High genomic risk by multigene assay in germline BRCA1/2 mutated tumors among patients with ER-positive/HER2-negative early breast cancer

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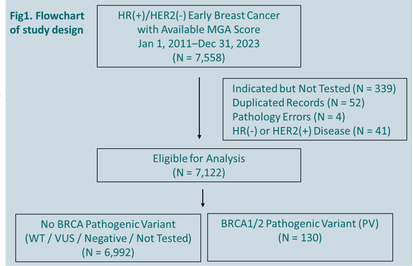
INTRODUCTION

Indication of BRCA testing is expanding with growing evidence on optimal surveillance and treatments for BRCA-associated breast cancer (BC). As BRCA-associated hormone receptor(HR) positive, HER2 negative metastatic BC has shown to display worse outcome from previous studies, we aim to investigate the genomic risk profile and subsequent outcome in early HR-pos/HER2-neg BRCA-associate BC compared to BRCA non-associated BC.

METHODS

A retrospective review of 7,558 early HRposHER2neg BC cases between Jan 2011 ~ Dec 2023 in three institutes was done. Among the 7,122 BRCA-tested patients, 130 (1.8%) was found to have germline BRCA pathogenic variant (PV) and 6,992 (98.2%) with BRCA wild type (WT)/VUS.

Fig1. Flowchart of study design



We compared genomic risk using Oncotype recurrence score (RS) (cut-off 26) and Mammaprint (MMP) and other multigene assay high vs low risk. Disease free survival and cumulative incidence of contralateral breast cancer was analyzed.

RESULTS

Median follow-up was 52.9 ± 27.4 months in BRCA WT/VUS vs 55.7 ± 29.2 months in BRCA PV. Age at diagnosis was significantly younger in BRCA PV carriers (46.7 ± 11.5 vs 50.5 ± 9.4 years). Tumor size ≤T1 was observed in 60.1% of WT/VUS and 56.2% of PV carriers. Node-negative disease was more frequent in PV carriers (76.0% vs 70.1%). BRCA PV carriers demonstrated higher MGA risk scores, higher histologic grade, more frequent HER2 2+ by IHC, and higher Ki-67 (≥20%). Treatment patterns were similar between groups, except for higher rates of chemotherapy in the MGA high-risk group. In the MGA-High group, chemotherapy rates were high for both PV and WT (85%). However, in the MGA-Low group, PV showed a notably higher chemotherapy rate compared to WT (23.4% vs 13.3%).

▼Table1. Baseline Characteristics by BRCA Status

Characteristic	BRCA(WT/VUS) N = 6992[1]	BRCA(PV) N = 130[1]	p-value[2]	Characteristic	BRCA(WT/VUS) N = 6992[1]	BRCA(PV) N = 130[1]	p-value[2]
Age at diagnosis	50.5 ± 9.4	46.7 ± 11.5	<0.01	HER2 status (IHC)			<0.01
Median f/u	52.9 ± 27.4	55.7 ± 29.2	0.3	*0*	2,258 (32.3%)	24 (18.5%)	
Tumor size			0.4	*1+*	2,815 (40.3%)	54 (41.5%)	
≤2cm	4,199 (60.1%)	73 (56.2%)		*2+*	1,919 (27.4%)	52 (40.0%)	
>2cm	2,793 (39.9%)	57 (43.8%)		Ki-67			<0.01
Nodal status			0.2	*<20%*	4,085 (62.1%)	45 (34.6%)	
N(-)	4,918 (70.3%)	99 (76.2%)		*≥20%*	2,488 (37.9%)	85 (65.4%)	
N(+)	2,074 (29.7%)	31 (23.8%)		Chemotherapy	1,686 (24.2%)	64 (49.2%)	<0.01
HG			<0.01	ETx duration			0.4
Grade 1-2	6,245 (89.6%)	101 (77.7%)		*5 years*	5,810 (83.1%)	104 (80.0%)	
Grade 3	721 (10.4%)	29 (22.3%)		*10 years*	1,082 (15.5%)	25 (19.2%)	
PR status			>0.9	OFS duration			0.018
Positive	6,286 (89.9%)	116 (89.2%)		*No*	4,538 (64.9%)	77 (59.2%)	
Negative	706 (10.1%)	14 (10.8%)		*2 years*	999 (14.3%)	30 (23.1%)	
				5 years	1,455 (20.8%)	23 (17.7%)	

[1]Mean ± SD; n (%) [2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

▼Fig2.Distribution of genomic risk according to BRCA mutation status

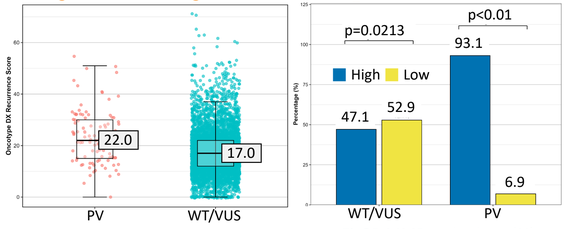


Fig2A.OncotypeDx RS

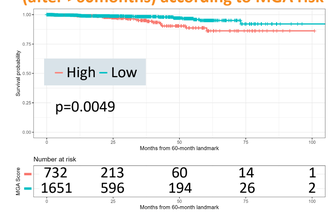
Fig2B.MMP and others (%)

▼Table2. Factors Asso. with High MGA Score

Characteristic	Multivariable OR (95% CI) OR	p-value
BRCA status		<0.01
PV	2.51 (1.69-3.74)	
Age		0.11
≤35	1.29 (0.95-1.74)	
Tumor size		<0.01
>2cm	1.62 (1.42-1.84)	
LN status		<0.01
N(+)	2.57 (2.24-2.95)	

Characteristic	Multivariable OR (95% CI) OR	p-value
HG		<0.01
Grade 3	3.71 (3.10-4.43)	
PR status		<0.01
Negative	3.36 (2.77-4.08)	
HER2 status		<0.01
2+	1.27 (1.11-1.46)	
Ki-67		<0.01
≥20%	3.86 (3.38-4.42)	

▼Fig4. Differences in late recurrence (after >60months) according to MGA risk



▼Table5. Cox regression survival analysis of late recurrence (after 60months)

Cox Regression: Disease-Free Survival (DFS)
Landmark at 60 months

Characteristic	N	Multivariable HR (95% CI) HR	95% CI	p-value
BRCA mutation status	2,383			0.6
WT/VUS		—	—	
PV		0.60	0.08, 4.59	
MGA score	2,383			**0.015**
Low		—	—	
High		2.69	1.26, 5.75	
Endocrine therapy duration	2,373			**0.032**
10-year		—	—	
5-year		2.10	1.05, 4.18	
Chemotherapy	2,370			0.8
No		—	—	
Yes		0.91	0.39, 2.13	
Age	2,383			**0.050**
>40		—	—	
≤40		2.16	1.04, 4.46	
Tumor size	2,383			0.8
≤2cm		—	—	
>2cm		0.93	0.47, 1.81	
Lymph node status	2,383			**0.049**
N(-)		—	—	
N(+)		2.00	1.03, 3.89	

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

▼Fig3.Differences in survival according to BRCA status and MGA risk

Fig3A.DFS and CBC by BRCA PV vs WT/VUS(ref)

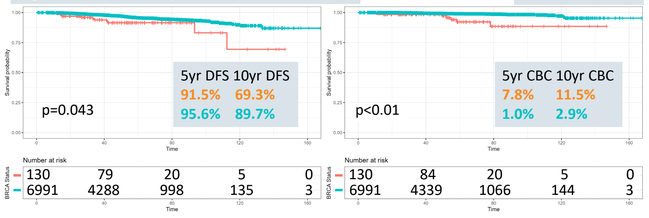


Fig3B.DFS by MGA high vs low(ref)

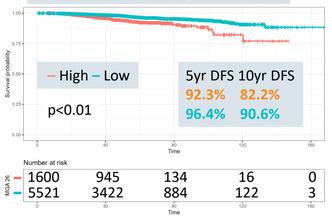


Fig3C. DFS by BRCA x MGA combined

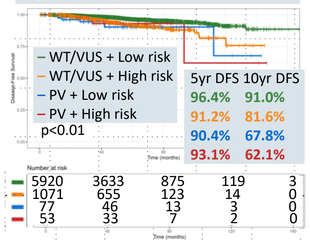


Fig2, Table2 BRCA PV carriers demonstrated significantly higher genomic risk. Among patients with MGA testing, the proportion of high-risk scores was 40.8% in BRCA PV vs 15.3% in BRCA WT/VUS. ODx recurrence scores were also higher in BRCA PV carriers (mean ± SD: 23.4 ± 10.5 vs 17.5 ± 8.7).

Fig4 High genomic risk group displayed worse long-term outcome than MGA-low group. BRCA mutation status did not significantly affect long-term late recurrence in this large cohort (data not shown)

Table5 Among 2,368 patients with no recurrence within 5yrs, 86 experienced recurrences. While BRCA mutation was not associated with late recurrence, high genomic risk, young age, LN involvement were associated with risk of recurrence after 5yr. Patients with extended endocrine therapy demonstrated a significant DFS (overall HR 2.10, 95% CI 1.05-4.18, p<0.032).

▼Table3.Cox: Disease-Free Survival (DFS)

Cox Regression: Disease-Free Survival (DFS)

Characteristic	N	Multivariable HR (95% CI) HR	95% CI	p-value
BRCA mutation status	7,121			0.3
WT/VUS		—	—	
PV		1.46	0.78, 2.73	
MGA score	7,121			**<0.001**
Low		—	—	
High		2.30	1.51, 3.50	
Chemotherapy	7,088			**0.027**
No		—	—	
Yes		0.62	0.40, 0.95	
Age	7,121			**<0.001**
>40		—	—	
≤40		1.96	1.46, 2.64	
Tumor size	7,121			**<0.001**
≤2cm		—	—	
>2cm		2.04	1.58, 2.65	

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Cox Regression: Disease-Free Survival (DFS)

Characteristic	N	Multivariable HR (95% CI) HR	95% CI	p-value
Lymph node status	7,121			0.053
N(-)		—	—	
N(+)		1.30	1.00, 1.70	
Histologic grade	7,095			0.5
Grade 1-2		—	—	
Grade 3		1.15	0.79, 1.69	
PR status	7,121			0.5
Positive		—	—	
Negative		1.14	0.76, 1.72	
HER2 status (IHC)	7,121			>0.9
0/1+		—	—	
2+		0.99	0.75, 1.31	
Ki-67	6,702			**0.006**
<20%		—	—	
≥20%		1.48	1.12, 1.95	

Fig3, Table3 BRCA PV was associated with worse DFS, but this effect was largely attributable to tumor characteristics. BRCA PV status was not an independent prognostic factor for DFS; however, it was the only significant independent risk factor for CBC.

▼Table4. Distribution of adj. CTx and ETx strategies according to BRCA status and MGA risk

Characteristic	BRCA PV MGA High N = 53[1]	BRCA PV MGA Low N = 77[1]	BRCA WT/VUS MGA High N = 1,072[1]	BRCA WT/VUS MGA Low N = 5,920[1]	p-value[2]
ETx					
5-year	42 (79.2%)	62 (80.5%)	893 (83.3%)	4,917 (83.1%)	0.8
10-year	11 (20.8%)	14 (18.2%)	160 (14.9%)	922 (15.6%)	0.6
CTx	46 (86.8%)	18 (23.4%)	902 (84.7%)	784 (13.3%)	<0.001

*ref of Table2,3. BRCA WT/VUS, Age>35, Age>40, Tumor size≤2cm, N(-), HG 1-2, PR(+), HER2 0/1+, Ki-67<20% ,
*Abbr.: CI = Confidence Interval, OR = Odds Ratio, HR= Hazard Ratio

Table4 Adjuvant systemic therapy pattern was similar for both BRCA PV carrier and WT patients. However, BRCA PV patients with low genomic group received chemotherapy more than WT/VUS group.

Discussion: Bullet points

▶ BRCA mutation, genomic Risk, and clinical outcome
-BRCA PV carriers demonstrated significantly higher MGA scores.
-Inferior DFS was observed in the group with BRCA PV carriers, but its significance disappeared in the multivariable analysis. On the contrary, high genomic risk was independently associated with worse outcomes in this large cohort.
-CBC events occurred more frequently according to genetic predisposition.

▶ Adjuvant Therapy Decisions
-Chemotherapy decisions were primarily guided by MGA risk.
-In the genomic low-risk group, PV tended to receive chemotherapy more than WT.
-While RR-BSO rate among BRCA carrier is unknown, OFS rates and EET (>5yr) rate were similar in both groups.

▶ Treatment Efficacy and long-term outcome
-3.6% of late-recurrence (after >5yr) was observed and was similar between BRCA PV group and WT/VUS group.
-MGA-high was a significant risk of both early and late recurrence while BRCA mutation was not, and the EET (>5yr) significantly reduced late recurrence.

CONCLUSION

In this large cohort, germline BRCA PV carriers demonstrated significantly higher MGA score and high genomic risk was independently associated with worse outcomes. BRCA PV patients with genomic low risk tended to receive more chemotherapy, and the absolute benefit of CT, EET and OFS are to be ellucidated in this population.

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