



Exploring the nuances between BRCA1 and 2: a multiomic analysis

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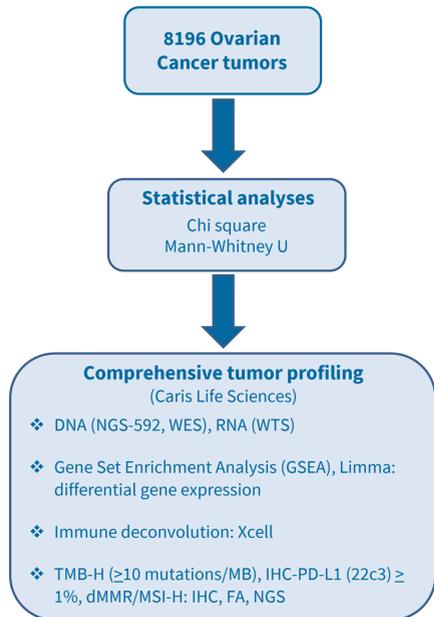


Background:

- Emerging data suggest that key differences exist between BRCA1 and BRCA2 associated OC
- The purpose of this study was to identify gene expression profiles, interacting pathways and immune microenvironment of BRCA1mut, BRCA2mut and homologous-recombination wild-type (HRwt) associated HGSOC utilizing the CARIS database

Methods:

- 8196 OC were classified into 3 groups: BRCA1mut, BRCA2mut or HRwt. HRwt was defined as samples negative for aberrations in both BRCA1 and BRCA2, as well as for 28 other homologous recombination genes



Results:

Table 1. Patient demographics.

Characteristics	All, N (%)	BRCA1, N (%)	BRCA2, N (%)	HRwt, N (%)
N	8196	677 (8.26)	439 (5.36)	7080 (86.4)
Age, median (range)	65 (15-90)	59.0 (26-90)	65.0 (21-90)	65.0 (15-90)
Histology, N(%)				
Carcinosarcoma	253 (3.09)	6 (0.9)	5 (1.1)	242 (3.4)
Clear Cell	322 (3.93)	3 (0.4)	3 (0.7)	316 (4.5)
Endometrioid	354 (4.32)	3 (0.4)	14 (3.2)	337 (4.8)
High-grade Serous	5110 (62.3)	523 (59.7)	306 (52.8)	4281 (44)
Low-Grade Serous	259 (3.16)	2 (0.3)	5 (1.1)	252 (3.6)
Mixed	23 (0.28)	0 (0)	1 (0.2)	22 (0.3)
Mucinous	157 (1.92)	0 (0)	1 (0.2)	156 (2.2)
Other	1718 (21)	140 (20.7)	104 (23.7)	1474 (20.8)

Fig 1. Top Mutated Genes in BRCAmt or HRPwt Serous Ovarian Cancer

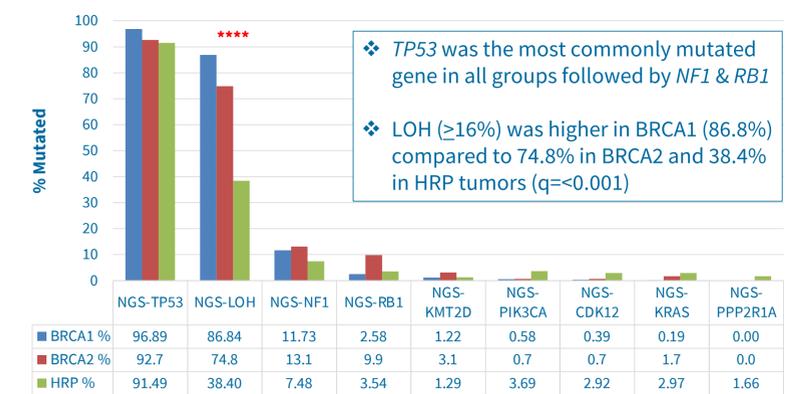


Fig 2. Top Amplified Genes in BRCAmt or HRPwt Serous Ovarian Cancer

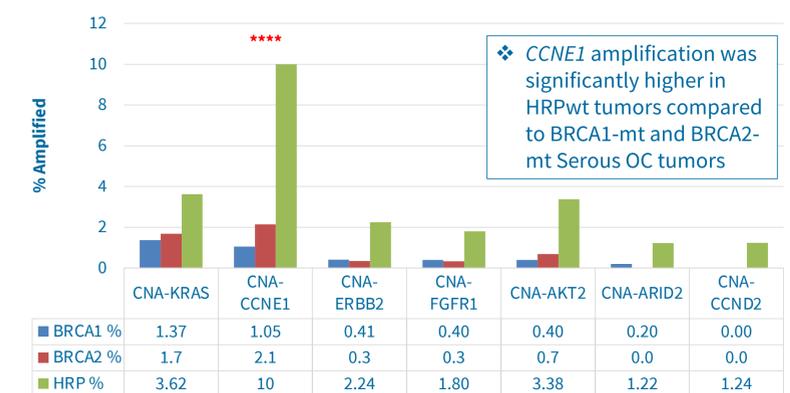
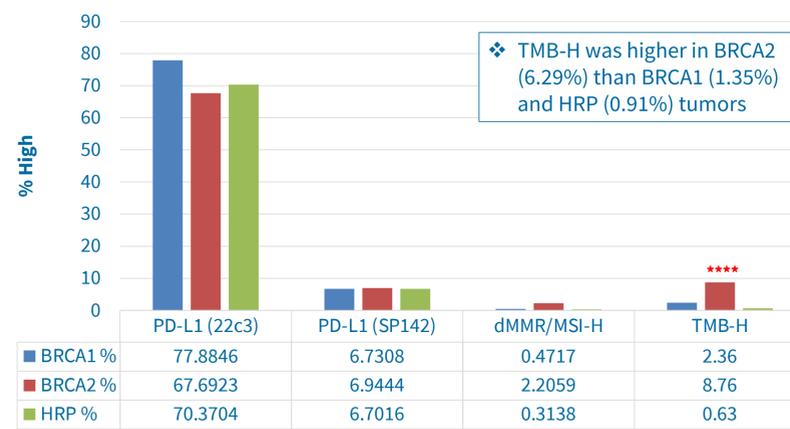


Fig 3. IO Therapy-related Biomarkers in (met) BRCA1/2 MT or HRPwt Serous Ovarian Cancer



- Expression of IC genes was significantly higher in BRCA1- and BRCA2-mt tumors (Table 2)
- HRP tumors had decreased M1 Macrophages and Dendritic cells infiltration (q<0.05) (Table 2)
- BRCA1 tumors had significantly increased NK cells (q<0.01), T-cell inflamed score and IFN score (q<0.001) (Table 2)

Table 3. GSEA Hallmarks pathway analysis in BRCA1-mt, BRCA2-mt and HRPwt Serous Ovarian Cancer tumors

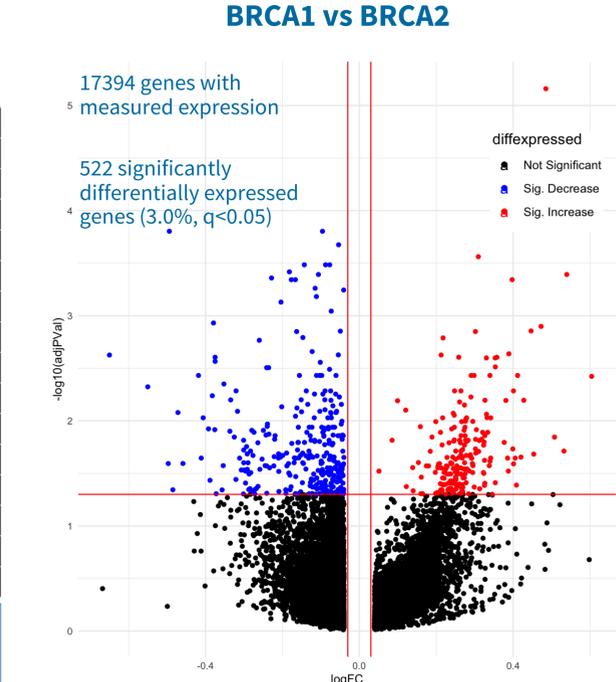
Pathways	BRCA1 vs 2		BRCA2 vs 1		BRCA1 vs HRP		BRCA2 vs HRP	
	NES	FDR	NES	FDR	NES	FDR	NES	FDR
INTERFERON_ALPHA_RESPONSE	1.51	0.68	-1.45	1.00	1.85	0.02	1.42	1
INTERFERON_GAMMA_RESPONSE	1.50	0.49	-1.39	1.00	1.86	0.04	1.40	0.749
ALLOGRAFT_REJECTION	1.47	0.42	-1.31	0.71	1.77	0.04	1.14	1
ADIPOGENESIS	1.46	0.40	-1.37	0.96	1.33	0.26	0.87	1
FATTY_ACID_METABOLISM	1.44	0.38	-1.23	0.60	1.34	0.26	1.11	1
ESTROGEN_RESPONSE_EARLY	1.40	0.44	-1.35	0.86	1.48	0.14	0.85	1
ESTROGEN_RESPONSE_LATE	1.37	0.40	-1.30	0.57	1.40	0.20	1.07	1
IL6_JAK_STAT3_SIGNALING	1.37	0.33	-1.31	0.65	1.63	0.04	1.30	0.671
COMPLEMENT	1.36	0.31	-1.22	0.60	1.43	0.17	0.70	0.938
INFLAMMATORY_RESPONSE	1.34	0.36	-1.33	0.73	1.70	0.04	1.27	0.714
TNFA_SIGNALING_VIA_NFKB	1.33	0.31	-1.34	0.82	1.45	0.17	0.98	1
OXIDATIVE_PHOSPHORYLATION	1.32	0.29	-1.21	0.58	1.34	0.26	0.98	1
UV_RESPONSE_UP	1.21	0.48	-1.16	0.57	1.30	0.29	1.15	1
MTORC1_SIGNALING	1.03	0.53	-0.95	0.68	1.38	0.22	1.21	0.936

- GSEA and ssGSEA pathway analysis identified differential regulation of Fatty Acid Metabolism, Myc targets, ROS pathway, Oxidative Phosphorylation, Wnt B-catenin signaling pathways between the 3 groups (Table 3)

Table 2. Immune Tumor Microenvironment of BRCA1-mt, BRCA2-mt and HRPwt Serous Ovarian Cancer tumors

Immune Microenvironment	BRCA1-mt	BRCA2-mt	HRP-wt	q-value
Macrophage	0.0802	0.0834	0.0758	1.00E-03
Macrophage M1	0.0741	0.0711	0.066	1.00E-04
T cell NK	0.0292	0.0195	0.0209	1.00E-04
Myeloid dendritic cell activated	0.2557	0.2537	0.2299	4.00E-03
Plasmacytoid dendritic cell	0.0176	0.0187	0.0095	4.60E-11
CD80	3.05	3.28	2.5	2.73E-06
CD86	7.51	6.64	5.92	3.28E-05
CD274	3.11	3.05	2.7	5.99E-04
CTLA4	1.25	1.28	0.97	7.75E-04
HAVCR2	15	13.8	12.1	2.73E-06
IFNG	0.36	0.33	0.29	7.83E-04
IDO1	6.2	5.75	3.89	2.44E-12
LAG3	1.17	1.26	1	9.74E-03
PDCD1	0.44	0.36	0.34	4.27E-03
PDCD1LG2	1.17	1.02	0.98	1.69E-03
Immune Signature IFN	-0.162	-0.188	-0.227	2.15E-06
T-Cell Inflamed	40	-8.5	-9	2.04E-05

Fig 4. Volcano plot showing differentially expressed genes in BRCA1-mt over BRCA2-mt Serous Ovarian Cancer tumors



Conclusions:

- We describe BRCA2 versus BRCA1 associated ovarian cancer in the largest sample of BRCA1 and 2 mutated OC to date
- BRCA1 mt tumors seem to have a more immunogenic phenotype compared to BRCA2 and WT tumors
- BRCA2 mt tumors had significantly higher TMB-H prevalence compared to BRCA1 mt and HRPwt tumors
- Further, metabolic pathways seem to be differentially altered between all groups
- Results can potentially inform targeted therapeutic studies based on unique BRCA phenotype

BRCA1 and BRCA2 mutated HGSOC have unique phenotypes that may lead to more personalized therapeutic approaches