Abstract #320

Treatment patterns and prognosis of patients with HER2-negative early breast cancer and germline pathogenic variants in BRCA1, BRCA2, ATM, CHEK2 and PALB2

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Background

- There is conflicting evidence on prognosis in germline BRCA1 & BRCA2 mutation carriers (MCs) with early breast cancer (BC)
- We see heterogeneity in demographics & treatment across the literature and studies limited by sample size
- Here, we describe treatment patterns & prognosis in hereditary BC susceptibility gene MCs with HER2-negative early BC and a comparison cohort of non-MCs from CancerLinQ
- CancerLinq is a health technology platform comprised of deidentified real-world data from over 2.5 million oncology patients across the US

Patients & Methods

- Patients with stage I-III HER2-negative BC & germline pathogenic variants (PVs) in the BC susceptibility genes (BRCA1, BRCA2, PALB2, ATM and CHEK2) between 2002-2023 were identified and sorted in the MC cohort
- A comparison cohort of non-MC carriers was identified from the patients initially queried
- Demographics, pathologic results, genomics test records, & administered cancer treatments were extracted
- Patients with metastases within 9 months of BC diagnosis, patients without stage information, & patients with somatic mutations alone were excluded
- Subgroup analyses in ER positive & TNBC subtypes were performed
- Patients reported to achieve complete therapeutic response or residual tumor stage R0 served as a proxy for patients who achieved pathological complete response (pCR)

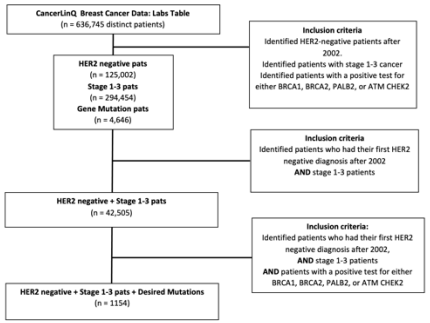


Figure 1: Patient Selection Diagram

Results

- MC cohort comprised of 1105 patients with germline PVs in *BRCA1* (360, 32.6%), BRCA2 (461, 41.7%), PALB2 (59, 6.9%), CHEK2 (70, 8.2%), and ATM (51, 6.0%) with median age at BC diagnosis of 49 (range 24-88) years
- 2129 patients in the non-MC cohort with median age at diagnosis of 51 (range 25-96) years
- MCs had a younger median age at diagnosis, a higher rate of TNBC disease, higher stage and grade when compared with the non-MC
- CR achieved in 382 (34.6%) patients in MC cohort and PR achieved in 253 (22.9%) patients; meanwhile, CR achieved in 421 (19.8%) patients in non-MC cohort and PR achieved in 185 (18.7%) patients
- Neoadjuvant chemotherapy used in 16.4% of patients in MC cohort and in 10.5% of patients in non-MC cohort
- Younger patients more likely to undergo mastectomy but no difference in the type of breast surgery based on race or ethnicity
- Mastectomy preferred over BCT in *BRCA1* (37.3% vs 27.8%) and BRCA2 MCs (42.5% vs 41.9%) but MCs with PV in *ATM*, *CHEK2* and *PALB2* more likely to undergo BCT
- Higher percentage of patients in the MC cohort underwent CPM when compared with non-MC cohort
- CPM associated with an improved iRFS in multivariate analyses; but, worse OS identified in Unilateral Mastectomy group compared to Breast Conserving Therapy (BCT) group
- Analyses between the MC and non-MC cohorts showed a lower iRFS in the MC group
- Kaplan Meier curves for the MC cohort showed no significant difference in OS by mutation type
- Median OS for all 3234 patients included in the survival analyses was 17 years while the median OS of the MC cohort was 18 years
- The median OS for non-MCs was not reached at the time of these analyses
- With regards to racial disparities, Black/African American patients found to have lower OS in analyses with all patients and among MCs alone

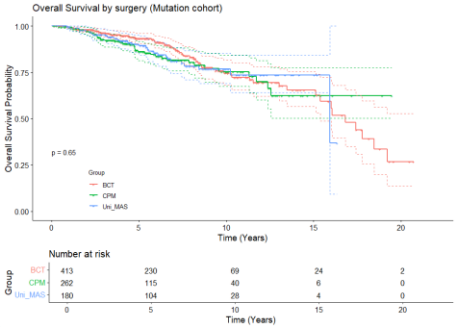


Figure 2: Overall Survival by Surgical Modality

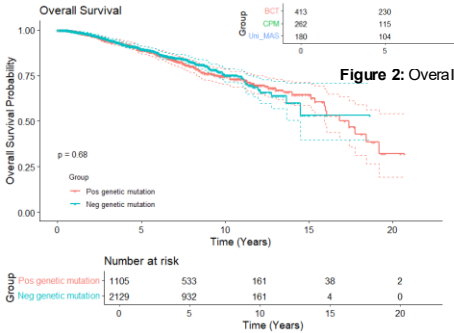


Figure 3: Kaplan Meier survival by Mutation

Characteristic	Overall (N = 3,234)	Mutation Carriers (N = 1,105)	Non-Mutation Carriers (N = 2,129)	p-value[2]
Age				<0.001
Median (Min, Max)	50 (24, 96)	49 (24, 88)	51 (25, 96)	
Race				0.002
Black or African American	318 (9.8%)	121 (11.0%)	197 (9.3%)	
Other	393 (12.2%)	127 (11.5%)	266 (12.5%)	
Unknown	462 (14.3%)	125 (11.3%)	337 (15.8%)	
White	2,061 (63.7%)	732 (66.2%)	1,329 (62.4%)	
N stage				
N0	1,898 (58.7%)	614 (55.6%)	1,284 (60.3%)	<0.001
N1	747 (23.1%)	303 (27.4%)	444 (20.9%)	
N2	172 (5.3%)	71 (6.4%)	101 (4.7%)	
N3	73 (2.3%)	25 (2.3%)	48 (2.3%)	
Unknown	344 (10.6%)	92 (8.3%)	252 (11.8%)	
Stage				
Stage1	1,518 (46.9%)	433 (39.2%)	1,085 (51.0%)	<0.001
Stage2	1,211 (37.4%)	453 (41.0%)	758 (35.6%)	
Stage3	505 (15.6%)	219 (19.8%)	286 (13.4%)	
Tumor grade				
G1	395 (12.2%)	64 (5.8%)	331 (15.5%)	<0.001
G2	790 (24.4%)	221 (20.0%)	569 (26.7%)	
G3	696 (21.5%)	330 (29.9%)	366 (17.2%)	
Unknown	1,353 (41.8%)	490 (44.3%)	863 (40.5%)	
Response to NAC				
CR	803 (24.8%)	382 (34.6%)	421 (19.8%)	<0.001
PR	438 (13.5%)	253 (22.9%)	185 (8.7%)	
Unknown	1,993 (61.6%)	470 (42.5%)	1,523 (71.5%)	
Adjuvant therapy				
No -- Neoadjuvant	187 (12.6%)	86 (16.4%)	101 (10.5%)	0.001
Yes - Adjuvant	1,297 (87.4%)	437 (83.6%)	860 (89.5%)	
Unknown/ Not applicable				
Surgical Procedure				<0.001
BCT	1,652 (60.0%)	413 (48.3%)	1,239 (65.3%)	
Mastectomy	1,100 (40.0%)	442 (51.7%)	658 (34.7%)	
CPM	510 (18.5%)	262 (30.6%)	248 (13.1%)	
Therapeutic Mastectomy Only	590 (21.4%)	180 (21.1%)	410 (21.6%)	

[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

Table 1: Demographics by Mutation Carrier Status

Characteristic	Overall (N = 855)[1]	Mastectomy (N = 442)[1]	BCT (N = 413)[1]	p-value[2]
Age at Diagnosis				<0.001
Median (Min, Max)	49 (24, 88)	48 (25, 72)	52 (24, 88)	
Race				0.8
Asian	34 (4.0%)	18 (4.1%)	16 (3.9%)	
African American	93 (10.9%)	43 (9.7%)	50 (12.1%)	
Other	60 (7.0%)	29 (6.6%)	31 (7.5%)	
Unknown	104 (12.2%)	58 (12.7%)	46 (11.6%)	
White	564 (66.0%)	296 (67.0%)	268 (64.9%)	
Germline mutation				<0.001
ATM	51 (6.0%)	18 (4.1%)	33 (8.0%)	
BRCA1	280 (32.7%)	165 (37.3%)	115 (27.8%)	
BRCA2	361 (42.2%)	188 (42.5%)	173 (41.9%)	
CHEK2	70 (8.2%)	25 (5.7%)	45 (10.9%)	
PALB2	59 (6.9%)	26 (5.9%)	33 (8.0%)	
Two mutations	34 (4.0%)	20 (4.5%)	14 (3.4%)	
Vital Status				0.9
Deceased	135 (15.8%)	69 (15.6%)	66 (16.0%)	
Alive	720 (84.2%)	373 (84.4%)	347 (84.0%)	
ER Status				0.025
Positive	458 (53.6%)	234 (52.9%)	224 (54.2%)	
Negative	270 (31.6%)	129 (29.2%)	141 (34.1%)	
Unknown	127 (14.9%)	79 (17.9%)	48 (11.6%)	
PR Status				0.7
Positive	407 (47.6%)	211 (47.7%)	196 (47.5%)	
Negative	324 (37.9%)	163 (36.9%)	161 (39.0%)	
Unknown	124 (14.5%)	68 (15.4%)	56 (13.6%)	
TNBC				0.2
Yes	249 (29.1%)	121 (27.4%)	128 (31.0%)	
No	443 (51.8%)	227 (51.4%)	216 (52.3%)	
Unknown	163 (19.1%)	94 (21.3%)	69 (16.7%)	
Tumor size				0.017
T1	436 (51.0%)	212 (48.0%)	224 (54.2%)	
T2	314 (36.7%)	173 (39.1%)	141 (34.1%)	
T3	75 (8.8%)	45 (10.2%)	30 (7.3%)	
T4	24 (2.8%)	12 (2.7%)	12 (2.9%)	
Unknown	6 (0.7%)	0 (0.0%)	6 (1.5%)	
Nodal stage				<0.001
N0	474 (55.4%)	213 (48.2%)	261 (63.2%)	
N1	230 (26.9%)	144 (32.6%)	86 (20.8%)	
N2	52 (6.1%)	30 (6.8%)	22 (5.3%)	
N3	18 (2.1%)	13 (2.9%)	5 (1.2%)	
Unknown	81 (9.5%)	42 (9.5%)	39 (9.4%)	
Tumor Grade				0.013
G1	50 (5.9%)	17 (3.9%)	33 (8.0%)	
G2	159 (18.7%)	92 (20.9%)	67 (16.3%)	
G3	266 (31.2%)	146 (33.2%)	120 (29.1%)	
Unknown	380 (44.2%)	187 (42.0%)	193 (46.6%)	

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2: Demographics by Surgical Modality

Conclusions/Future Directions

- One of the largest real-world analyses in hereditary BC susceptibility gene MCs (*BRCA1, BRCA2, PALB2, CHEK2 and ATM*) with HER2-negative early BC
- Majority of patients found to have pathogenic variants in germline BRCA1 (32.6%) and BRCA2 (41.7%)
- No significant difference in OS between MCs and MCs; however, iRFS significantly worse in MC cohort
- No survival difference between mastectomy and BCT
- Racial disparities were identified irrespective of MC status with black patients having lower OS
- CPM use was more often pursued in younger patients with no survival benefit
- Despite US FDA approval in March 2022, few eligible patients received adjuvant Olaparib
- Additional large scale studied are required to better understand survival outcomes and treatment patterns in germline MCs