TNBC subtype and clinical estrogen receptor status of genomically basal breast tumors in Caucasian, African American, and Latin American patients

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BACKGROUND

Triple negative breast cancer (TNBC) is an aggressive histological subtype with few targeted therapies and worse prognosis compared to other BC types. The heterogeneity of TNBC is underpinned by distinct transcriptional profiles including basal-like immunoactive (BLIA), basal-like immunosuppressed (BLIS), luminal androgen receptor (LAR), and mesenchymal (MES) subtypes [1]. These subtypes are associated with differences in survival and may assist in treatment decisions. Studies showed that African American (AA) and Hispanic BC patients have a higher frequency of TNBC tumors and worse survival rates compared to non-Hispanic Caucasian BC patients [2]. Furthermore, previous studies report a significantly higher frequency of BLIS subtype tumors in Hispanic TNBC patients, higher frequency of BLIA and BLIS subtypes in AA TNBC patients, and higher frequency of LAR subtype in Asian American and European American TNBC patients [3-4].

The 80-gene BluePrint assay genomically defines breast tumors as basal, luminal, or HER2-enriched independently of IHC expression. Here, we report the distribution of TNBC subtypes in BluePrint-defined basal tumors from Caucasian American (CA), African American (AA), and Latin American (LA) patients, and the association of estrogen receptor (ER) positivity by immunohistochemistry (IHC).

METHODS

FLEX Registry: The FLEX Registry (NCT03053193) is an ongoing, prospective study evaluating primary tumors from stage I-III breast cancer patients who receive MammaPrint (MP) risk of recurrence and BluePrint (BP) molecular subtype testing and consent to clinically annotated full transcriptome data collection.

Patient Cohort: 143 BP basal-type tumors from patients with self-reported ethnicity (60 CA, 59 AA, and 24 LA) were evaluated.

ER status: Tumors were identified as ER+ if 1% or more tumor cells stained positive for estrogen receptor by immunohistochemistry.

Subtype Classification: TNBC subtypes BLIA, BLIS, LAR, and MES were derived using an adjusted version of the Burstein centroid signature [1].

Statistical Analysis: Differences in MP index and BP index were assessed by one-way ANOVA. Differences in TNBC subtype and pathological ER expression between ethnicities were assessed by Fisher's exact test.

RESULTS

Table 1. Clinical Characteristics (unknowns excluded)

	Caucasian American (n=60)	African American (n=59)	Latin American (n=24)	*p-value*
Age, years				0.02
Median	59	59	49.5	
Mean (±SD)	57.1 (±14.1)	56.9 (±13.5)	50.2 (±10.0)	
Menopausal Status				<0.01
Pre or Peri	12 (20%)	10 (21%)	15 (63%)	
Post	48 (80%)	38 (79%)	9 (37%)	
Tumor Stage				0.02
cT1	23 (53%)	19 (53%)	3 (17%)	
cT2	17 (40%)	14 (39%)	12 (66%)	
cT3	3 (7%)	1 (3%)	3 (17%)	
cT4	0	2 (5%)	0	
Nodal Stage				0.28
N0	32 (76%)	30 (81%)	11 (65%)	
N1	8 (19%)	5 (14%)	5 (29%)	
N2	2 (5%)	0	1 (6%)	
N3	0	2 (5%)	0	
Grade				0.35
G1	2 (4%)	2 (4%)	0	
G2	8 (15%)	2 (4%)	2 (10%)	
G3	45 (81%)	49 (92%)	19 (90%)	
Tumor Type				0.64
IDC	53 (96%)	48 (92%)	21 (91%)	
Mixed IDC/ILC	0	1 (2%)	0	
Other	2 (4%)	3 (6%)	2 (9%)	
BMI Category				0.02
Normal	11 (19%)	6 (11%)	5 (23%)	
Overweight	21 (36%)	10 (19%)	10 (45%)	
Obese	26 (45%)	37 (70%)	7 (32%)	

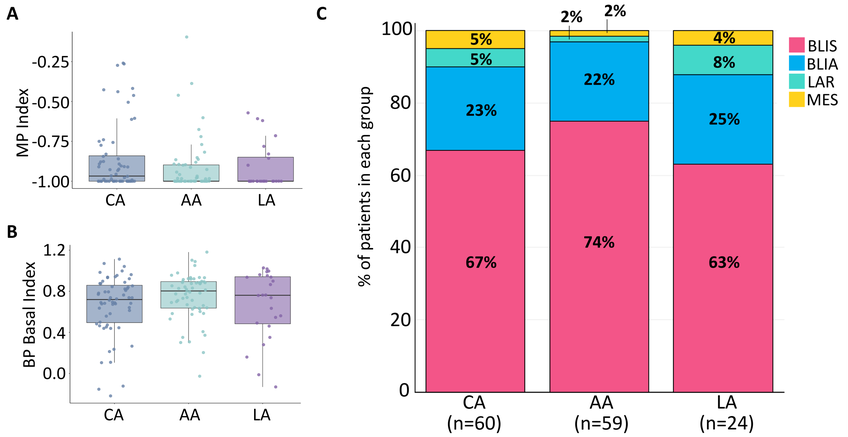
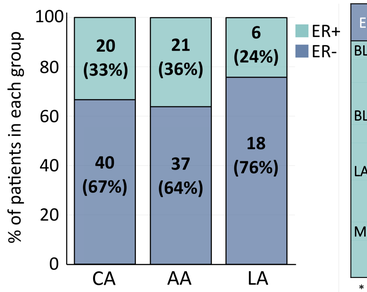


Figure 1: Distribution of TNBC subtypes across ethnicities. All tumors were classified as MP High Risk and BP basal-type. MP and BP basal indices were not influenced by patient ethnicity (p = 0.207 and p=0.182 respectively; **Figure 1A-B**). The majority of tumors in all ethnic groups were BLIS subtype, followed by BLIA subtype, with low frequency of LAR and MES subtypes (**Figure 1C**). The frequency of each subtype did not vary significantly by ethnicity (p = 0.671).



ER status	CA (n=60)	AA (n=58)*	LA (n=24)
BLIS			
ER+	11 (28%)	15 (35%)	4 (27%)
ER-	29 (72%)	28 (65%)	11 (73%)
BLIA			
ER+	7 (50%)	5 (38%)	1 (17%)
ER-	7 (50%)	8 (62%)	5 (83%)
LAR			
ER+	1 (33%)	0	1 (50%)
ER-	2 (67%)	1	1 (50%)
MES			
ER+	1 (33%)	1	0
ER-	2 (67%)	0	1

* 1 patient with multicentric lesion excluded

Figure 2: Frequency of basal-type tumors that are ER+ by IHC. IHC defined ER+ tumors were detected in basal-type tumors of each ethnicity (33% CA, 36% AA, 24% LA). ER status was not significantly associated with a specific TNBC subtype (p = 0.8) or ethnicity (p = 0.76).

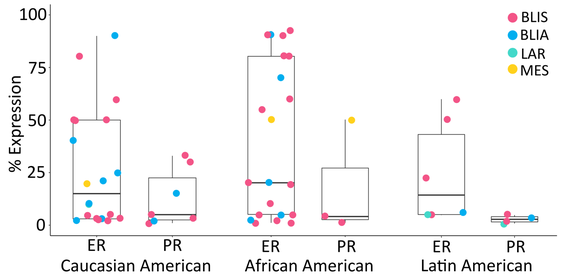


Figure 3: ER and PR expression across ethnicity and TNBC subtype. ER expression ranged from 2-90% in CA patients, 1-92% in AA patients, and 5-60% in LA patients. PR expression ranged from 1-30% in CA patients, 1-50% in AA patients, and 1-5% in LA patients. ER and PR expression was not associated with a specific TNBC subtype or ethnicity.

CONCLUSIONS

- This analysis demonstrates that genomically classified basal-type tumors encompass the 4 TNBC subtype categories, a majority of which were BLIS and BLIA subtypes.
- **In contrast to previous reports, this analysis finds no association between TNBC subtype and patient ethnicity.** This difference may be due to intrinsic variations between traditional IHC and genomic methods of identifying TNBC/basal tumors.
- **Approximately 1/3 of BluePrint basal-type tumors are ER+ by IHC, suggesting that BluePrint identifies a subset of clinically luminal (ER+) tumors as genomically basal-type, independent of ethnicity.** Previous studies have shown these cancers to respond to chemotherapy similar to TNBC [5].
- The frequency of IHC ER+ tumors does not vary significantly across TNBC subtypes.
- ER and PR expression levels were not associated with ethnicity or TNBC subtype.
- These findings confirm the heterogeneous nature of basal breast tumors in CA, AA, and LA patients and highlight the clinical need to delineate basal biology in the ER+ cohort to advance treatment for basal-like tumors.

FUTURE DIRECTIONS

- The current study was restricted by small sample sizes in non-Caucasian groups, which may have resulted in limited power to assess meaningful differences. Future studies will evaluate the distribution of TNBC subtypes and ER status in a larger dataset.
- Future studies will explore the relationship between BluePrint subtypes and TNBC molecular subtypes within IHC defined TNBC tumors.
- Future aims will investigate treatment response and prognosis in TNBC subgroups.

References

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