Racial Disparities in Breast Cancer and Effect of Obesity: MammaPrint®, BluePrint® and Whole Transcriptome Analyses of Tumors in Latin American Patients in FLEX Trial

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Introduction

- Latin Americans (LA) are more likely to be diagnosed with aggressive early-stage breast cancer compared to Non-Hispanic White (NHW) in the US[1]. Multiple factors such as metabolic and genetic may contribute to this.
- In a previous study[2], we identified upregulated immune pathway genes in Luminal B tumors from obese Black patients compared to NHW patients.
- In this study, we report transcriptomic profiles of breast tumors from LA and NHW patients enrolled in FLEX as well as their metabolic and genomic characteristics to enhance understanding of factors contributing to aggressive tumor biology in Latin patients.
- We also compared transcriptome of tumors from Luminal B and obese LA and Black patients to assess population differences in high- risk groups.

Methods

FLEX trial and genomic testing:

- FLEX (NCT03053193) is a prospective, observational trial that includes patients with stage I-III breast cancer.
- MammaPrint® (MP) is a 70-gene risk of distant recurrence signature that classifies patients into Low Risk (further stratified in UltraLow, Low) and High Risk (further stratified in High 1, High2) categories.
- BluePrint® (BP) is an 80-gene molecular subtyping signature, categorizes tumors as Luminal-, HER2- or Basal-Type. MP further groups Luminal into A (Low Risk) and B (High Risk).
- ImPrint is a 53-gene immune signature that has been shown to predict the likelihood of achieving pCR with PD1-PDL1 immune checkpoint inhibitors[3] in patients with HR+ disease.

Patients:

- Tumors from 311 LA and 311 NHW breast cancer patients enrolled in FLEX were matched by patient age, T-, N- stage and clinical subtype (ER/PR and HER2 status).
- In Luminal B obese subgroup, 61 LA and 61 Black patient tumors were matched using the same characteristics.

Statistical analyses:

- Arsenal R package was used for comparisons with chi-squared and fisher exact test based on number of patients. Two-proportions z-test was used for comparison of MP and BP result categories.

Whole transcriptome analyses:

- Whole transcriptome comparisons were made, using limma R package, between LA and NHW patients stratified by BluePrint subtype Luminal and body-mass-index (BMI) weight categories normal and obese.
- Gene set enrichment analysis (GSEA) was conducted using fgsea R package.

Table 1A. Matched tumors from LA and NHW patients – Metabolic characteristics

	LA	NHW	p-value
Diabetic status			
Type 2	68 (23.3%)	24 (8.5%)	< 0.001
Type 1	1 (0.3%)	3 (1.1%)	
Pre-diabetes	0 (0.0%)	1 (0.4%)	
No diabetes	223 (76.4%)	253 (90.0%)	
BMI category			
Obese	148 (49.0%)	119 (39.4%)	< 0.001
Overweight	106 (35.1%)	91 (30.1%)	
Normal	43 (14.2%)	85 (28.1%)	
Underweight	5 (1.7%)	7 (2.3%)	

Table 1B. Matched tumors from LA and NHW patients – Genomic test results

	LA	NHW	p-value
MP			
High 2	74 (23.8%)	59 (19.0%)	0.473
High 1	96 (30.9%)	100 (32.2%)	
Low	93 (29.9%)	105 (33.8%)	
Ultralow	48 (15.4%)	47 (15.1%)	
BP			
Luminal A (MP Low)	141 (45.3%)	152 (48.9%)	0.190
Luminal B (MP High)	114 (36.7%)	122 (39.2%)	
Basal*	46 (14.8%)	29 (9.3%)	
HER2	10 (3.2%)	8 (2.6%)	
ImPrint			
ImPrint+	30 (12.0%)	13 (5.1%)	0.005
ImPrint-	219 (88.0%)	242 (94.9%)	

Table 2. Matched tumors from LA and Black patients – Genomic test results (Luminal B and obese)

	LA	Black	p-value
MP			
High 2	9 (14.8%)	10 (16.4%)	0.803
High 1	52 (85.2%)	51 (83.6%)	
ImPrint			
ImPrint+	10 (18.5%)	3 (5.2%)	0.028
ImPrint-	44 (81.5%)	55 (94.8%)	

Table 1 and 2:

- Matching was done using age, T stage, N stage, hormone receptor (HR) status
- Unknowns were excluded from the tables, starting number of patients given in the Methods
- BMI categories: Underweight BMI <18.5, Normal 18.5 ≤ BMI < 25, Overweight 25.0 ≤ BMI < 30, Obese ≥ 30

* Two-proportions z-test in Basal group, p-value = 0.049

Figure 1. Multidimensional scaling with top 500 variable

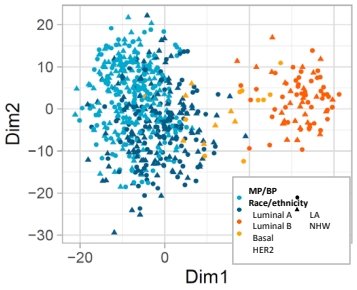


Figure 2. Volcano plots of whole genome differential expression nalyses

Figure 2A – Luminal B obese LA vs NHW

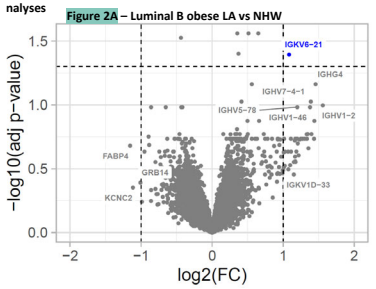


Figure 3. GSEA in Luminal B obese comparisons

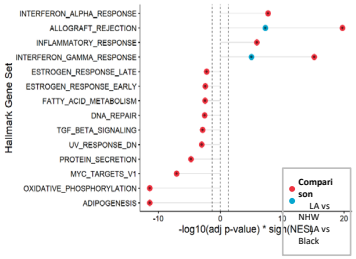
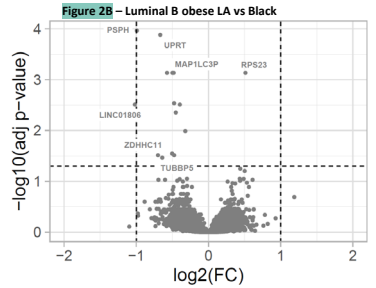


Figure 2B – Luminal B obese LA vs Black



Conclusion

- Transcriptomic differences between matched tumors from Luminal B obese LA and NHW breast cancer patients showed upregulated immune response and downregulated oxidative phosphorylation in tumors of LA patients that may contribute to the aggressive tumor biology. Transcriptomic differences involving immune response were also observed between LA and Black patients.
- Based on these results, obesity seems to affect LA and Black breast cancer biology differently than NHW patients. Immune system differences derived from genetic ancestry may be involved.
- Further studies with larger cohorts are needed to confirm and to further study these pathway responses in LA patients.

Results

Table 1A and 1B:

- When matched for age and tumor characteristics, LA patients had higher percentages of the following compared to NHW:
  - Type 2 diabetes (23.3% vs 8.5%)
  - BMI obese (49.0% vs 39.4%)
  - BluePrint Basal (14.8% vs 9.3%)
  - ImPrint+ in the HR+ subgroup (12.0% vs 5.1%)

Table 2:

- In the Luminal B obese cohort, LA patients had higher percentages of ImPrint+ in the HR+ subgroup (18.5% vs 5.2%) when compared to Black patients.

Figure 1:

- Top 500 variable genes showed separation of MP/BP subtypes, but no clear separation was observed based on ethnicity.

Figure 2A:

- Whole transcriptome analysis of Luminal B obese group showed immunoglobulin genes upregulated more than 2-fold in LA compared to NHW, although not all genes statistically significant. There were no differentially expressed genes in other comparisons of LA vs NHW in Luminal and weight categories: Luminal A normal, Luminal A obese and Luminal B normal groups.

Figure 2B:

- Whole transcriptome comparison between LA and Black patients showed upregulation of PSPH gene which was observed in a previous study where Black and NHW Luminal patients were compared[2].

Figure 3:

- Enrichment of interferon alpha/gamma response, allograft rejection and inflammatory response pathways were observed in the upregulated genes, while enrichment of oxidative phosphorylation and MYC targets v1 were observed in downregulated genes in LA compared to NHW patients. GSEA also revealed upregulated allograft rejection and interferon gamma response pathways in LA compared to Black patients, which could be in line with the ImPrint+ differences observed.

References

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2. Hoskins et al. Journal of Clinical Oncology. 2021. 39:15_suppl, 1009
3. Mittempergher et al. Journal of Clinical Oncology. 2022. 40:16_suppl, 514

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