Homologous Recombination Deficiency in Breast Cancer: Exploratory Analysis of a Brazilian Cohort with Germline Genetic Testing

A. K. Souto[1], F. C. Koyama[2], S. S. Koide[3], B. B. Souza[4], J. D. Massaro[5], L. J. Oliveira[6], L. Yamamoto[7], T. A. Santana[8], M. L.Bulcão[9], C. B. Fernandes[10], C. A. Resende[11], M. S. Mano[12], L. C. Landeiro[13], G. O. Bretas[14], B. C. B. Miranda[15], R. Dienstmann[16], R. L. Sandoval[17]; [1-11/14-16] Oncoclínicas&Co, BRAZIL; [12]Hospital Albert Einstein, São Paulo, BRAZIL; [17]Hospital Sírio Libanês, Brasília, BRAZIL.

Introduction

Breast cancer (BC) is the most prevalent malignancy among women, and 5-10% are associated with germline pathogenic/likely pathogenic variants (PVs) in high-penetrance BC genes, mostly *BRCA1/2*. These genes encode proteins involved in the homologous recombination repair (HRR) pathway, whose dysfunction leads to homologous recombination deficiency (HRD). Germline PVs, somatic alterations, and/or epigenetic modifications in HRR pathway genes can induce the HRD tumor phenotype. Although well characterized in ovarian cancer, data on HRD in BC remain scarce, particularly in the Brazilian population.

Study Objectives

To assess the prevalence of HRD in a cohort of Brazilian patients with BC.

To characterize the molecular profile of these tumors, including PVs in genes involved in the HRR pathway.

To evaluate differences between HRD-positive (HRD+) and HRD-negative (HRD–) groups regarding clinicopathological features such as molecular subtype, age, and tumor stage.

Methods and Materials

This retrospective single-center study included women with BC treated between 2020-2023 whose formalin-fixed paraffin-embedded tumor samples were available for analysis at Oncoclínicas Precision Medicine laboratory (OCPM). The laboratory database was used to identify eligible samples. All tumor samples were submitted to pathology review. HRD analysis assessed genomic scars (loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) by sequencing 13,809 single nucleotide polymorphisms, plus mutational profiling of 15 genes involved in the HRR pathway. HRD status was defined using a validated assay by OCPM. Genomic instability score **cutoff of 65 or higher**. HRD profiles were described in relation to clinicopathological and molecular features.

Results

Among 134 identified samples, 55 patients were consecutively selected for tumor analysis according to the study budget. Eight samples were excluded due to inadequate material for molecular analysis. Among 47 cases eligible for HRD analysis, 9 samples were excluded due to post-analytical failures.

Study Cohort Characteristics

HRD profiling was performed on **38 BC tumor samples.**

Tumor Sample Origin:

- 50% from primary tumors
- 50% from metastatic sites

Overall HRD Prevalence: 31.6% (12/38)

Profile of Patients with HRD+ Tumors (n=12):

- 75% were premenopausal.
- Younger mean age at diagnosis: **47.6 years**.
- 41.7% presented with **locally advanced disease (Stage III)**.
- 75% of analyzed samples were **primary tumors**.

Germline Status in the HRD+ Group:

33.3% (4/12) of HRD+ patients carried **germline PVs** in HRR genes:
Genes*: BRCA1* (2), *BLM* (1), *RAD51C* (1)
60% of these PVs were truncating variants (nonsense/frameshift)

Variable	Cohort (n=38)	HRD+ (n=12)	HRD- (n=26)	p-vaue
Age (years)	51,4	47,6	52,8	0,28 (t-test)
Menopausal Status				
Premenopausal	20 (52,6%)	9 (75%)	11 (42,3%)	0,049 (χ^2)
Postmenopausal	18 (47,4%)	3 (25%)	15 (57,7%)	0,049 (χ^2)
Molecular Subtipe				
Triplo-negative	12 (31,6%)	8 (66,7%)	4 (15,4%)	0,001 (χ^2)
Luminal B-like	18 (47,4%)	3 (25%)	15 (57,7%)	0,049 (χ^2)
Luminal A-like	6 (15,8%)	1 (8,3%)	5 (19,2%)	0,65 (Fisher)
HER2+	1 (2,6%)	0 (0%)	1 (3,8%)	1,00 (Fisher)
Unknown	1 (3,8%)	-	1 (3,8%)	-
Staging				
Stage I	6 (15,8%)	1 (8,3%)	5 (19,2%)	0,65 (Fisher)
Stage II	10 (26,3%)	4 (33.3%)	6 (23.1%)	0.69 (χ^2)
Stage III	12 (31,6%)	5 (41.7%)	7 (26.9%)	0.47
Stage IV	7 (18,4%)	2 (16.7%)	5 (19.2%)	1.00
Germline Status				
PVs in HRR genes	8 (21%)	4 (33.3%)	4 (15.4%)	0.23 (Fisher)
VUS in HRR genes	22 (57%)	4 (33,3%)	18 (69.3%)	0.027 (χ^2)

Table . Comparative Analysis: HRD+ (n=12) vs. HRD- (n=26)

Discussion

Clinical and Hormonal Profile

Although mean age differed numerically (HRD+: 47.6 vs HRD-: 52.8 years; p=0.28), the strong HRD+/premenopausal association (75% vs 42.3%; p=0.049) is clinically relevant. The limited sample size (n=38) requires validation in larger cohorts.

Association with TNBC Molecular Subtype

The strongest correlation was observed in TNBC, with 66.7% of HRD+ tumors classified within this subtype (OR = 10.5; 95% CI: 2.1–52.3; p = 0.001).

Discussion

This distribution aligns with literature evidence demonstrating higher prevalence of HRD in TNBC. Importantly, it is estimated that 50–60% of TNBC cases may exhibit a "*BRCAness*" phenotype—molecular characteristics similar to BRCA-mutated tumors, even in the absence of *BRCA* PVs[1-3].

Discussion

No Correlation with Staging

No significant differences were observed in tumor stage distribution between the groups.

Germline Genetic Profile

The germline analysis of the cohort (n = 38) showed a 10.5% prevalence of *BRCA1/2* PVs, consistent with national and international reports in early-onset breast cancer[4-5]. Pvs in non-*BRCA* HRR genes were also found in 10.5% of patients and in 13.3% of those with TNBC, highlighting the value of expanding testing beyond *BRCA*[6]. Although not statistically significant (p = 0.23), HRD+ patients showed a higher frequency of HRR PVs (33.3% vs 15.4%; OR = 2.8), including variants in *BRCA1*, *BLM*, and *RAD51C*. The predominance of truncating variants supports the role of complete loss of HRR gene function in driving the HRD phenotype[7].

Conclusions

This is the **first Brazilian study** to evaluate HRD in breast cancer, revealing a prevalence of **31.6%**, consistent with international data. HRD was more frequent in aggressive tumor subtypes, younger patients, and those with germline pathogenic variants in HRR genes. The identification of alterations beyond classic *BRCA1/2* mutations expands the molecular spectrum of HRD.

Contact

Andreza Souto
Oncoclínicas&Co, BRAZIL
andrezakarine@hotmail.com

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