Evidence of more highly activated anti-tumor immunity in Hispanic/Latinx patients with breast cancer and associated social determinants of health

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INTRODUCTION

Breast cancer (BC) is the leading cause of cancer-related death among women in the U.S.

Despite the increasing use of immune checkpoint inhibitors (ICIs), only some patients respond well to these treatments.

- **Breast tumors are highly immune-suppressed** and have mechanisms of intrinsic resistance.
  - **GOAL**: **Characterize important immune cell populations surrounding breast tumors** to target the innate immunosuppressive tumor microenvironment (TME) and overcome intrinsic resistance.

Hispanic/Latinx (H/L) patients with BC often are diagnosed younger, with larger tumors, often with more ER- subtypes.

- **Younger age at diagnosis**: 29% of H/L women diagnosed under 50, vs. 15% of Non-Hispanic White (NHW) women.
- **Larger tumors**: 45% of H/L patients have tumors >2.0 cm, vs. 38% NHW.
- **More ER-negative subtypes**: 18% H/L vs. 14% NHW.

H/L patients also experience differential incidence and survival, compared to NHW, largely linked to barriers and inequities linked to various social drivers of health (SDOH).

- **Insurance**: 17% of H/L individuals are uninsured.
- **Poverty**: H/L individuals are 1.5x more likely to live in poverty than NHW populations.
- **Healthcare access barriers**: H/L women frequently encounter discrimination in healthcare settings due to language differences, lack of culturally competent care, immigration status, etc.
  - **GOAL**: To understand differences in SDOH that affect H/L vs NHW women with BC, we must **clarify the social context in which NHW and H/L are located and identify SDOH that contribute most to their surrounding societal experience**.

BIG PICTURE: To address differences in outcomes in H/L vs NHW women with BC, **it is imperative to characterize their respective immune suppression profiles while simultaneously integrating pertinent SDOH**.

CLINICAL SIGNIFICANCE: Although standard clinical therapies have been promising, **a comprehensive understanding** of **both epigenetic and immunological factors** influencing breast cancer outcomes and anti-tumor immunity **can lead to providing personalized treatment options to improve outcomes in patients with breast cancer**.

Figure 1. Understanding social drivers of health in relation to the tumor microenvironment.

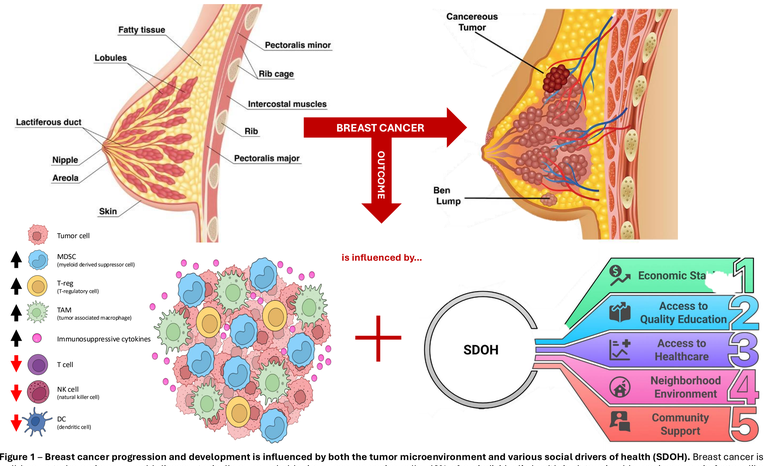


Figure 1 – Breast cancer progression and development is influenced by both the tumor microenvironment and various social drivers of health (SDOH). Breast cancer is well-known to be an immune-cold disease, typically surrounded by immunosuppressive cells. 40% of an individual's health is determined by socioeconomic factors like annual income and highest level of education.

HYPOTHESIS

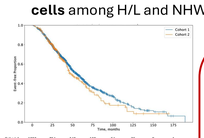
We hypothesize that **higher levels of social deprivation contribute to a more activated immunosuppressive tumor microenvironment** in H/L breast cancer patients compared to NHW patients, potentially contributing to disparities in clinical outcomes.

APPROACH

We utilized a **multi-dimensional approach** to investigate our hypothesis...

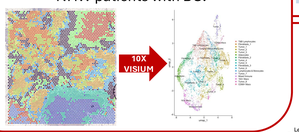
CLINICAL OUTCOMES

Determine whether there are **significant differences in circulating immunosuppressive cells** among H/L and NHW patients with BC.



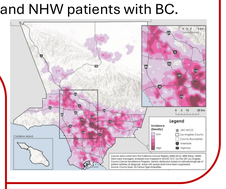
TUMOR MICROENVIRONMENT

Determine whether there are significant differences in the tumor microenvironment in solid tumor samples among H/L and NHW patients with BC.

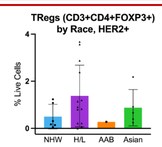


POPULATION DATA

Examine the **differences in incidence rate in LA County** among H/L and NHW patients with BC.

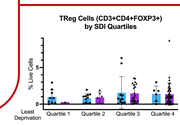


CIRCULATING IMMUNITY



Determine whether there are **significant differences in circulating immunosuppressive cells** among H/L and NHW patients with BC.

SOCIAL DEPRIVATION INDEX



Determine if **there is a differential presence in immunosuppressive cells with increasing social deprivation** among H/L and NHW patients with BC.

Figure 2. Multi-dimensional analysis of clinical outcomes in H/L vs. NHW patients with. BC in relation to immunosuppression and social context. We implemented a comprehensive framework assessing differences in clinical outcomes, tumor microenvironment, circulating immunity, population incidence, and social deprivation between Hispanic/Latinx (H/L) and Non-Hispanic White (NHW) patients with BC. Data integration included immune profiling, spatial transcriptomics (Visium), geographic incidence mapping, and social deprivation index (SDI) to evaluate immunosuppressive cell prevalence and associated social disparities.

RESULTS

H/L patients with BC, nationwide, exhibit lower event-free survival when compared to NHW patients.

Figure 3. H/L women with early-stage breast cancer have 6m shorter median event-free survival, while lung metastatic patients demonstrate 11.7m longer survival, than NHW.

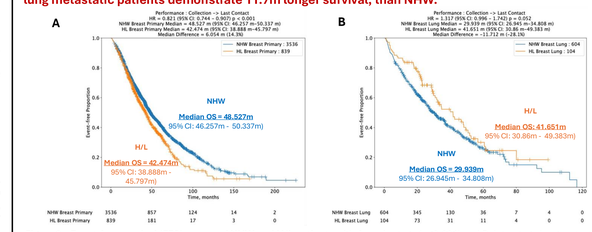


Figure 3 – Event-free survival (EFS) curves of NHW and H/L patients with **A.** early stage (**p<0.001**) and **B.** late-stage lung metastatic breast cancer (**p=0.052**). Data were generated by Caris Life Sciences integrating molecular profiling data (e.g., genomic, transcriptomic) from tumor samples with clinical outcomes data. Kaplan-Meier analysis was then used to plot EFS curves, and statistical tests were applied to assess differences between NHW and H/L patients.

Table 1. Immune scores in H/L and NHW primary breast tumors (all subtypes) show that H/L breast tumors were more immunosuppressive.*

	Median %		p/q value NHW vs HL	
	All NHW Primary	All HL Primary	p-value	q-value
IFNγ score	-0.34	-0.30	**<0.001**	0.003
T-Cell Inflamed Score	9.00	19.00	0.31	0.71
MAPK Activation Score	-0.96	-0.91	0.50	0.83

*Cancer data was from the Caris Life Sciences database. Retrospective investigation of next generation RNAseq analysis by Quantiseq was used to quantify the median % expression of predefined gene signatures in primary breast tumors of NHW and H/L patients.

Table 2. Immune cell subsets in H/L and NHW patients with early-stage disease and liver metastases (all subtypes)*

	Median %		p/q value NHW vs. HL		Median %		p/q value NHW vs. HL	
	All NHW Primary	All HL Primary	p-value	q-value	All NHW Liver	All HL Liver	p-value	q-value
B cell	5.31	5.02	0.10	0.46	4.87	5.04	0.15	0.75
Monocyte	0	0	0.86	0.96	0	0	0.40	0.88
Macrophage M1	2.77	2.73	0.67	0.90	2.43	2.51	0.58	0.93
Macrophage M2	4.4	3.98	**<0.0001**	**0.003**	4.73	4.60	0.46	0.90
Neutrophil	3.67	3.43	**0.04**	0.29	3.69	3.21	**0.008**	0.43
DC	2.63	2.69	0.50	0.83	2.68	2.77	0.58	0.93
NK cell	3.02	2.96	0.74	0.92	3.20	3.01	**0.03**	0.57
T cell CD4+	0	0	0.85	0.96	0	0	0.31	0.84
T cell CD8+	0.26	0.45	**<0.0001**	**0.0002**	0	0	0.36	0.86
Tregs	1.74	1.88	**0.004**	0.07	1.12	1.32	**0.02**	0.53

*Cancer data was from the Caris Life Sciences database. Retrospective investigation of next generation RNAseq analysis by Quantiseq was used to predict immune cell type expression in primary breast tumors and liver metastases of NHW and H/L patients.

Patients with BC in California primarily present with early-stage, HR+ disease.

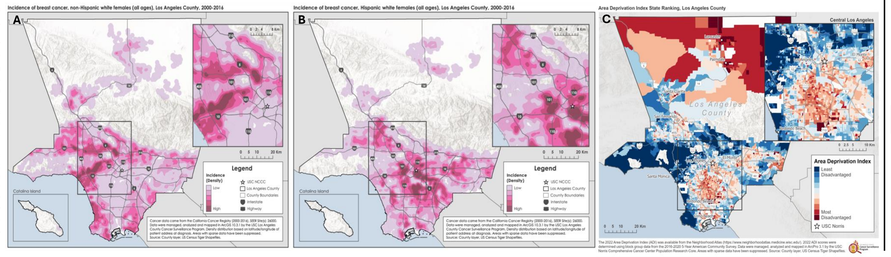
Table 3. Characteristics of patients with BC and respective tumors by age group in the California Cancer Registry, 2013-2022*

	Age at Diagnosis							
	<18yrs		18-49		50-64		65+	
	n=4,206		n=69,905		n=145,391		n=252,146	
	n	%	n	%	n	%	n	%
Stage at diagnosis								
Localized	1,207	1	27,428	15	58,417	33	90,945	51
Regional	595	1	15,851	18	29,332	33	42,859	48
Distant	1,809	2	11,902	11	29,120	28	60,793	59
missing= 101,390								
Insurance								
Uninsured	34	0	2,006	28	3,563	49	1,652	23
Private	1,801	1	45,131	24	88,282	46	55,801	29
Public	2,068	1	17,857	8	41,152	18	166,744	73
Unknown	303	1	4,911	11	12,394	27	27,949	61
Socioeconomic Status (SES)								
Lowest SES	1,893	1	24,095	18	45,591	33	64,536	47
Middle SES	1,312	1	23,725	15	50,908	31	87,509	54
Highest SES	1,001	1	22,085	13	48,892	28	100,101	58
Tumor Subtype								
HER2 negative (HER2-); equivocal	0	0	5,531	19	10,193	34	14,179	47
HER2 positive (HER2+)	0	0	1,358	27	2,051	40	1,682	33
Test ordered, results not in chart	0	0	39	19	84	42	79	39
Unknown	**	0	2,215	19	4,379	37	5,316	45
missing = 424,541								
Vital Status								
Alive	3,640	1	57,498	20	103,504	36	123,816	43
Died	566	0	12,407	7	41,887	23	126,330	70

*Cancer data was from the California Cancer Registry (2013-2022), SEER Site: 26000, all ages, diagnosed in Los Angeles County and analyzed with SAS 9.4 by the USC Norris Comprehensive Cancer Center Population research Core (analytic file version: Jul25epi; released: July 24, 2025). Sparse data (cell counts <10) are indicated by a double asterisk (**).

H/L patients in LA County show a higher incidence of breast cancer, while residing in more disadvantaged areas, compared to NHW patients.

Figure 4. Rates of breast cancer incidence in H/L and NHW patients in LA County. Area maps of showing age-adjusted incidence rate of breast cancer in A. NHW and **B.** H/L patients in Los Angeles (LA) County, CA (2000-2016). **C.** Area Deprivation Index (ADI) scores were determined using block group data from the 2016-2020 5-Year American Community survey from LA county residents. Scores were mapped in relation to LA County, CA.



RESULTS

Spatial immune profiling of H/L patients with early-stage, HR+HER2- breast cancer show significantly higher T-reg and lower CD8+ T-cell infiltration.

Figure 5. H/L patients with early-stage, HR+HER2- BC possess lower anti-tumor immune activating cells, and higher pro-immune activating cells in primary tumors.

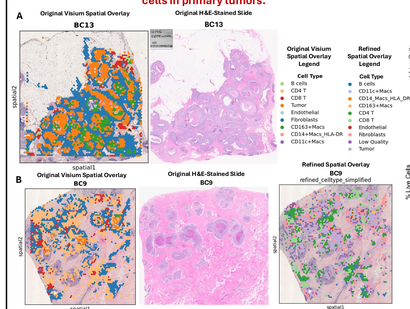
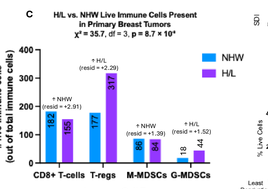


Figure 7 – Spatial immune profiling of primary breast tumors in NHW and H/L patients. **A.** Representative image of a primary breast tumor from an NHW patient. **B.** Representative image from a H/L patient. Images show spatial distribution of immune cells in relation to tumor cells analyzed using CITEgeist, a deconvolution algorithm developed at UPMC, to integrate protein expression (neighborhood protein stains) with gene transcripts, including: 1. Construction of local and global neighborhood matrices; 2. Superficial layer gene expression profiling; and 3. Selection of the top 25% of cells based on protein staining intensity and local neighborhood context. Initial overlays show color-coded dots representing immune cell types. Refined overlays display validated immune cells—filtered by matched protein and gene expression (≥1% threshold)—to ensure accuracy in immune cell identification. **C.** Bar chart of sum of number of live immune cells out of total immune cells of tissue collected from HR+HER2- H/L and NHW patients with primary breast tumors. H/L (n=5), 6695 total immune cells); NHW (n=9), 5810 total immune cells) patients with breast cancer. 5-10 unstained slides from 16 patients with HR+HER2- breast cancer, utilizing both archived and fresh primary breast tumor samples. Visium 10x technology was used for spatial transcriptomics and multi-parametric protein analysis. Analysis of gene expression was completed using Seurat, DESeq2, and Limma conducted in R. Chi-square test of independence was used to analyze immune cell type distributions between NHW and H/L. Chi-square statistic (χ^2): 35.70, df=3; **p<0.001**. Significance threshold: residuals > |2| indicate increasing contribution toward overall statistical significance.



H/L patients in our USC catchment demonstrate an enrichment of cells consistent with an immunosuppressive immune profile.

Figure 6. H/L patients (n=68) with BC trend towards increased exhausted CD8+ T cells, T-regs, G-MDSCs, and macrophages.

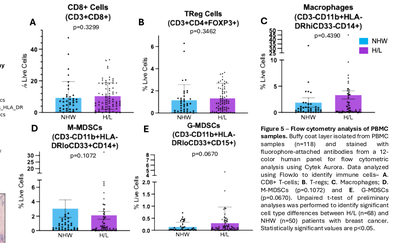


Figure 5 – Flow cytometry analysis of PBMC samples. Buffy coat layer isolated from PBMC samples (n=119) and stained with fluorophore-attached antibodies from a 12-color human panel for flow cytometric analysis using Cytek Aurora. Data analyzed using FlowJo to identify immune cells– **A.** CD8+ T-cells; **B.** T-regs, **C.** Macrophages; **D.** M-MDSCs (p=0.1072) and **E.** G-MDSCs (p=0.0670). Unpaired t-test of preliminary analyses was performed to identify significant cell type differences between H/L (n=68) and NHW (n=50) patients with breast cancer. Statistically significant values are p<0.05.

Figure 7. H/L patients with breast cancer experience greater deprivation; circulating T-regs and G-MDSCs increase with greater deprivation.

Figure 6 – Flow cytometry analysis of PBMC samples, overlayed with Social Deprivation Index (SDI) quartiles (n=118). SDI are developed by the American Census Bureau's American Community Survey for each ZIP Code and ranked quartile cutoffs reflect the distribution across the full population. SDI are used to estimate the average level of social determinants of health experienced in one's environment. Higher SDI quartile indicates higher social deprivation experienced. **A.** Average SDI values comparing NHW to H/L. Percentage of immune cells per SDI quartile were reported as follows– **B.** CD8+ T-cells; **C.** CD4+ T-cells; **D.** T-regs; **E.** M-MDSCs and **F.** G-MDSCs. ANOVA of preliminary analyses was performed to identify cell type differences between H/L and NHW patients with breast cancer. Statistically significant values are p<0.05.

CONCLUSIONS

Retrospective analysis of next generation sequencing suggests significant differences in survival between H/L and NHW patients with BC.

- H/L patients with early-stage disease demonstrate **shorter** median event-free survival.
- INF-gamma signature and PD-L1 expression, supporting trends towards immune activation in early-stage disease.

Circulating immune suppressor cells (Tregs and G-MDSCs) follow trends that are higher in H/L patients across BC subtypes.

Spatial immune profiling of early-stage tumors also shows a trend of greater T-regs and G-MDSCs, similarly observed in the circulating immunity data.

FUTURE DIRECTIONS

Circulating immunity–
- Expand numbers to evaluate significance of trends observed.
- Run prospective analyses on patients with full human flow panel to expand immune profile of patients with BC, including functional markers.

Social determinants of health–
- Identify and correlate SDOH from survey responses that contribute to varying SDIs experienced.
- Correlate SDOH to immunosuppressive environments – run concurrent analyses on patients with full human flow panel and SDOH surveys.

Tumor microenvironment–
- Expand analysis to examine possible interactions between tumor cells and surrounding immune cells.

General–
- Focus on evaluation of patients with HR+ BC first to ensure resources support cohort with highest chance of reaching power to detect differences.

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