementary Figure 8, available online).

Among CD4$^+$ T-cell subsets, the fraction of T follicular helper (T$_{FH}$) cells, as estimated by CIBERSORT algorithm (23), showed the most statistically significant difference between Black and White patients in WCHS and TCGA (Supplementary Figure 9, available online). In a recent pan-cancer TCGA analysis, it was reported that rs3366 in the 3' untranslated region (UTR) of *SIK1* was associated with the fraction of T$_{FH}$ cells present in bulk tumor tissues (24). We thus assessed the racial differences in the distribution of this variant. According to gnomAD data (25), the allele associated with a higher T$_{FH}$ fraction had a markedly higher frequency in Black than in White populations (0.45 vs 0.09). This corroborated our findings of higher fractions of T$_{FH}$ cells in Black than in White breast cancer patients.

Consistent with a stronger CD4$^+$ T-cell response, B-cell fractions and B-cell receptor (BCR) clonality were also higher in Black than White patients in TCGA, but not T-cell receptor clonality (Supplementary Figure 10, available online). Moderate-to-strong

correlations were noted between the fractions of CD4$^+$ T cells and B cells and BCR diversity and richness (Supplementary Figure 11, available online).

T-Cell Exhaustion Markers and "ExCD8-r" Signature

Because no consistent racial differences were seen in the CD8$^+$ T-cell fractions (Figure 2), the major immune cell subtype with antineoplastic activity, we examined the expression of 4 major inhibitory receptors (IRs: PD-1, LAG-3, CTLA-4 and TIGIT) and the PD-1 ligand. The co-expression of these markers represents cardinal features of T-cell exhaustion and serves as targets of immune checkpoint inhibitors (26). As expected, these IRs and the PD-1 ligand displayed a strong co-expression pattern (Supplementary Figure 12, available online). When the expression levels were analyzed relative to the absolute fraction of CD8$^+$ T cells, PD-1, LAG-3, and CTLA-4 were statistically significantly higher in breast tumors from Black patients in comparison with White patients in both WCHS and TCGA (all $P < .001$; Figure 3).

To develop an expression signature reflecting the balance between the cytotoxic and exhausted states of CD8$^+$ T cells, we leveraged the co-expression pattern of PD-1 and LAG-3 as hallmarks of T-cell exhaustion, demonstrated in previous studies from our group and others (27-29). Because Eomesodermin (Eomes) is a key transcription factor upregulated in terminally differentiated exhausted T cells (30), we defined the resultant signature "ExCD8-r" as the ratio of the aggregated expression of PD-1, LAG-3, and Eomes to the absolute CD8$^+$ T-cell fraction. The signature scores were statistically significantly higher in tumors from Black patients (all $P \leq .002$; Figure 3), regardless of hormone receptor status (Supplementary Figure 13, available online), suggesting that the CD8$^+$ T-cell responses in breast tumors from Black women were more likely to assume an exhausted state than in Whites. In analysis of a recently
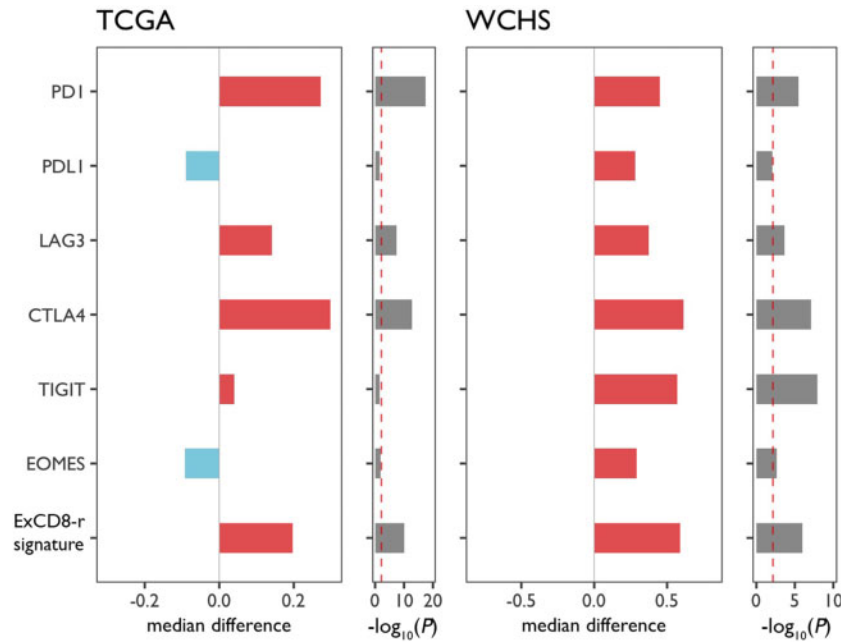
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Figure 3. Racial differences in T-cell exhaustion markers and ExCD8-r signature between Black and White breast cancer patients. The differences between Blacks and Whites in the expression levels of T-cell exhaustion markers relative to the absolute fractions of $CD8^+$ T cells, as well as the ExCD8-r signatures, are plotted in bar graphs, with **red** indicating higher immune cell estimates in Blacks, and **blue** indicating higher estimates in Whites. P values from Wilcoxon test are log10-transformed, negated, and plotted as bar graphs along the median differences. The **red reference line** indicates $\log_{10}(0.05/6) = 2.1$. Patient populations from Women's Circle of Health Study (WCHS) and The Cancer Genome Atlas (TCGA) were used for cross-validation. PD-1 = programmed cell death protein 1; PD-L1 = PD-1 ligand; LAG-3: lymphocyte-activation gene 3; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; TIGIT = T Cell Immunoreceptor With Ig And ITIM Domains.

developed T-cell exhaustion signature by Cai et al. (31), a strong correlation was noted with the signature we developed prior to adjusting for the absolute $CD8^+$ T-cell fraction ($r = 0.89$; $P < 2.2 \times 10^{-16}$); the signature scores by Cai et al. were also statistically significantly higher in tumors from Black vs White patients in WCHS (Supplementary Figure 14, available online).

Prognostic Value of ExCD8-r Signature

We next examined the relationships of the ExCD8-r signature with patient survival in WCHS, TCGA, and METABRIC with all races combined because of limited sample size for race-stratified analysis. A higher ExCD8-r signature was consistently associated with poorer all-cause mortality (Figure 4) and disease-specific mortality (Supplementary Figure 14, available online). The associations remained statistically significant after adjusting for age and clinical prognostic factors (Supplementary Table 2, available online, for all-cause mortality, and Supplementary Table 3, available online, for disease-specific mortality). Further adjusting for other immune cell subsets in the models had no substantial effects. Upon stratification by hormone receptor status, the prognostic value of ExCD8-r signature was limited to hormone receptor–positive breast cancer and not statistically significant in hormone receptor–negative cancer (Figure 4; Supplementary Tables 2 and 3, available online).

Because high absolute fractions of $CD8^+$ T cells have been consistently associated with better prognosis among hormone receptor–negative breast cancer patients (32), we sought to determine the prognostic value of ExCD8-r signature in the context of $CD8^+$ abundance. Notably, the absolute fractions of $CD8^+$ T cells were statistically significant only in hormone receptor–negative

patients in METABRIC but not in WCHS or TCGA, possibly because of limited sample size. In METABRIC, when $CD8^+$ T-cell fractions were combined with the ExCD8-r signature, patients classified as $CD8^{low}ExCD8-r^{high}$ had the highest all-cause mortality and disease-specific mortality; although unexpectedly, those classified as $CD8^{high}ExCD8-r^{high}$, instead of $CD8^{high}ExCD8-r^{low}$, had the lowest mortality (Supplementary Figure 15 and Supplementary Table 4, available online).

Lastly, we compared the proportions of the 4 subgroups defined by the combination of the absolute fractions of $CD8^+$ T cells and the ExCD8-r signature between Black and White patients. As shown in Figure 5, in both WCHS and TCGA, a $CD8^{low}ExCD8-r^{high}$ profile was the most common subgroup in Black patients, in contrast to the $CD8^{high}ExCD8-r^{low}$ profile being the most prevalent in White patients. Even among those with high $CD8^+$ T-cell fractions, Black patients were still more likely than White patients to have tumors with $CD8^{high}ExCD8-r^{high}$ features. Similar findings were observed when stratified by tumor hormone receptor status (Supplementary Figure 16, available online).

Discussion

Our findings of stronger overall immune response in breast tumors from Black women compared with White women are consistent with results from a prior TCGA analysis showing that African ancestry was associated with a higher leukocyte fraction in breast tumors (21), as well as those from a study in colorectal cancer, showing a stronger lymphocytic reaction in Black patients (33). As Black individuals tend to exhibit stronger inflammation-related systemic immunity (8-10), these data together suggest that it may give rise to stronger immune responses in the TME among Black women with breast cancer.
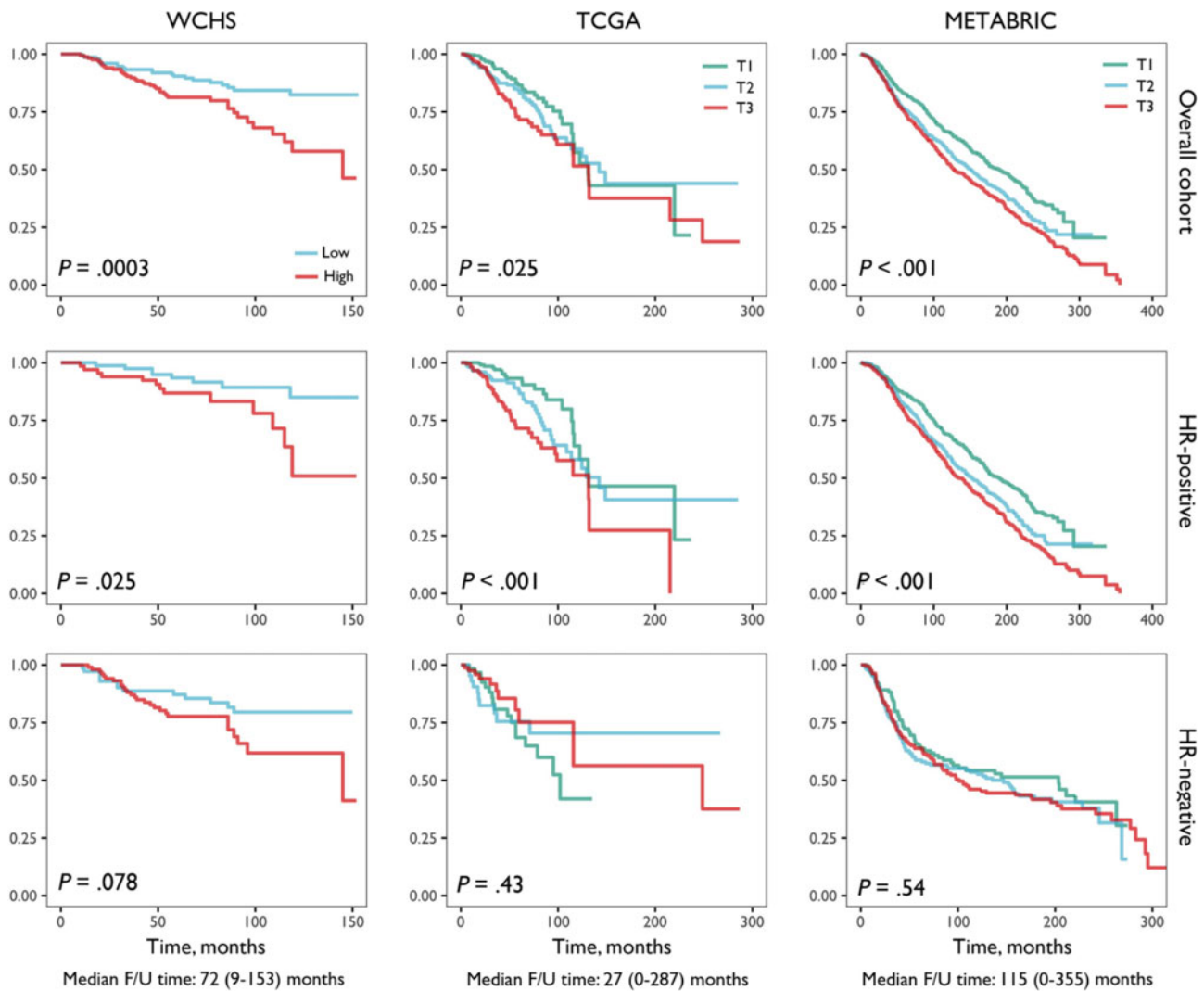
Figure 4. Kaplan-Meir survival curves of all-cause mortality by the levels of ExCD8-r signature. Kaplan-Meier survival curves of all-cause mortality by the levels of ExCD8-r signature are plotted for Women's Circle of Health Study (WCHS), The Cancer Genome Atlas (TCGA), and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) datasets, with and without stratification by tumor hormone receptor (HR) status. The signature levels in WCHS were categorized into binary based on the median because of limited sample size and categorized into thirds in TCGA and METABRIC datasets with large sample sizes. P values from log-rank test are displayed within the plots. The medians and ranges of the follow-up (F/U) time are shown at the bottom. The analyses were conducted with all races combined because of limited sample size of Black patients in the cohorts.

Our data support the notion that the composition and quality of immune infiltrates may be as important as their absolute presence in the TME. Black patients have tumor immune reactions shifted toward humoral immunity characterized by higher levels of $CD4^+$ T cells, T_{FH} cells, B cells, and BCR clonality. Although the antineoplastic activity of humoral immunity has been less well understood than cellular immunity, several recent studies have demonstrated the importance of T_{FH} cells and B cells in immunotherapy (34-37). Moreover, Black patients also exhibited a T-cell response of exhaustion features associated with poor survival, possibly because of diminished effector cytokine production and cytolytic activity (26). Thus, it may be the higher proportion of the T-cell exhaustion feature among Black patients that accounts for the seeming contradiction of poorer survival outcomes, despite the stronger overall immune presence of TILs in the TME.

The greater presence of exhausted immune phenotypes in tumors from Black women is consistent with the premise that a more active and prolonged inflammatory immune response in individuals of African descent, shaped over millennia in tropical Africa, could be related to more aggressive breast cancer (7,38). Host immunity is among the biologic mechanisms most frequently subject to natural selection (39,40) driven by infectious pathogens, a major environmental force in recent human evolutionary history (41). Because tropical regions in Africa are rich in pathogenic agents, early populations likely benefited from a more active immune defense, and genetic variants that enhance immune responses were likely positively selected. Indeed, allele frequencies of immune genes often display large, and sometimes extreme, racial differences (42,43). A potential approach to further investigate this hypothesis is to identify germline genetic variants in association with tumor immunophenotypes in racially diverse populations, ideally through genome-wide methods. Probably more than a coincidence, the only genome-wide significant association identified in a recent study of tumor immunophenotypes was between a variant in
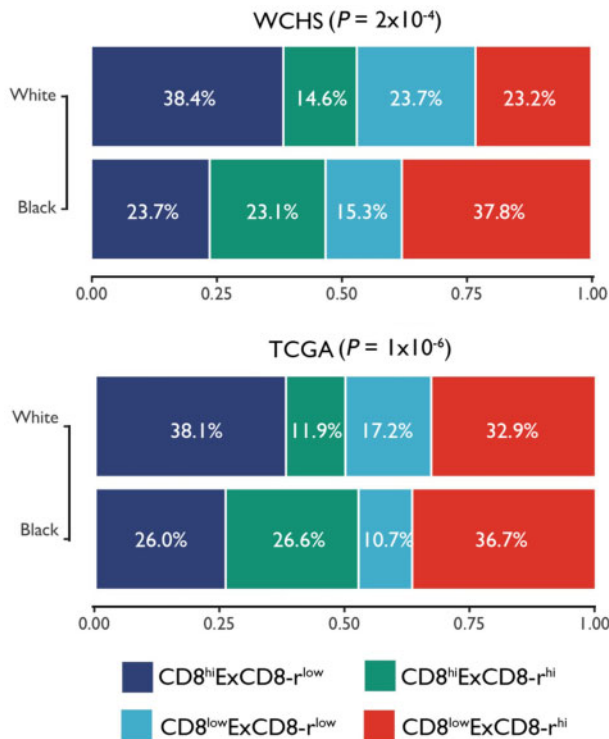
Figure 5. Breast cancer patient subgroups defined by the combination of the absolute CD8$^+$ T-cell fractions and the ExCD8-r signature in Blacks and Whites. Stacked bar graphs of the proportions of the 4 patient subgroups were defined on the basis of the combination of the absolute fractions of CD8$^+$ T cells and the ExCD8-r signature in Black and White breast cancer patients. The bar height of each subgroup corresponds to the percentage of that group within the racial group. P values from χ^2 test between subgroup and race are displayed for Women's Circle of Health Study (WCHS) and The Cancer Genome Atlas (TCGA) datasets.

SIK and T$_{FH}$ cells (24), which happened to be the most statistically significantly differentially occurring CD4$^+$ T-cell subset found in our study, and the variant has a much higher allele frequency in Blacks than in Whites. Given the limited sample size of our study, a genome-wide study of genetic variations is out of scope, but future studies in this area are warranted.

The literature indicates that hormone receptor–negative breast cancers are more immunologically "hot" than hormone receptor–positive tumors (44,45), and our data support that premise. Interestingly, the ExCD8-r signature was prognostic only among hormone receptor–positive but not hormone receptor–negative cancers. A new study using single cell proteomics also revealed CD8$^+$ T-cell exhaustion in a subset of hormone receptor–positive breast cancers characterized by increased PD-1 and IR co-expression (46). In another study of patients with estrogen receptor–positive cancer, expression feature of CD8$^+$ PD-1$^+$/CTLA-4$^+$ predicted response to immunotherapy (47). These data suggest that even among the immunologically "cold" hormone receptor–positive breast cancers, tumor immune response is relevant to patient survival and could potentially be targeted for immunotherapy, which is currently being evaluated in clinical trials. The finding may also have relevance to breast cancer health disparities, because some studies reported that the most persistent Black–White differences in breast cancer survival occurred within hormone receptor–positive cancers (48).

Our findings of distinct tumor immune responses in Black breast cancer patients may have clinical implications. Immune checkpoint inhibitors target the inhibitory receptors expressed on T cells, and their corresponding ligands on tumor or stromal populations such as myeloid cells, to reinvigorate the exhausted effector CD8$^+$ T cells. The apparently stronger but more exhausted lymphocytic state in Black patients implies that a higher response rate to checkpoint inhibitors might be expected. Further, the stronger B-cell response in Black patients and the newly discovered role of tumor-infiltrating B cells in regulating response to immunotherapy provide further support this postulation. To our knowledge, however, few clinical trials on immune checkpoint inhibitors have reported race-specific outcome data. Enhanced recruitment of racial and ethnic minorities into clinical trials is warranted to close the gaps in cancer disparities and to ensure that all groups of patients will benefit from advances in cancer therapeutics (49).

In summary, we found statistically significant and consistent racial differences in immune infiltrates in the breast TME, in particular, a CD8$^+$ T-cell response shifted toward an exhausted state in Black patients. These findings may explain the contradiction of a strong immune presence in the breast TME of Black patients, yet poorer survival, providing a new immunobiological perspective to underlying causes of breast cancer racial disparities.

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Notes

SY, LY; Supervision: KT, TK, CBA; Funding acquisition: CBA; Project administration: SY, KT, CBA.

Data Availability

The tumor gene expression data from the NanoString panel were deposited into Gene Expression Omnibus (GEO) database for public access (GSE163418).

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