Investigating pro-tumor immunity and social determinants of health to address outcome disparities in patients with breast cancer

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Keck Medicine of USC

INTRODUCTION

Breast cancer (BC) is the leading cause of cancer-related death among women in the U.S. Despite advances in receptor-specific therapies, survival outcomes remain unequal.

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.

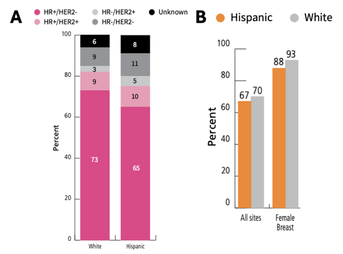

Figure 1 – Breast cancer (BC) clinical outcome disparities persist between Hispanic/Latinx (H/L) and Non-Hispanic White (NHW) women. A. Distribution of BC subtypes by race and ethnicity, US, 2017-2021 (Adapted from Breast Cancer Facts & Figures 2024-2025). HR = hormone receptor; HER2 = human epidermal growth factor receptor 2. White = NHW. Race is exclusive of Hispanic origin. Numbers may not sum to 100 due to rounding. **B. Five-year relative survival rates (%) in H/L and NHW women, US,** 2014-2020 (Adapted from Cancer Facts & Figures for Hispanic/Latino People 2024-2026). White = 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**: Identify specific adverse SDOH that alter tumor immune suppression to contribute to outcome disparities in patients with BC in LA County.

As immune checkpoint inhibitors (ICIs) emerge as promising therapies, therapeutic resistance remains a major barrier to durable remission in BC.

- **Breast tumors are highly immune-suppressed** and have mechanisms of intrinsic resistance due to the breast tumor microenvironment (TME) being populated with regulatory T-cells (T-regs), myeloid-derived suppressor cells (MDSCs), and other immunosuppressive cells.
- **GOAL**: **Characterize important immune cell populations surrounding breast tumors** to target the innate immunosuppressive tumor microenvironment (TME) and overcome intrinsic resistance.

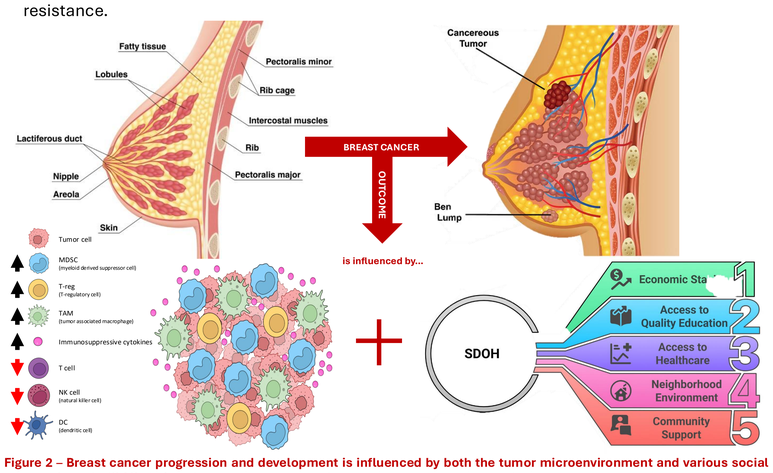

Figure 2 – Breast cancer progression and development is influenced by both the tumor microenvironment and various social drivers of health (SDOH). Breast cancer is well-known to be an immune-cold disease, typically surrounded by immunosuppressive cells. 40% of an individual's health is determined by socioeconomic factors like annual income and highest level of education.

HYPOTHESIS

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

RESULTS

NATIONWIDE

H/L patients exhibit lower event-free survival when compared to NHW patients.

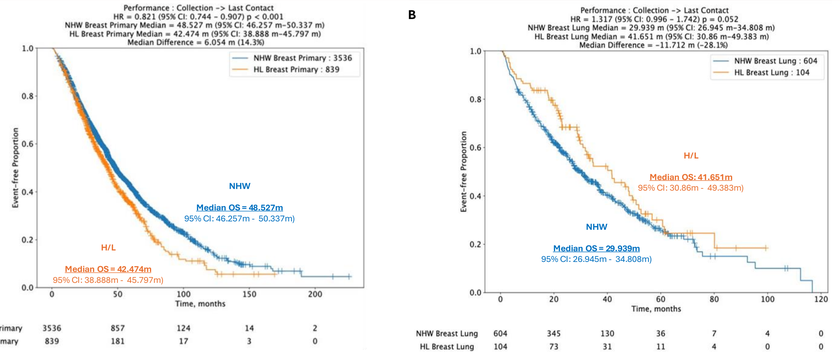

Figure 3 – Event-free survival (EFS) curves of NHW and H/L patients with **A.** early stage (**p<0.001**) and **B.** late-stage lung metastatic breast cancer (**p=0.052**). Data were generated by Caris Life Sciences integrating molecular profiling data (e.g., genomic, transcriptomic) from tumor samples 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. Significance, p<0.05.

H/L patients have higher PD-L1 expression compared to NHW patients.

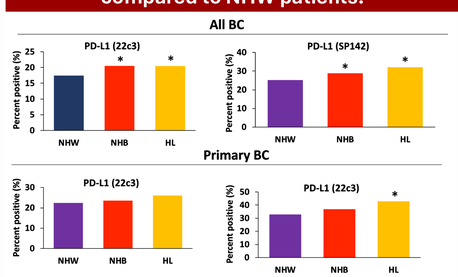

Figure 4 – PD-L1 positivity of breast tumors from African-American (AAB) and H/L patients. PD-L1+ was tested by IHC using 22c3 (Dako) and immune cell fraction was calculated by QuantiSeq. Statistical significance was adjusted for multiple comparisons. Significance, p-value, * = p<0.05.

H/L patients demonstrate higher markers of immunogenicity.

	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

Table 1. Immune scores in H/L and NHW primary breast tumors (all subtypes) show that H/L breast tumors were more immunosuppressive. 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. Significance, p<0.05.

	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

H/L and NHW patients have differential immune cell infiltration.

Table 2. Immune cell subsets in H/L and NHW patients with early-stage disease and liver metastases (all subtypes). 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. Significance, p<0.05.

LOS ANGELES COUNTY-WIDE

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

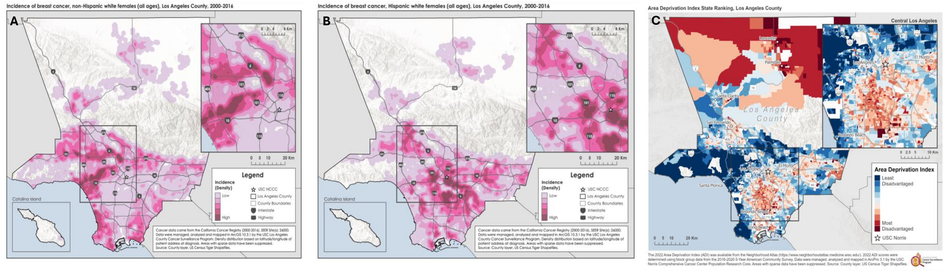

Figure 5 – Rates of breast cancer incidence in H/L and NHW patients in LA County. Area maps of showing age-adjusted incidence rate of breast cancer in **A.** NHW and **B.** H/L patients in Los Angeles (LA) County, CA (2000-2016). **C.** Area Deprivation Index (ADI) scores were determined using block 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

USC CATCHMENT

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.

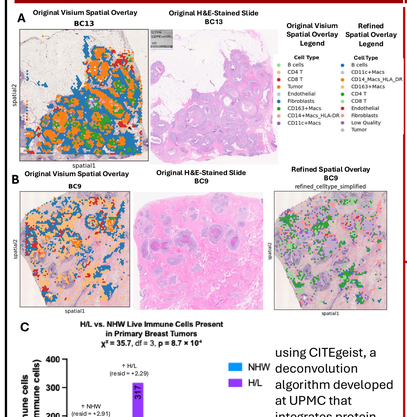

Figure 6 – Spatial immune profiling of primary breast tumors in NHW and H/L patients. A. Representative HR+HER2– primary breast tumor from a Non-Hispanic White (NHW) patient and **B.** a Hispanic/Latina (H/L) patient, showing spatial distribution of immune and tumor cells using CITEgeist, a deconvolution algorithm developed at UPMC that integrates protein expression with gene transcripts (REF). **C.** Bar chart showing the proportion of live immune cells out of total immune cells present in HR+HER2– primary tumors from 5 H/L and 9 patients. Significance, p<0.05.

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

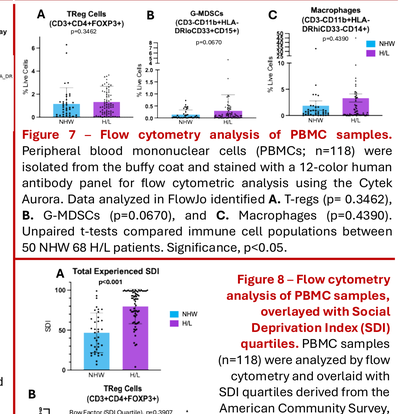

Figure 7 – Flow cytometry analysis of PBMC samples. Peripheral blood mononuclear cells (PBMCs; n=118) were isolated from the buffy coat and stained with a 12-color human antibody panel for flow cytometric analysis using the Cytek Aurora. Data analyzed in FlowJo identified **A.** T-regs (p= 0.3462), **B.** G-MDSCs (p=0.0670), and **C.** Macrophages (p=0.4390). Unpaired t-tests compared immune cell populations between 50 NHW 68 H/L patients. Significance, p<0.05.

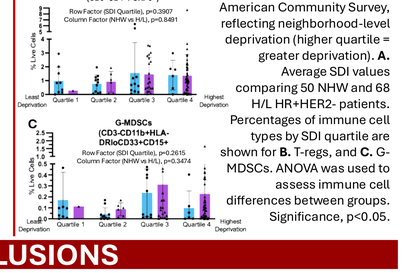

Figure 8 – Flow cytometry analysis of PBMC samples, overlayed with Social Deprivation Index (SDI) quartiles. PBMC samples (n=118) were analyzed by flow cytometry and overlaid with SDI quartiles derived from the American Community Survey, reflecting neighborhood-level deprivation (higher quartile = greater deprivation). **A.** Average SDI values comparing 50 NHW and 68 H/L HR+HER2- patients. Percentages of immune cell types by SDI quartile are shown for **B.** T-regs, and **C.** G-MDSCs. ANOVA was used to assess immune cell differences between groups. Significance, 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, support 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

Compare immunosuppressive immune profiles and SDOH across LAG and Keck patients to identify the social factors most linked to increased immune suppression.

- Determine differences in immunosuppressive phenotypes in the TME in breast tumor samples of patients at LAG vs. Keck hospitals.
- Investigate differences in circulating immunosuppressive phenotypes in patients with BC at LAG and Keck.
- Determine which SDOH correlates with immunosuppressive phenotypes, and which correlate with place of care.
- Define genetic ancestry using germline sequencing.

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