# Distinct Immune and Metabolic profiles in Latin American Breast Cancer Patients With Obesity Enrolled in FLEX

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## Introduction

- Latin American (LA) women are more often diagnosed with aggressive early breast cancer (EBC) than Non-Hispanic White (NHW) women[1].
- Prior work showed elevated immune gene expression in BluePrint® (BP) Luminal B tumors from LA patients (pts) with obesity vs Black and NHW cohorts[2].
- Although high immune activation is characteristic of aggressive subtypes such as Basal breast cancer[2]—and can be associated with improved survival—its role in the distinct biology observed in LA women remains unclear
- In this study, we present:
  - i. updated clinical comparisons between LA, NHW, and Black pts with EBC.
  - ii. Whole transcriptome analysis (WTA) comparing BP Luminal B and Basal BC in pts with obesity.

## Methods

### Study Cohort

- 15,577 pts (Latin American, Black, NHW, Table 1) from the FLEX Study (NCT03053193).
- All received MammaPrint® (MP), BP, and consented to WTA.
- ImPrint® 53-gene immune signature classified HR+ EBC tumors as immune-positive (+) or immune-negative (–)
- WTA comparisons were performed within each BP Luminal B and BP Basal, matching BMI-obese LA pts to NHW and Black pts by age, T stage, and LN status (Table 2).

### Statistics

- Chi-square and t-tests were conducted on clinical groups using arsenal R package.
- Differentially expressed genes (DEGs) were evaluated using limma, and pathway enrichment was performed using gene set enrichment analysis (GSEA) with Hallmark gene sets.
- P-values were adjusted for multiple testing using Benjamini–Hochberg. Significant results were reported with adjusted p < 0.05.

## Results

**Table 1.** Clinical Characteristics Overall

| Characteristic | LA (n=1446) (%) | Black (n=1656) (%) | NHW (n=12,475) (%) | p value Black vs LA | p value NHW vs LA |
|---|---|---|---|---|---|
| **Age (Years)** | | | | | |
| **Median** | 57 | 59 | 63 | <0.001 | <0.001 |
| **Mean (SD)** | 56.6 (±12) | 58.4 (±13) | 61.5 (±12) | | |
| **Menopausal Status** | | | | <0.001 | <0.001 |
| **Pre-/Peri-** | 434 (21.3) | 390 (25.6) | 2338 (20.0) | | |
| **Post-** | 931 (68.2) | 1133 (74.4) | 9375 (80.0) | | |
| **Type 2 Diabetes** | | | | 0.274 | <0.001 |
| **Yes** | 283 (26.9) | 399 (28.9) | 1452 (13.4) | | |
| **No** | 769 (73.1) | 981 (71.1) | 9369 (86.6) | | |
| **BMI** | | | | <0.001 | <0.001 |
| **<18.5** | 17 (1.2) | 13 (0.8) | 199 (1.6) | | |
| **18.5-24.9** | 229 (16.2) | 184 (11.6) | 3141 (26.0) | | |
| **25-29.9** | 451 (31.9) | 406 (25.6) | 3665 (30.4) | | |
| **>30** | 718 (50.7) | 984 (62.0) | 5058 (41.9) | | |
| **T Stage** | | | | 0.373 | <0.001 |
| **T1** | 483 (57.5) | 627 (55.0) | 4911 (65.7) | | |
| **T2** | 274 (32.6) | 406 (35.6) | 2141 (28.6) | | |
| **T3** | 63 (7.5) | 73 (6.4) | 329 (4.4) | | |
| **T4** | 20 (2.4) | 33 (2.9) | 96 (1.3) | | |
| **N Stage** | | | | <0.001 | 0.001 |
| **LN-** | 640 (78.4) | 784 (71.1) | 5941 (83.0) | | |
| **LN+** | 176 (21.6) | 310 (28.3) | 1221 (17.0) | | |
| **Grade** | | | | <0.001 | <0.001 |
| **G1** | 336 (25.3) | 330 (22.0) | 3389 (29.7) | | |
| **G2** | 652 (49.1) | 672 (44.7) | 5923 (51.8) | | |
| **G3** | 339 (25.5) | 500 (33.3) | 2113 (18.5) | | |
| **Ki67%** | | | | <0.001 | <0.001 |
| **0-10** | 322 (29.2) | 247 (22.4) | 2718 (33.3) | | |
| **11-20** | 266 (24.1) | 229 (20.7) | 2125 (26.1) | | |
| **>20** | 514 (46.4) | 629 (56.9) | 3308 (40.6) | | |
| **MammaPrint** | | | | <0.001 | <0.001 |
| **UltraLow Risk** | 225 (15.6) | 151 (9.1) | 1962 (15.7) | | |
| **Low Risk** | 465 (32.2) | 410 (24.8) | 4618 (37.0) | | |
| **High Risk 1** | 464 (32.1) | 653 (39.4) | 4351 (34.9) | | |
| **High Risk 2** | 292 (20.2) | 442 (26.7) | 1543 (12.4) | | |
| **BluePrint** | | | | <0.001 | <0.001 |
| **Luminal A** | 667 (47.3) | 545 (33.9) | 6307 (52.6) | | |
| **Luminal B** | 506 (35.9) | 694 (43.1) | 4344 (36.2) | | |
| **HER2** | 65 (4.6) | 74 (4.6) | 411 (3.4) | | |
| **Basal** | 173 (12.3) | 297 (18.4) | 925 (7.7) | | |
| **ImPrint HR** | | | | 0.049 | <0.001 |
| **ImPrint-** | 870 (91.0) | 1066 (88.4) | 9418 (95.3) | | |
| **ImPrint+** | 86 (9.0) | 140 (11.6) | 460 (4.7) | | |

Data presents n (%) unless indicated otherwise. Unknowns not listed. p<0.05 indicates significance.

**Table 2.** Clinical characteristics of obese pts matched by age, T, and N stage

| Basal Characteristics | LA (n=77) (%) | Black (n=77) (%) | NHW (n=77) (%) | p value |
|---|---|---|---|---|
| **Age** | | | | 0.698 |
| **Median** | 50 | 52 | 52 | |
| **Mean (SD)** | 52.45 (±14) | 53.61 (±13) | 51.73 (±14) | |
| **Menopausal** | | | | 0.234 |
| **Pre-/Peri** | 26 (36.6) | 24 (33.3) | 34 (46.6) | |
| **Post** | 45 (63.4) | 48 (66.7) | 39 (53.4) | |
| **Type 2 Diabetes** | | | | 0.153 |
| **Yes** | 15 (27.3) | 10 (14.9) | 10 (15.4) | |
| **No** | 40 (72.7) | 57 (85.1) | 55 (84.6) | |
| **Tumor Stage** | | | | 0.986 |
| **T1** | 16 (29.1) | 17 (30.9) | 16 (30.8) | |
| **T2** | 26 (47.3) | 24 (43.6) | 26 (50.0) | |
| **T3** | 10 (18.2) | 10 (18.2) | 8 (15.4) | |
| **T4** | 3 (5.5) | 4 (7.3) | 2 (3.8) | |
| **N Stage** | | | | 0.697 |
| **LN-** | 35 (66.0) | 38 (73.1) | 36 (72.0) | |
| **LN+** | 18 (34.0) | 14 (26.9) | 14 (28.0) | |
| **Grade** | | | | 0.43 |
| **G1** | 0 (0) | 1 (1.4) | 1 (1.4) | |
| **G2** | 12 (17.6) | 6 (8.3) | 8 (11.0) | |
| **G3** | 56 (82.4) | 65 (90.3) | 64 (87.7) | |

| Luminal B Characteristic | LA (n=215) (%) | Black (n=215) (%) | NHW (n=215) (%) | p value |
|---|---|---|---|---|
| **Age** | | | | 0.961 |
| **Median** | 56 | 56 | 56 | |
| **Mean (SD)** | 55.9 (±12) | 56.18 (±11) | 55.92 (±11) | |
| **Menopausal** | | | | 0.705 |
| **Pre-/Peri** | 65 (32.8) | 58 (29.3) | 65 (32.5) | |
| **Post** | 133 (67.2) | 140 (70.7) | 135 (67.5) | |
| **Type 2 Diabetes** | | | | 0.002 |
| **Yes** | 56 (33.1) | 59 (31.4) | 35 (18.2) | |
| **No** | 113 (66.9) | 129 (68.6) | 157 (81.8) | |
| **Tumor Stage** | | | | 0.582 |
| **T1** | 71 (53.0) | 76 (56.3) | 72 (55.0) | |
| **T2** | 51 (38.1) | 48 (35.6) | 54 (41.2) | |
| **T3** | 9 (6.7) | 9 (6.7) | 5 (3.8) | |
| **T4** | 3 (2.2) | 2 (1.5) | 0 (0) | |
| **N Stage** | | | | 0.695 |
| **LN-** | 101 (74.8) | 104 (76.5) | 95 (72.0) | |
| **LN+** | 34 (25.2) | 32 (23.5) | 37 (28.0) | |
| **Grade** | | | | 0.478 |
| **G1** | 23 (11.6) | 25 (13.2) | 28 (14.1) | |
| **G2** | 119 (60.1) | 106 (55.8) | 124 (62.6) | |
| **G3** | 56 (28.3) | 59 (31.1) | 46 (23.2) | |

**Fig.1 WT comparison in obese EBC across race/ethnicity.** Volcano plots show DEGs between obese LA vs Black pt (A,B) or LA vs NHW pt (C,D) cohorts, matched by age, T, and N stage. Analyses were stratified by BP subtypes Basal (A,C) and Luminal B (B,D).

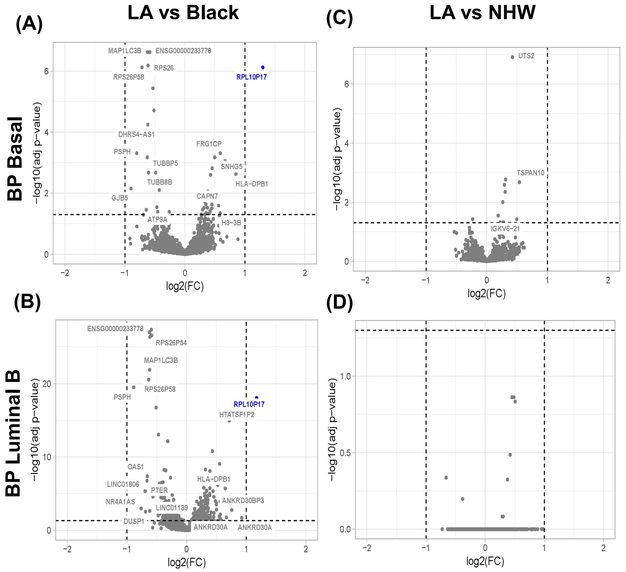
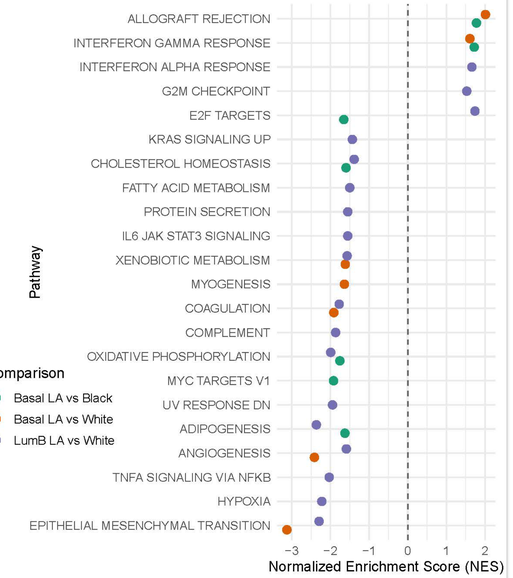



**Fig.2 Pathway enrichment analysis of obese EBC across racial/ethnic groups.** GSEA of obese EBC comparing LA vs Black and NHW patients by BP Basal and Luminal B subtypes. NES indicates pathway regulation direction and magnitude; pathways with adjusted p value < 0.05 are shown.






- Latin American (LA) patients were younger and more frequently premenopausal compared with Black and NHW pts (Table 1).
  - Both LA and Black pts exhibited significantly higher rates of obesity compared with NHW pts (Table 1).
  - MP High Risk 2, BP Basal, and ImPrint+ tumor subtypes were significantly more common in LA and Black pts than in NHW patients (Table 1).
- LA pts had a higher prevalence of type 2 diabetes compared to NHW pts within both matched cohorts (BP Luminal B cohort: p = 0.002) (Table 2).
- Among obese EBC pts, metabolic pathways (adipogenesis, angiogenesis, epithelial–mesenchymal transition, oxidative phosphorylation) were significantly downregulated in LA pts relative to NHW and Black cohorts (Fig.3).
- Immune-related pathways (including allograft rejection and interferon gamma response) were enriched in LA pts with Basal cancers compared to NHW and Black pts (Fig.3).

## Conclusions

- Obese LA EBC pts show significant suppression of metabolic pathways compared with NHW and Black cohorts, suggesting distinct metabolic vulnerabilities.
- Basal tumors in obese LA pts display enriched immune activation, indicating a unique inflammatory profile that may have potential implications for immune checkpoint therapy.
- These findings highlight potential therapeutic targets and underscore the need for racially and ethnically diverse representation in clinical trials to better define population-specific drivers of EBC outcomes.

**References:** [1] Fejerman L, et al; *Breast Cancer Risk and Mortality in Women of Latin American Origin*. Chapter 4. 2019. [2]Canola MM, et al; SABCS *2023*.