Characteristics of Colorectal Cancer (CRC) Patients with BRCA1 and BRCA2 Mutations

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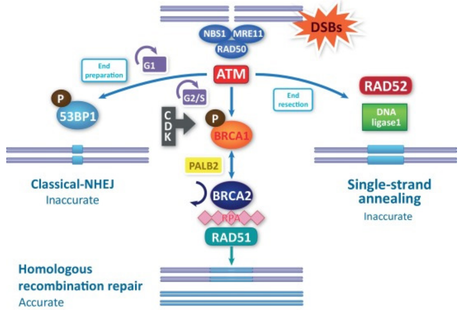
Introduction

- BRCA1 and BRCA2 are important tumor suppressor proteins involved in double-stranded DNA break repair using homologous recombination.[1]
- In 1994, the Breast Cancer Linkage Consortium presented an increased risk of colorectal cancer (CRC) among BRCA1 mutation carriers, which ushered more research into BRCA1 genetic alterations in CRC.[1]
- To date, studies have shown that BRCA1/2 mutations increase the risk of CRC and are associated with early-onset disease, younger age, MSI and left-sided tumors.[2,3] However, further characterization of these mutations in CRC is needed to better understand their prognostic role.



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Methods

- A total of 6396 CRC tumor samples were tested with Next-Generation Sequencing (NGS) on a 592-gene panel
- Pathogenic or presumed pathogenic variants were counted as mutations (mt).
- Microsatellite instability (MSI) and tumor mutational burden (TMB) were tested by NGS.
- Statistical correlations were investigated using ANOVA, Chi-square and t-test.

References

1-Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer. 2012;12(1):68-78.
2-Garcia JM, Rodriguez R, Dominguez G, Silva JM, Provencio M, Silva J, et al. Prognostic significance of the allelic loss of the BRCA1 gene in colorectal cancer. Gut. 2003;52(12):1756-63.
3-Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017;35(10):1086-+.

Results

Demographics

n= 6396 tumors sequenced

	BRCA1		BRCA2	
Results	N	%	N	%
Wild Type	5983	93.5%	5574	87.1%
Benign	6	0.1%	24	0.4%
Presumed Benign	48	0.8%	241	3.8%
Variant of uknown significance	213	3.3%	365	5.7%
Presumed pathogenic	5	0.1%	4	0.1%
Pathogenic	67	1.0%	175	2.7%
indeterminate	74	1.2%	13	0.2%
Total of tumors sequenced	6396			

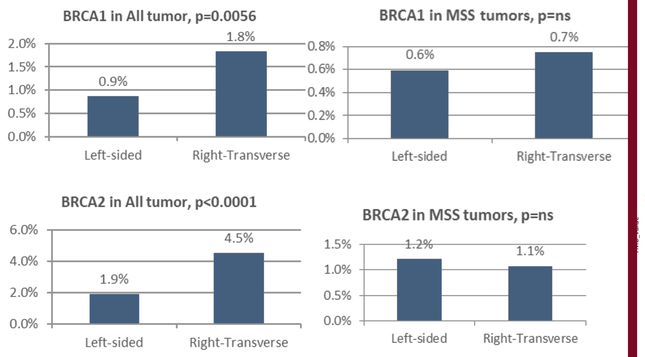
N indicates number of tumors sequenced. When multiple mutations are found, results are shown for the most significant : pathogenic>presumed pathogenic>VUS etc.

BRCA1 mutations more prevalent in Females

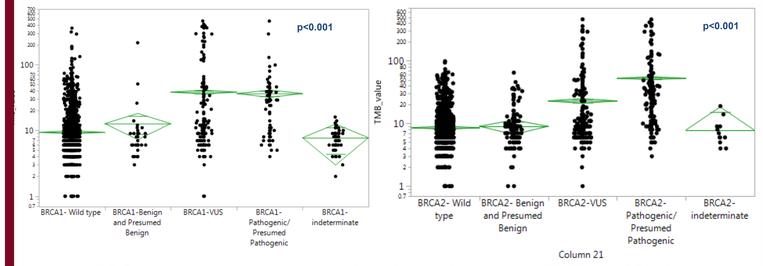
	BRCA1			BRCA2		
	Female	Male	Total	Female	Male	Grand Total
Wild Type	2788	3195	5983	2603	2971	5574
Benign	3	3	6	10	14	24
Presumed Benign	24	24	48	122	119	241
Variant of Unknown Significance	102	111	213	184	181	365
Presumed pathogenic	4	1	5		4	4
Pathogenic	43	24	67	75	100	175
indeterminate	36	38	74	6	7	13
Presumed pathogenic+Pathogenic	47	25	72	75	104	179
Grand Total	3000	3396	6396	3000	3396	6396

1.5% vs. 0.74%, p=0.0019 2.5% vs. 3.1%, p=ns

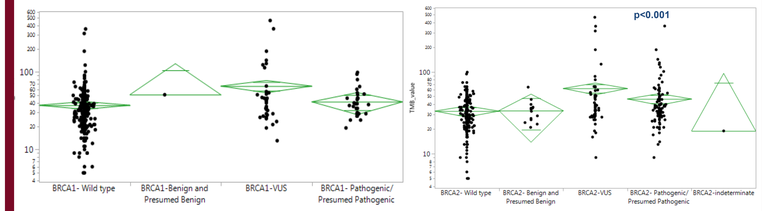
Both BRCA1/2 mutations are associated with Right-sided CRCs secondary to MSI-high status



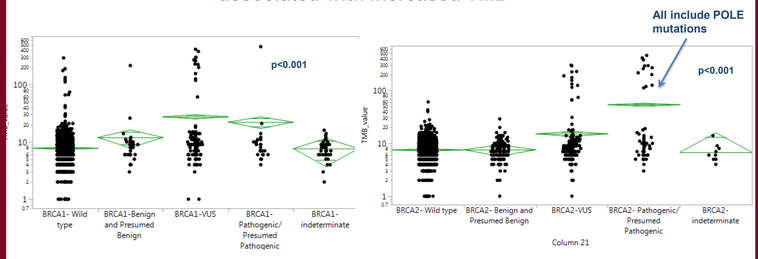
Mutations in BRCA1/2 are associated with increased TMB in all CRCs



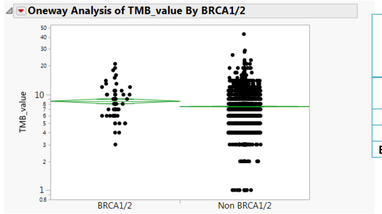
BRCA2 mutations are associated with increased TMB in MSI-H tumors, not BRCA1



Pathogenic Mutations in BRCA1/2 in MSS CRCs are associated with increased TMB



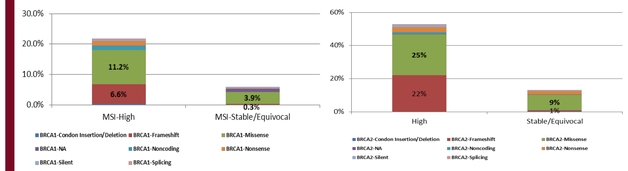
Both BRCA1/2 increase TMB irrespective of MSI or POLE mutation status



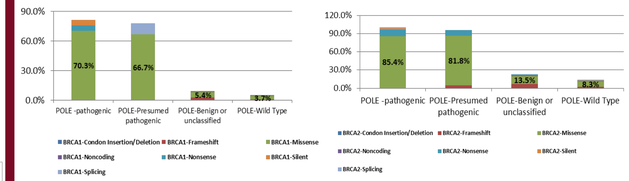
TMB (mut/MB) in MSS and POLE WT cohort

	Mutated	No Mutation	p values
BRCA1	8.69	7.53	0.03
BRCA2	8.47	7.53	0.02
BRCA1 or 2	8.55	7.52	0.0011

MSI-H CRCs have more frameshift and missense mutations in BRCA1/2



CRCs with pathogenic POLE mutations have more point mutations in BRCA1/2



Conclusions

- This is the first study to show that BRCA1/2 mutations are more frequent in MSI-H, independently associated with higher TMB, pathogenic POLE mutations, and right-sided tumors in CRCs.
- Given their relationship with TMB in MSS tumors, the presence of BRCA1/2 mutations are indicator for impaired DNA damage repair and could be potential predictive biomarkers for checkpoint or PARP inhibitors in CRC, a finding that should be prospectively evaluated.