A Comprehensive Landscape of *BRCA1* vs *BRCA2* Associated Molecular Alterations and Survival Outcome Across 35 cancer types

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Background

Hereditary breast and ovarian cancer syndrome (HBOC) due to a *BRCA1* or *BRCA2* gene mutation is inherited in an autosomal dominant fashion [1]. Poly (ADP-ribose) polymerase inhibitors (PARPi) are effective therapies for some patients with either germline or somatic *BRCA1/2* mutations or with homologous recombination repair deficiency (HRD) [2]. While *BRCA1* and *BRCA2* perform similar functions in DNA damage repair, they encodes completely distinct proteins, and big differences exist in terms of the types of cancers [3] and the histopathological characteristics associated with mutations within these genes [4]. In addition, some evidence shows that mutations in *BRCA1* and *BRCA2* may have a prognostic value [5]. Nevertheless, molecular differences between patients carrying *BRCA1* vs *BRCA2* pathogenic variations and whether these differences may have impact on prognosis and/or prediction of PARP inhibitors efficacy is not well-described [6].

For these reasons, we aimed to describe the molecular landscape of solid tumors harboring pathogenic variations in *BRCA1* vs *BRCA2* genes. In addition, we further sought to investigate whether different associations exist with microsatellite instability (MSI), tumor mutational burden (TMB) and other HRD-related genes between *BRCA1* vs *BRCA2* mutated populations using real world data (RWD). We investigated the molecular differences between *BRCA1* vs *BRCA2* mutated tumors by tumor location and the molecular differences between different tumor types among *BRCA1/2* mutated population. Finally, we evaluated the impact of *BRCA1* vs *BRCA2* mutations on outcomes and response to treatment (PARP inhibitors and/or platinum-based therapy).

Methods

- A total of 17,640 tumors that underwent comprehensive genomic profiling by Caris Life Sciences (Phoenix, AZ) were identified from a retrospective database.
- Whole Exome Sequencing was done on genomic DNA isolated from a microdissected, formalin-fixed paraffin-embedded tumor sample using the Illumina NovaSeq 6000 sequencers. A hybrid pull-down panel of baits designed to enrich for more than 700 clinically relevant genes at high coverage and high read-depth was used, along with another panel designed to enrich for an additional >20,000 genes at lower depth. A 500Mb SNP backbone panel (Agilent Technologies) was added to assist with gene amplification/ deletion measurements.
- MSI was examined by a combination of fragment analysis, NGS and immunohistochemistry.
- TMB was measured by counting all non-synonymous missense, nonsense, inframe insertion/deletion and frameshift mutations found per tumor that had not been previously described as germline alterations in dbSNP151, Genome Aggregation Database (gnomAD) databases or benign variants identified by Caris geneticists. A cutoff point of >=10 mutations per MB was used.
- Chi-square/Fisher-Exact tests were performed for comparative analysis using SPSS v23 (IBM SPSS Statistics), and significance was determined by $p < 0.05$ after adjusting for multiple comparison.
- Real-world overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patient cohorts.

References

1. Petrucelli N, et al. GeneReviews. 1993
2. Sachdev E, et al. Target Oncol 2019
3. Casaubon JT. StatPearls 2021
4. Vocka M, et al. Cancers (Basel) 2019
5. Byrd LM, et al. Cancer Epidemiol Biomarkers Prev 2008
6. Rebbeck TR, et al. JAMA 2015.

Results

Table 1: BRCA1 and 2 mutations in the investigated cohort

Tumor testing results: Whole Exome Sequencing				
Cancer types	**BRCA1m**	**BRCA2m**	**BRCA1/2 comutated**	**Total MT**
Ovarian Surface Epithelial Carcinomas	138	83	2	221
Breast Carcinoma	60	78	0	138
Lung Non-small cell lung cancer (NSCLC)	42	58	0	100
Prostatic Adenocarcinoma	8	53	0	61
Pancreatic Adenocarcinoma	8	40	0	48
Endeometrial Cancer	16	29	5	45
Bladder Cancer	9	13	1	22
Cancer of Unknown Primary	8	14	1	22
Gastric Adenocarcinoma	4	14	0	18
Esophagogastric Junction Carcinoma	4	8	0	12
Glioblastoma	4	6	0	10
Small Intestinal Malignancies	4	6	2	10
Head and Neck Cancers	3	7	0	10
Cholangiocarcinoma	1	9	0	10
Melanoma	6	3	0	9
Uterine Serous Carcinoma	2	6	0	8
Cervical Cancer	1	6	0	7
Female Genital Tract Malignancy	1	4	0	5
Colorectal Adenocarcinoma	0	4	0	4
Lung Small Cell Cancer (SCLC)	2	1	0	3
Kidney Cancer	1	2	0	3
Squamous Cell Skin Cancer	1	2	0	3
Soft Tissue Tumors	0	3	0	3
Esophageal Carcinoma	1	1	0	2
Malignant Pleural Mesothelioma	1	1	0	2
Vulvar Cancer (squamous cell carcinoma)	1	1	0	2
Neuroendocrine tumors-GI	0	2	0	2
Anal Carcinoma	1	0	0	1
Anaplastic Thyroid Carcinoma	0	1	0	1
Bone Cancer - Chordoma	0	1	0	1
Extrahepatic Bile Duct Adenocarcinoma	0	1	0	1
Liver Hepatocellular Carcinoma	0	1	0	1
Male Genital Tract Malignancy	0	1	0	1
Nodal Diffuse Large B-Cell Lymphoma	0	1	0	1
Peritoneal Mesothelioma	0	1	0	1
Grand Total	327	461	12	788

Figure 1: lollipop plots of BRCA1 (top) and BRCA2 (bottom) mutations

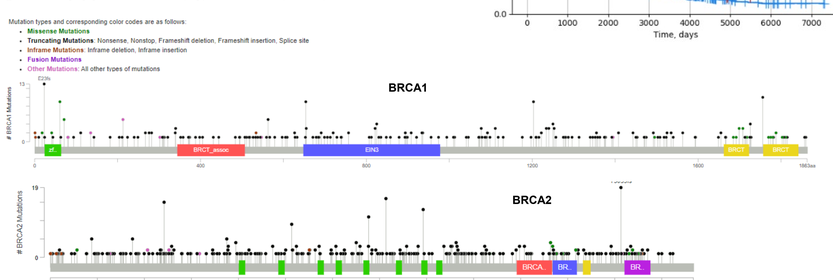


Figure 2: molecular comparison in all tumors carrying BRCA1 mutation vs. BRCA2 mutations (: adjusted p values <0.05; *: p<0.05)**

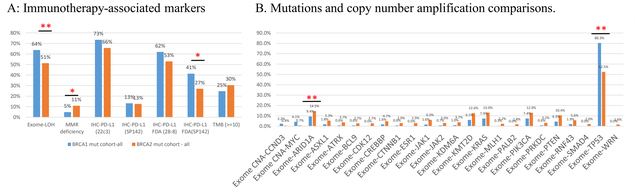
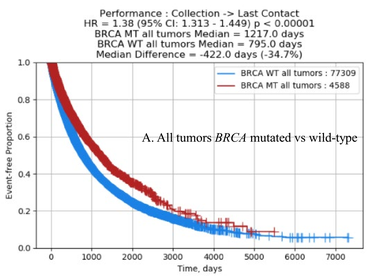
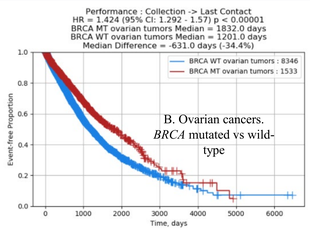
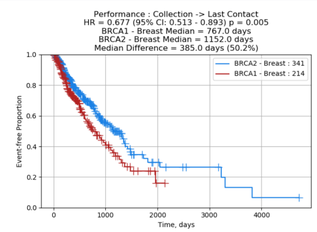


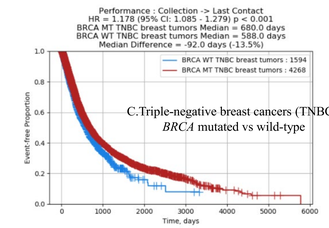
Figure 3. Real-world overall survival (OS) comparison in molecularly defined cancer groups. Favorable prognostic effects of *BRCA* mutations (*BRCA1/2*) were seen in all tumors (A), ovarian tumors (B) and TNBC (C); longer survival was seen in *BRCA2-mt* tumors compared to *BRCA1-mt* in breast tumors (D) and tumors treated with PARPi (E).

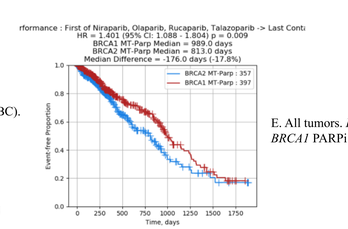






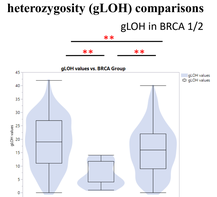
D. Breast cancers. *BRCA2* vs *BRCA1* mutated





E. All tumors. *BRCA2* vs *BRCA1* PARPi treated-patients

Figure 3: Genomic Loss of heterozygosity (gLOH) comparisons



Conclusions

- In total, 17,640 tumors were included, of which 776 (4.3%) had tumor-based *BRCA1/2* mutations.
- *BRCA1/2* mutations were most commonly seen in ovarian (N = 221/2187, 10.1%), breast (138/2506, 5.5%), prostate (61/1131, 5.4%), pancreatic (48/1430, 3.4%), and non-small cell lung (100/4046, 2.5%) cancers.
- *BRCA1* mutations were more common in younger patients (median age, 61 vs 65 years, $p < .001$).
- When compared to *BRCA2* mutations, *BRCA1* were more often associated with gLOH-H and *TP53* mutations
- In univariate analyses, overall *BRCA1/2* mutations were associated with improved OS compared to wild type. This effect was seen in ovarian and triple-negative breast cancers (TNBC)
- In all breast cancers, *BRCA2* mutations had a superior OS compared to *BRCA1*
- Using RWD, PARPi treated-patients with *BRCA2* mutations had worse OS than *BRCA1* mutations
- *BRCA1* and *BRCA2* mutations had variable power to be prognostic and predictive for PARPi efficacy among different cancer types using RWD.

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