

Racial/Ethnic Differences Among Tumor Infiltrating Lymphocytes in Breast Cancer Tumors

Surbhi Bansil

University of Hawai'i at Manoa John A Burns School of Medicine

Anthony Silva

University of Hawai'i at Manoa John A Burns School of Medicine

Alana Taniguchi

HRP: Hawaii Residency Programs Inc

Christina Wiedmer

HRP: Hawaii Residency Programs Inc

Mayumi Fernandez

University of Hawai'i at Manoa John A Burns School of Medicine

Ian Pagano

UH Cancer Center: University of Hawai'i Cancer Center

Koah Vierkoetter

Queen's Medical Center

Jeffrey Killeen

Kapi'olani Medical Center for Women and Children

Jami Fukui (✉ jfukui@cc.hawaii.edu)

University of Hawai'i Cancer Center <https://orcid.org/0000-0002-0248-266X>

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Abstract

Purpose

Tumor infiltrating lymphocytes (TILs) have emerged as a predictor of cancer treatment response and patient outcomes, including for breast cancer. Current studies investigating racial/ethnic differences in TILs and immune profiles in breast cancer offer varying results. Our study hopes to address the paucity of data in breast cancer tumor microenvironment from different racial/ethnic groups not well represented in the literature.

Methods

We reviewed 183 cases of women diagnosed with early stage breast cancer who received neoadjuvant treatment at two large health systems in Hawaii between 2008 and 2020. We evaluated clinical and demographic information including: age at diagnosis, race/ethnicity, tumor stage, tumor subtype according to ER, PR, and HER2 receptor status and compared them with obtaining a pathologic complete response (pCR) and amount of stromal TILs (sTILs).

Results

We found a significantly greater amount of sTILs in Asians (37.7%, $p=0.01$) and Native Hawaiian/Pacific Islander (NHPI) (37.2%, $p=0.02$) patients compared to White patients on multivariate analysis. We found no significant differences in pCR among the different racial/ethnic groups.

Conclusions

Racial/ethnic differences in the amount of sTILs in breast cancer tumors suggest that higher sTIL percentages alone do not predict for pCR. Increases in sTILs in Asian and NHPI patients suggest differences in immune cell profiles in the breast tumor microenvironment. This may in part contribute to known outcome disparities in these populations.

Introduction

The tumor microenvironment, specifically tumor infiltrating lymphocytes (TILs) in breast cancer, have been gaining more attention. TILs incorporate a heterogeneous composition of T-cells, B-cells, and other lymphocytes, and it is an emerging biomarker that is both predictive of cancer treatment response and prognostic of cancer outcomes [1]. Certain breast cancer subtypes—triple negative (TN, ER-/PR-/HER2-) and HER2+—which are known to have higher stromal TIL (sTIL) amounts, have also been associated with improved prognosis and response to chemotherapy [2] which can aid clinicians in predicting response to neoadjuvant chemotherapy. Specific TILs, namely CD8+ T cells, are associated with an increase in obtaining a pathologic complete response (pCR) after neoadjuvant therapy, regardless of breast cancer subtype [3].

Differences in TILs among various racial/ethnic groups have been evaluated. The Women's Circle of Health Study examined differences in TILs, particularly CD8+ T cells, in breast tumors between Black and White women and found that Black women with TN breast cancer and high CD8+ T cell density were found to have better overall survival than patients with low CD8+ T cell density [4]. Another study in HER2+ breast tumors showed the presence of CD8+ T cells was associated with a decrease in mortality [5]. Chen et al, examined gene expression microarray data of Asian and White patients with breast cancer, and found Asians to have significantly higher TILs than White patients, particularly in patients with breast cancer of luminal B and HER2+ subtypes [6].

We examined sTILs in early stage breast tumors who had received neoadjuvant treatment from two major health systems in Hawaii from 2008-2020. Our study hopes to address the paucity of data in breast cancer tumor microenvironment from different racial/ethnic groups not well represented in the literature.

Methods

This study evaluated 183 cases of early stage breast cancer who received neoadjuvant treatment from two large health systems from 2008-2020. A retrospective chart review was performed along with pathological evaluation from core biopsies and subsequent surgical excisions. sTILs were determined according to recommendations proposed by the International Immuno-Oncology Biomarker Working Group in 2017, separating the percent of stromal and intratumoral TILs [7,8]. Diagnostic core biopsies stained with hematoxylin and eosin were evaluated for stromal lymphocyte infiltration. Areas evaluated include central tumor stroma and stroma at the invasive margin. Tumor cell areas, areas of necrosis and scarring were not included. Lymphocytes and plasma cells were included while neutrophils were excluded. Cases were reported as "percent stromal lymphocytes".

A clinical chart review was performed on the neoadjuvant breast cancer cases and included demographic and clinical information: age at diagnosis, self-reported ethnicity/race, tumor subtype as well as treatment history: neoadjuvant/adjvant therapies, including chemotherapy, HER2 directed therapy, endocrine therapy, surgery, radiation. Patient charts were also reviewed for recurrence of breast cancer and death.

This study was reviewed and approved by the Hawaii Pacific Health and Queens Medical Center Institutional Review Boards for human subjects research. Statistical analysis was performed using the SAS 9.4 (SAS Institute Inc., Cary, NC) software. The REG procedure applied linear regression analyses on the continuous TILs (percentage tumor infiltrating lymphocytes) outcome. The predictor variables were race, age, subtype and health system. For the HPH subset analysis the variables included were: race, age, BMI, stage, chemotherapy, subtype and pCR. We ran both univariable (unadjusted) and multivariable (adjusted for other predictors) models.

Results

A total of 183 cases of early stage breast cancer from patients who received neoadjuvant treatment were evaluated. The most commonly represented ethnicity was Asian with 72 cases (39.3%), followed by Native Hawaiian/Pacific Islander (NHPI) with 53 cases (29%), White with 48 cases (26.2%), and Other with 10 cases (5.5%) (Table1). The most common subtype was ER-/PR-/HER2- with 62 cases (33.9%), followed by ER-/PR-/HER2+ with 56 cases (30.6%), ER+ or PR+/HER2+ with 50 cases (27.3%), and ER+ or PR+/HER2- with 15 cases (8.2%). The ethnicity with the most predominant proportion of cases with a pCR was Other with 5 cases (50.0%), followed by NHPI with 26 cases (49.1%), Asian with 29 cases (40.3%), and White with 18 cases (37.5%) (Table 1).

Table 1 pCR according to Patient Race, Age and Subtype

Variable		N (%)	pCR N (%)
Race	Asian	72 (39.3)	29 (40.3)
	NHPI	53 (29)	26 (49.1)
	White	48 (26.2)	18 (37.5)
	Other	10 (5.5)	5 (50)
Age	30-39	19 (10.4)	12 (63.1)
	40-49	34 (18.6)	13 (38.2)
	50-59	46 (25.1)	23 (50)
	60-69	53 (29)	19 (35.8)
	70+	31 (16.9)	11 (35.5)
Subtype	ER-/PR-/HER2-	62 (33.9)	19 (30.6)
	ER+ or PR+/HER2-	15 (8.2)	2 (13.3)
	ER-/PR-/HER2+	56 (30.6)	37 (66.1)
	ER+ or PR+/HER2+	50 (27.3)	20 (40)

The percentage of sTILs in breast cancer tumors of all patients based on age at diagnosis, race and breast cancer subtype were evaluated. On univariable analysis, we found significantly greater percentages of sTILs among women who identified as Asian, NHPI and Other (33.4%, 33.7% and 40.5%, $p=0.04$, $p=0.05$ and $p=0.04$ respectively) (Table 2). On multivariable analysis, this remained significant for Asian and NHPI only (37.7% and 37.2%, $p=0.01$ and $p=0.02$ respectively) (Table 2). On univariable analysis, significantly lesser percentages of sTILs were seen among women between the ages of 60-69 years, however on multivariable analysis there were no significant differences found according to patient age (Table 2). With both univariable and multivariable analysis, there were significantly greater percentages of sTILs found among women who had ER-/PR-/HER2+ or TN breast cancer subtypes (Table 2).

Table 2 Percent sTILs for all breast cancer patients receiving neoadjuvant treatment

Variable		N	%	UNIVARIABLE				MULTIVARIABLE			
				Mean	LCL	UCL	P	Mean	LCL	UCL	P
Race	Asian	72	39.3	33.4	28.0	39.3	.04	33.6	28.2	39.5	.01
	NHPI	53	29.0	33.7	27.4	40.6	.05	34.3	28.0	41.2	.01
	White	48	26.2	23.6	17.3	31.3		22.0	16.1	29.4	
	Other	10	5.5	40.5	26.5	56.2	.04	35.1	22.3	50.4	.08
Age	30-39	19	10.4	41.1	30.5	52.5		35.6	25.1	47.8	
	40-49	34	18.6	32.0	24.3	40.8	.20	33.5	25.6	42.4	.76
	50-59	46	25.1	33.3	26.6	40.8	.25	33.0	26.5	40.4	.70
	60-69	53	29.0	28.1	22.0	35.3	.05	27.7	21.7	34.6	.22
	70+	31	16.9	27.1	19.3	36.7	.05	26.0	18.7	34.9	.17
Subtype	ER-/PR-/HER2-	62	33.9	34.8	29.0	41.1		35.3	29.3	41.7	
	ER+ or PR+/HER2-	15	8.2	25.0	14.7	39.2	.20	19.4	10.5	33.3	.04
	ER-/PR-/HER2+	56	30.6	36.3	30.2	42.9	.73	35.7	29.6	42.3	.92
	ER+ or PR+/HER2+	50	27.3	23.3	17.2	30.8	.02	23.7	17.8	30.9	.02

We evaluated additional variables from 79 cases including: BMI at diagnosis, stage, treatment regimen and pCR (Table 3). On univariable analysis, patients who obtained a pCR had a significantly higher sTIL percent (40.6% vs 28.6%, p=0.04) but this was not found on multivariable analysis (Table 3). Additionally, there were statistically significant race/ethnic differences in sTILs on both univariable and multivariable analysis where NHPI and Asian patients had significantly greater percentages of sTILs in their tumors compared to White patients (38.2%, 34.3% vs 20.7%, p=0.01 and p=0.05 respectively) (Table 3).

Table 3 Percent sTILs on subset of neoadjuvant cases with additional variables

Variable		N	%	UNIVARIABLE				MULTIVARIABLE			
				Mean	LCL	UCL	P	Mean	LCL	UCL	P
Race	Asian	22	27.8	33.9	24.4	44.8	.20	34.3	24.7	45.3	.05
	NHPI	25	31.6	41.0	31.8	50.9	.02	38.2	28.1	49.5	.01
	White	25	31.6	24.4	16.1	35.4		20.7	13.3	30.7	
	Other	7	8.9	44.3	27.4	62.6	.05	39.5	22.1	60.0	.06
Age	30-39	10	12.7	35.0	21.5	51.4		27.4	14.3	46.0	
	40-49	14	17.7	40.0	28.0	53.4	.63	50.1	35.3	64.9	.06
	50-59	25	31.6	40.0	30.8	50.0	.59	37.0	28.1	46.9	.32
	60-69	21	26.6	22.4	13.6	34.6	.18	19.4	11.5	30.9	.39
	70+	9	11.4	34.4	20.4	51.8	.96	24.9	13.6	40.9	.82
BMI	< 25	38	48.1	31.7	24.2	40.4		28.3	20.7	37.3	
	25-30	17	21.5	35.0	23.9	47.9	.66	30.7	20.1	43.8	.75
	> 30	24	30.4	37.1	27.5	47.8	.42	36.1	26.6	46.9	.25
Stage	1A	9	11.4	30.6	16.9	48.8		23.8	12.0	41.7	
	1B	13	16.5	31.9	20.0	46.8	.90	28.1	16.4	43.9	.69
	2A	23	29.1	39.2	29.5	49.8	.40	37.9	27.0	50.2	.15
	2B	17	21.5	38.2	27.2	50.7	.47	37.9	25.5	52.1	.21
	3A	7	8.9	19.3	6.7	44.1	.40	12.6	2.7	42.8	.39
	3B	10	12.7	31.5	18.3	48.6	.93	33.4	18.7	52.3	.44
Treatment	ACT	22	27.8	33.0	23.3	44.3	.66	41.1	23.7	60.9	.39
	Letrozole	4	5.1	16.2	3.0	54.7	.26	14.6	3.0	48.3	.06
	TC	15	19.0	36.7	25.0	50.2		50.6	34.2	66.9	
	TCHP	25	31.6	34.4	25.3	45.0	.79	21.3	11.1	37.0	.03
	THP	13	16.5	37.7	25.1	52.1	.92	23.2	11.9	40.4	.05
Subtype	ER-/PR-/HER2-	21	26.6	36.4	26.5	47.7		24.9	11.9	44.8	
	ER+ or PR+/HER2-	15	19.0	25.0	14.4	39.7	.20	19.0	8.9	36.0	.51
	ER-/PR-/HER2+	28	35.4	39.5	30.6	49.1	.67	44.5	29.2	61.0	.21
	ER+ or PR+/HER2+	15	19.0	29.7	18.6	43.7	.43	31.3	18.1	48.4	.64
pCR	no	43	54.4	28.6	21.7	36.7		28.6	21.0	37.7	
	yes	36	45.6	40.6	32.7	48.9	.04	34.2	26.1	43.4	.39

Percentage of pCR in breast cancer tumors of all patients based on age at diagnosis, race, and breast cancer subtype were evaluated (Table 4). In both univariable and multivariable analyses, we did not see significant differences in pCR among racial/ethnic groups studied (Asian, NHPI and Other) compared to White women. On univariable analysis, there was a significantly less likelihood of a pCR among women between the ages of 60-69 years compared to other age groups; however there were no significant differences found among all ages on multivariable analysis. In both univariable and multivariable, there was a significantly higher likelihood of obtaining a pCR among women who had ER-/PR-/HER2+ breast cancer (3.02 and 3.06 vs 0.6 and 0.59, p=0.01 and p=0.02 respectively) compared to ER+/PR+/HER2- breast cancer (Table 4).

Table 4 Pathologic complete response (pCR) for all breast cancer patients

Variable	N	%	UNIVARIABLE				MULTIVARIABLE				
			Mean	LCL	UCL	P	Mean	LCL	UCL	P	
Race	Asian	72	39.3	33.4	28.0	39.3	.04	33.6	28.2	39.5	.01
	NHPI	53	29.0	33.7	27.4	40.6	.05	34.3	28.0	41.2	.01
	White	48	26.2	23.6	17.3	31.3		22.0	16.1	29.4	
	Other	10	5.5	40.5	26.5	56.2	.04	35.1	22.3	50.4	.08
Age	30-39	19	10.4	41.1	30.5	52.5		35.6	25.1	47.8	
	40-49	34	18.6	32.0	24.3	40.8	.20	33.5	25.6	42.4	.76
	50-59	46	25.1	33.3	26.6	40.8	.25	33.0	26.5	40.4	.70
	60-69	53	29.0	28.1	22.0	35.3	.05	27.7	21.7	34.6	.22
	70+	31	16.9	27.1	19.3	36.7	.05	26.0	18.7	34.9	.17
Subtype	ER-/PR-/HER2-	62	33.9	34.8	29.0	41.1		35.3	29.3	41.7	
	ER+ or PR+/HER2-	15	8.2	25.0	14.7	39.2	.20	19.4	10.5	33.3	.04
	ER-/PR-/HER2+	56	30.6	36.3	30.2	42.9	.73	35.7	29.6	42.3	.92
	ER+ or PR+/HER2+	50	27.3	23.3	17.2	30.8	.02	23.7	17.8	30.9	.02

Discussion

Our findings showed significantly higher percentages of sTILs in tumors of Asians and NHPIs compared to those of White breast cancer patients. We however did not see any significant difference in pCR among these racial/ethnic groups. This study addresses a gap in the literature by examining differences in sTILs among understudied racial/ethnic groups, particularly Native Hawaiian/Pacific Islander (NHPI) and Asian women. These findings expand upon a subset of this data that was previously reported by our group showing significantly higher percentages of sTILs in Asian, NHPI, and Other women compared to White women [9]. Chen et al. showed Asian patients were found to have significantly higher amounts of tumor-infiltrating immune cells compared to White patients, particularly CD4+ T cells and in Luminal B and HER2+ tumors [6]. Our results may suggest differences in immune cell profiles of TILs in Asians and NHPI tumors that may vary from those in Whites, which should be further evaluated and characterized. Jiang et al. showed significantly higher overall survival in patients with breast cancer tumors enriched with specific TILs including: B cells, NK cells, CD8+ T cells, CD4+ activated T cells, and low $\gamma\delta$ T cells, neutrophils, and activated mast cells [10]. Additional data show that TIL immune profiles high in M2 macrophages may also be associated with poorer clinical outcomes while those high in CD4+ Th1 helper T cells may be more strongly associated with improved survival [6, 11]. Higher percentages of sTILs in

tumors of Asians and NHPI may reflect increased tumor infiltration of immune cells that have weaker associations with immunological response, pCR, and patient clinical outcomes/prognosis.

Current studies regarding differences in TILs and their contributions to patient prognosis among different racial/ethnic groups have shown inconsistent results. O'Meara et al. showed that TILs amount and immune gene expressions are not significantly different between Whites and Blacks with TN breast cancer [12]. In contrast, Abdou et al. found breast cancer tumors from Black patients had higher CD8+ T cell tumor infiltrating densities than in White patients [4]. In previous studies, Black breast cancer patients had a higher amount of macrophage infiltrating tumors with a high number of CD163+ macrophages and increased macrophage proliferation [13]. Carrio et al. showed CD68+ macrophages were significantly more abundant in tumors from Black and Latina patients but showed no differences in overall survival when compared to White patients [14]. Another study found higher levels of Proliferating Cell Nuclear Antigen positive (PCNA+) tumor-associated macrophages and shorter disease-free survival in Latina patients compared to White patients [15]. Given the poor prognosis seen among the NHPI breast cancer patients [16], characterizing these TILs is an important future step to better understand how the tumor microenvironment may contribute to these disparities.

Some studies have also noticed differences in TIL amount when stratified for variables other than patient race. In Black women, CD8+ T cell density was seen to be higher in patients who were younger or with hormone-negative high grade tumors [4]. However, in western Kenyan patients, immune cell infiltration density was significantly associated with increased tumor proliferation index but not significantly correlated with molecular subtype or tumor grade [17]. In another study, no differences in sTIL percentages were observed to be associated with patient age or BMI at diagnosis or tumor stage [9].

Similarly, the literature shows inconsistencies with regards to relationships between TIL count/density and grade/stage of breast tumors across racial groups. O'Meara et al. showed no significant difference in TIL amount between Black and White breast cancer patients [12]. However, Abdou et al. showed higher TILs amount can be found in tumors of younger patients, hormone-negative tumors, and high grade tumors in both Black and White patients, irrespective of race [4].

We saw significantly lower rates of pCR among women between the ages of 60-69 years compared to other age groups. Although we did not see differences in sTILs according to age in our study, prior data show lower percentages of sTILs among women in this patient age. There are known lower TIL percentages in tumors of older patients [4]. Our findings support data showing older cancer patients receiving treatment are less likely to have a pathologic complete response irrespective of race/ethnicity. In our subset of patients being analyzed for additional variables, we did not see any differences in sTILs according to BMI at diagnosis, stage or treatment regimen.

Limitations to this study include incomplete patient medical records with variable neoadjuvant treatment data. Although we were able to obtain a subset of cases with complete medical data, we did not see differences when accounting for those additional variables. Although the pathologic TILs evaluations were performed according to the International Immuno-Oncology Biomarker Working Group, the cases

were evaluated by two sets of different pathologists, introducing possible variability. This approach however, provides an avenue to broadly incorporate TILs measurement in pathology reports. Our medical center has already routinely reported on sTILs percent and volume for all neoadjuvant TN and HER2+ breast cancer cases. Finally, neoadjuvant cases prior to 2015 are sparse as TN and HER2+ historic treatment strategies did not routinely focus on the neoadjuvant approach.

Conclusions

Racial/ethnic differences in the amount of sTILs in breast cancer tumors suggest that higher sTIL percentages alone do not predict for pCR. Increases in sTILs in Asian and NHPI patients suggest differences in immune cell profiles in the breast tumor microenvironment. This may in part contribute to known outcome disparities in these populations.

Declarations

Author's contributions

All authors made substantial contributions to conception and design, analysis and interpretation of data, and critical review of the manuscript. JF conceived of the study, coordinated the data acquisition and analysis, generated tables and figures and helped to draft the manuscript. IP contributed to the statistical methods, data analysis, generated tables and figures and helped to draft the manuscript. AS and SB contributed to the data analysis and helped to draft the manuscript. AT, KV, CW and MF contributed to the data acquisition and analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest/Competing interest

The authors declare that they have no competing interests.

Ethics approval and Consent to participate

The Institutional Review Boards at the University of Hawaii, Hawaii Pacific Health and Queens Medical Center approved this study. All aspects of the investigation complied with current rules for research involving Human Subjects.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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