Defining the spectrum of germline variants among African American patients with triple negative breast cancer

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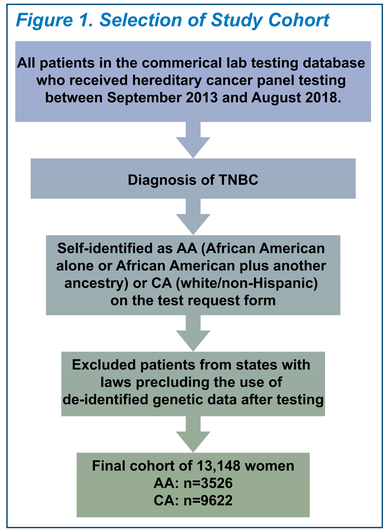
BACKGROUND

- African American (AA) women are more likely to have breast cancer at a younger age and be diagnosed with triple negative breast cancer (TNBC), a pattern which is not yet understood.
- In this study, we examined results of multi-gene panel testing in AA women with TNBC tested at a large commercial laboratory to assess the utility of gene panels and findings in this population.

METHODS

Figure 1. Selection of Study Cohort



- Clinical data was collected from provider-completed test request forms.
- Comparisons were performed using descriptive statistics, t-tests (continuous variables), and chi-square tests (categorical variables), adjusting for multiple testing when necessary.

RESULTS

- Compared to CA women, AA women were significantly more likely to meet NCCN guidelines (97.1% vs. 96.2%, p=0.011) and significantly less likely to have an additional personal (15.8% vs. 21.6%, p<0.001) or family (79.4% vs. 86.1%, p<0.001) history of cancer.

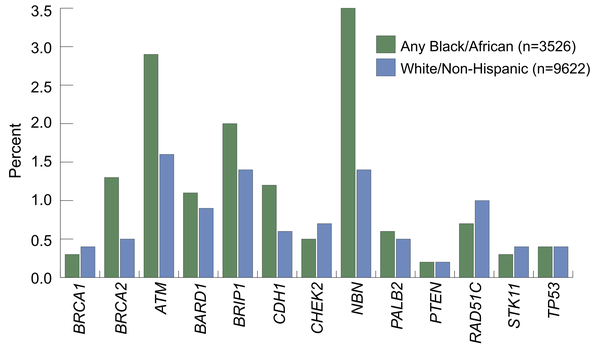
Table 1. Distribution of PVs According to Race

Gene / Gene Group	AA (N=3526)	CA (N=9622)	Total (N=13148)
Breast Genes	373 (10.6%)	1176 (12.2%)	1549 (11.8%)
BRCA1	143 (4.1%)	531 (5.5%)	674 (5.1%)
BRCA2	101 (2.9%)	247 (2.6%)	348 (2.6%)
ATM	6 (0.2%)	27 (0.3%)	33 (0.3%)
BARD1	23 (0.7%)	72 (0.7%)	95 (0.7%)
BRIP1	23 (0.7%)	50 (0.5%)	73 (0.6%)
CDH1	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
CHEK2	2 (0.1%)	37 (0.4%)	39 (0.3%)
NBN	2 (0.1%)	10 (0.1%)	12 (0.1%)
PALB2	47 (1.3%)	144 (1.5%)	191 (1.5%)
PTEN	2 (0.1%)	4 (<0.1%)	6 (<0.1%)
RAD51C	21 (0.6%)	43 (0.4%)	64 (0.5%)
STK11	0	1 (<0.1%)	1 (<0.1%)
*TP53**	2 (0.1%)	9 (0.1%)	11 (0.1%)
Mismatch Repair Genes	10 (0.3%)	49 (0.5%)	59 (0.4%)
EPCAM	0	1 (<0.1%)	1 (<0.1%)
MLH1	2 (0.1%)	1 (<0.1%)	3 (<0.1%)
MSH2	0	7 (0.1%)	7 (0.1%)
MSH6	3 (0.1%)	24 (0.2%)	27 (0.2%)
PMS2	5 (0.1%)	16 (0.2%)	21 (0.2%)
Other Genes	12 (0.3%)	26 (0.3%)	38 (0.3%)
APC	1 (<0.1%)	2 (<0.1%)	3 (<0.1%)
MYH	0	2 (<0.1%)	2 (<0.1%)
RAD51D	8 (0.2%)	10 (0.1%)	18 (0.1%)
CDKN2A (P14ARF)	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
CDKN2A (P16)	2 (0.1%)	11 (0.1%)	13 (0.1%)
Multiple PVs	6 (0.2%)	29 (0.3%)	35 (0.3%)
Any Gene**	401 (11.4%)	1280 (13.3%)	1681 (12.8%)

*Chi-square p-value = 0.003; **4 appear to have Compret LFS.

- Overall, 11.4% of AA women were found to carry a pathogenic variant (PV) compared to 13.3% of CA women (p=0.003; Table 1).
- The prevalence of PVs in *BRCA1*, *CHEK2* and the Lynch syndrome genes was higher in CA women, whereas the prevalence of *BRCA2* PVs was higher in AA women (Table 1).
  - Similar ancestry-associated patterns of gene-specific variant of uncertain significance (VUS) distribution were also observed (Figure 2).

Figure 2. Gene Distribution by VUS Rate in Breast Cancer-Related Genes According to Race

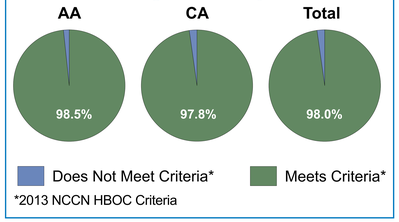


- While the prevalence of PVs in individual genes was not significantly different according to ancestry after adjusting for multiple comparisons, AA women were significantly less likely to have a PV in any breast cancer-related gene compared to CA women (10.6% vs. 12.2%, p=0.047; Table 1).
- AA women were significantly more likely to have a VUS (33.1% vs. 20.6%; p<0.001) and to have >1 VUS (7.0% vs. 2.6%, p<0.001).
- Compared to CA women, AA women with a PV were significantly younger at diagnosis (46.6 vs. 49.5 years of age; p<0.001).
- Regardless of ancestry, patients diagnosed before age 40 were more likely to carry a PV (20.5% AA, 21.8% CA; Table 2).
  - The prevalence of PVs among patients diagnosed after age 60 was still striking (9.0% AA, 10.6% CA).
  - The PV prevalence among patients diagnosed between 40-60 (9.8% AA, 12.3% CA) was similar to those diagnosed after 60.

Table 2. Age at Diagnosis According to Race

Diagnosis Age	PV-positive	No PV
All Patients		
<40	381 (21.4%)	1401 (78.6%)
40-60	1028 (11.6%)	7818 (88.4%)
>60	232 (10.3%)	2020 (89.7%)
AA		
<40	107 (20.5%)	416 (79.5%)
40-60	243 (9.8%)	2226 (90.2%)
>60	41 (9.0%)	415 (91.0%)
CA		
<40	274 (21.8%)	985 (78.2%)
40-60	785 (12.3%)	5592 (87.7%)
>60	191 (10.6%)	1605 (89.4%)

Figure 3. Proportion of PV-Carrying Patients Meeting Criteria by Race*



- In this cohort, AA and CA women who carry a PV met criteria for testing at similar rates (Figure 3).

CONCLUSIONS

- The current analysis does not suggest that TNBC in AA women is a molecularly distinct disease, leaving the question of why AA women have increased TNBC and lower ages of diagnosis.
- Given the higher rate of VUS in AA patients, it is important to educate patients undergoing testing about the likelihood and implications of a VUS.
- As more research is conducted and increasingly more AA women are clinically tested, the pathogenicity of VUS in AA women will further be clarified.
- In the era of multi-gene panel testing, this large cohort of patients with TNBC supports the use of panel testing in AA women with TNBC regardless of age or additional personal/family history of cancer.

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