Effect of homologous recombination deficient (HRD) breast cancers on a distinct immune marker phenotype by comprehensive genomic and immune profiling (CGIP)

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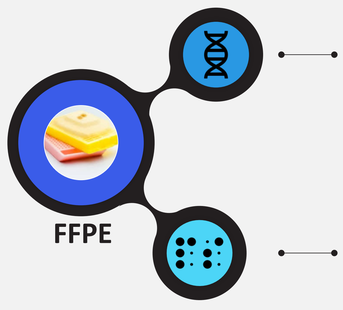
Introduction

- Immune checkpoint inhibitors (ICIs) have transformed the treatment paradigm for various advanced solid tumors, providing durable anti-tumor response and survival benefits in patients.
- However, in breast cancer, the use of ICIs has been primarily limited to triple-negative breast cancer given the heterogeneity in the immune microenvironment among different molecular subtypes.
- Preclinical evidence suggests that breast cancer with features of genomic instability may upregulate the host antitumor immune response by producing neoantigens through DNA damage and increasing interferon production through the stimulator of interferon genes (STING) pathway[1].
- In this study, we evaluated the association between features of genomic instability and immune response in a real-world breast cancer patient population.

Methods

- A retrospective cohort of **529** breast tumors tested in the real-world clinical setting were evaluated by comprehensive genomic and immune profiling (CGIP) of the tumor microenvironment (Figure 1).
- HRD phenotype was defined as tumor with any single nucleotide variants (SNV), indels, copy number variations (CNV) or fusions in the following genes: **ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA, MRE11A, NBN, PALB2, RAD50 and RAD51**. If a tumor does not exhibit alterations in the HR genes listed, then it is classified as HR-proficient.



Genomic Profiling

SNV/INDEL/Fusion/CNV for 523 genes[2]
Tumor mutational burden (TMB)
Microsatellite Instability (MSI)

Immune Profiling

- RNA-seq expression profiling of 395 immune transcripts[3]
- PD-L1 IHC[3]
- Cell Proliferation[4]
- Tumor Inflammation[4]
- Cancer Testis Antigen Burden[5]

Figure 1. CGIP methods description.

- Over-representation and proportion analysis using chi-squared test was applied to determine association of HRD to immune correlates

References
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4. Pabla S et al. Integration of tumor inflammation, cell proliferation, and traditional biomarkers improves prediction of immunotherapy resistance and response. Biomark Res 9, 56 (2021).
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Breast cancer with mutations in the HR genes demonstrated immune features of greater susceptibility to immune checkpoint inhibitors.

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Table 1. Cohort characteristics.

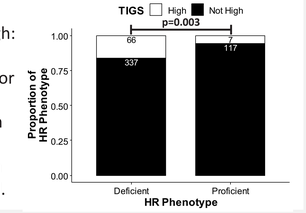
Variable	Group	N (%)
Age	Median: 63.2 years, Range: 25.5-93.5 years	529 (100%)
Gender	Female	519 (98%)
	Male	10 (1.9%)
HR Phenotype	Deficient	405 (77%)
	Proficient	124 (23%)
Sample Source	Lymph node	72 (14%)
	Metastatic	232 (44%)
	Primary breast	224 (42%)
Tumor Histology	Invasive ductal carcinoma, NOS	287 (54%)
	Invasive lobular carcinoma	26 (4.9%)
	Mammary adenocarcinoma, NOS	207 (39%)
	Other	10 (1.9%)
All Samples		529 (100%)

Results

HRD phenotype and markers of genomic instability

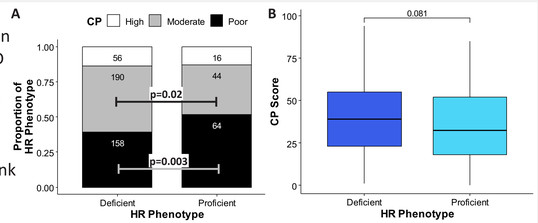
- Compared to those with HRP phenotype, HRD tumors demonstrated a higher TMB proportion (16% vs. 5.6%, p=0.003).

Figure 2. TMB group (TMB High: > 10 mut/Mb) distribution in for each HRD phenotype with total patient number in each group indicated.



- While HRP tumors showed a relatively low cell proliferation, HRD tumors were associated with a higher but moderate cell proliferation score (p = 0.081).

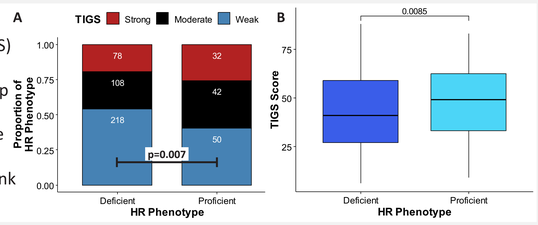
Figure 3. Cell proliferation (CP) distributions by HRD phenotype: A) CP group prevalence for each HRD phenotype; B) CP score distribution in each HRD phenotype. Wilcoxon Rank Sum p values indicated.



HRD phenotype and tumor inflammation

- However, HRD phenotypes had significantly higher proportion of weakly inflamed tumors, as represented by weaker TIGS scores (p=0.0085).

Figure 4. Tumor immunogenic score (TIGS) distributions by HR phenotype: A) TIGS group prevalence for each HR phenotype; B) TIGS score distribution in each HR phenotype. Wilcoxon Rank Sum p values indicated.



- No significant difference in PD-L1 or CTAB was found between HRD and HRP phenotypes.

Conclusions

- Breast tumors with mutations in the HR genes demonstrated **greater markers of genomic instability** such as TMB and moderate CP index of both tumor and immune cells. These suggest **presence of higher tumor neoantigens** and therefore **greater susceptibility to immune checkpoint inhibitors**.
- However, this cohort l**acked** elevated markers of immune infiltration (TIGS), indicating a mechanism of **potential tumor immune evasion**.

Future Directions for Research:

- Although further clinical validation of these immune biomarkers is required, this study demonstrates the potential for CGIP to support clinical trial selection for therapies targeting the complex interplay of genomic and immune components of breast cancer.

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