Comprehensive Characterization of Androgen Receptor Expression in Breast Cancer

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BACKGROUND

- The androgen receptor (*AR*) is a hormone-regulated transcription factor that plays an important role in breast cancer (BC) pathogenesis.
- While estrogen receptor inhibitors are well-studied in BC, the role of *AR* on prognosis and therapy is less well-known.
- Here we aim to characterize the clinicopathologic and molecular features of *AR* expression in BC.

METHODS

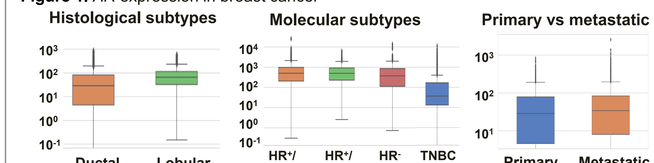
- 21,169 BC samples were tested by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ).
- Microsatellite-instability (MSI) was tested by fragment analysis, immunohistochemistry (IHC), and next generation sequencing (NGS).
- Tumor mutational burden (TMB) totaled somatic mutations per tumor (high≥10 mt/MB).
- Tumors with *AR*-high and *AR*-low expression were classified by top and bottom quartile, respectively.
- RNA-deconvolution using QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment.
- Real world OS was extracted from insurance claims and calculated using Kaplan-Meier estimates for molecularly defined cohorts from tissue collection to last contact.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q < 0.05).

Table 1: Patient demographics

Variables	
Count (N)	27169
Median age (range)	59 [0 - >89]
Gender	
Female	26839 (98.8%)
Male	330 (1.2%)
Histological subtypes (count)	
Ductal	7116 (26.1%)
Lobular	1033 (3.8%)
Mixed	209 (0.76%)
Other/Unclear	18811 (69.2%)
Molecular subtypes (count)	
HR$^-$/HER2$^+$	819 (3.0%)
HR$^+$/HER2$^+$	1057 (3.8%)
HR$^+$/HER2$^-$	11791 (43.3%)
TNBC	6552 (24.1%)
Other/Unclear	6950 (25.5%)
Tumor site	
Primary	10410 (38.3%)
Metastatic	16753 (61.6%)
Other/Unclear	6 (0.02%)

RESULTS

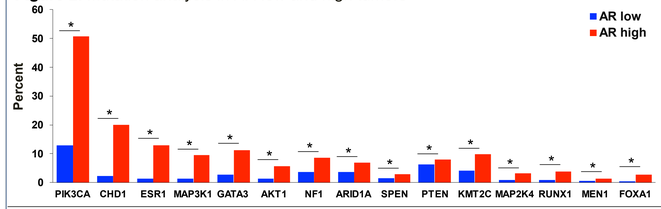
Figure 1. *AR* expression in breast cancer



	Ductal	Lobular	HR$^+$/HER2$^-$	HR$^+$/HER2$^+$	HR$^-$/HER2$^+$	TNBC	Primary	Metastatic
N	3559	538	5960	468	336	2980	4494	6749
Median	27.78	62.87	50.28	50	37.43	3.68	28.66	34.22

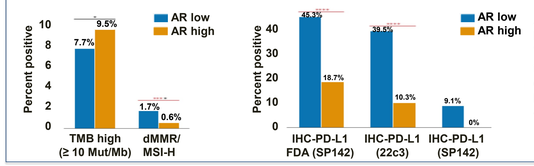
Median *AR* expression was higher in lobular compared to ductal carcinoma (2.2-fold) and in HR$^+$/HER2$^-$ compared to TNBC (13.9-fold).

Figure 2. Mutation analysis in *AR* low and high tumors



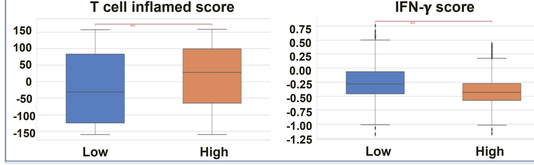
Compared to *AR*-low, *AR*-high BC had higher frequency of *PIK3CA* (50.6% vs 12.7%), *CDH1* (20% vs 2.2%), *ESR1* (12.8% vs 1.4%), *MAP3K1* (9.4% vs 1.4%), *GATA3* (11.2% vs 2.7%), *AKT1* (5.7% vs 1.4%), *NF1* (8.6% vs 3.6%), *ARID1A* (6.9 vs 3.6), *SPEN* (2.8% vs 1.5%), PTEN (6.24% vs 7.91%), KMT2C (4.17% vs 9.8%), MAP2K4 (0.87% vs 3.14%), RUNX1 (0.88% vs 3.86%), MEN1 (0.52% vs 1.3%) and FOXA1 (0.4% vs 2.68%). (*p < 0.05).

Figure 3. Immune markers in *AR* expressing breast cancer



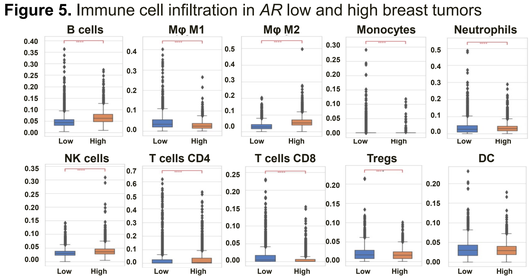
AR-high BC had higher frequency of TMB and lower frequency of dMMR/MSI-H and PD-L1 positivity. (*p < 0.05).

Figure 4. T cell inflamed and IFNγ score in *AR* low and high tumors



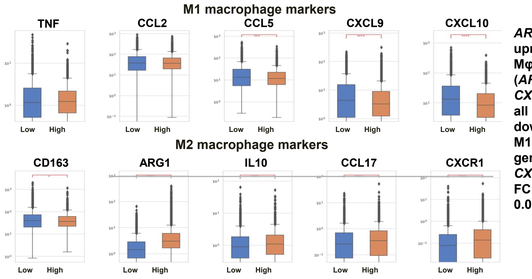
AR-high BC had higher T cell inflamed scores (27.0 vs -31.5) and lower IFNγ score (-0.43 vs -0.28). (*p < 0.05).

Figure 5. Immune cell infiltration in *AR* low and high breast tumors



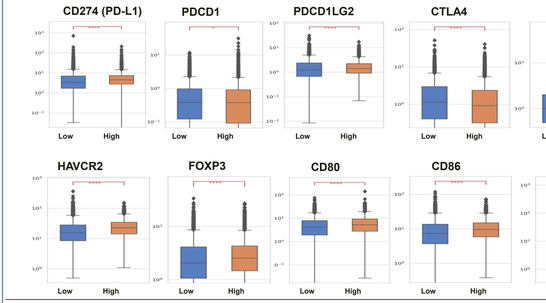
AR-high BC had increased immune cell infiltration of B cells (6% vs 4%), M2 Mφ (5% vs 2%), and NK cells (3% vs 2%), but decreased infiltration of M1 Mφ (2% vs 3%) (all p < 0.05).

Figure 6. M1 and M2 macrophage-related gene expression in *AR* low and high tumors



AR-high BC had upregulation of M2 Mφ related genes (*ARG1, IL10, CCL17, CXCR1*, FC: 1.2-1.8, all p < 0.05) and downregulation of M1 Mφ related genes (*CCL2, CCL5, CXCL9, CXCL10*, FC: 1-1.5, all p < 0.05).

Figure 7. Immune-related gene expression in *AR* low and high breast tumors

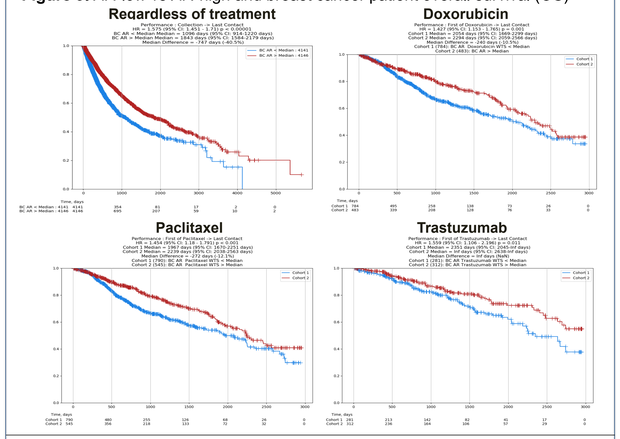


AR-high BC had higher expression of immune checkpoint genes (*CD274, PDCD1LG2, LAG3, HAVCR2, FOXP3*, FC: 1.1-1.4, all p < 0.05)

Figure 8. Gene set enrichment analysis (GSEA)

AR-high BC had gene set enrichment of the IL2-STAT5 signaling, Myogenesis, Adipogenesis and Complement compared to *AR* low tumors. A Negative NES imply *AR*-high tumors are enriched with gene set.

Figure 9. *AR*-low vs *AR*-high and breast cancer patient overall survival (OS)



AR-high BC was associated with improved OS compared to *AR*-low BC (mOS: 1843 vs 1096 days; HR 0.6, 95% CI 0.5-0.7, p < 0.00001), and with doxorubicin (2294 vs 2054 days; HR 0.7, 95% CI 0.5-0.9, p < 0.001) , paclitaxel (2239 vs 1967 days; HR 0.7, 95% CI 0.5-0.9, p < 0.001) and trastuzumab (inf vs 2351 days; HR 0.6, 95% CI 0.4-0.9, p < 0.01) treatment.

CONCLUSIONS

Our data suggest a strong association between *AR* expression and increased mutations in several cancer related genes, immune checkpoint markers, the *IL2-STAT5* pathway, differential immune cell infiltration, and improved overall survival.