Demographics and Clinical Decision Making in Patients with Germline Moderate Penetrance non-BRCA Mutations in Breast Cancer Related Genes

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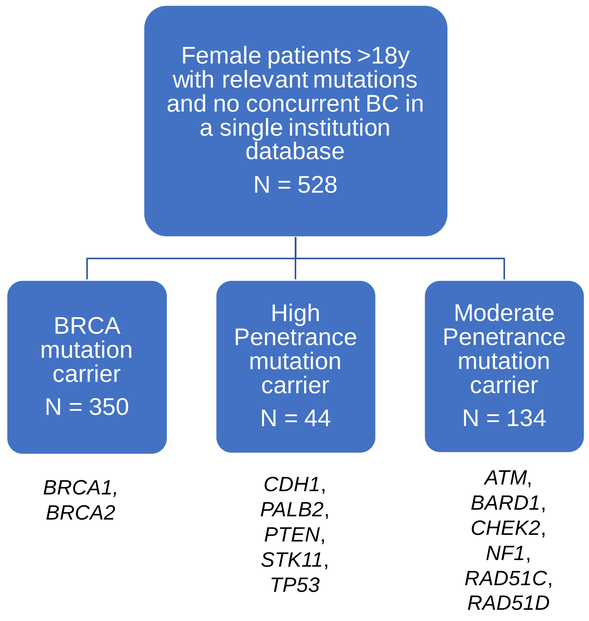
Introduction

- 5-10% of all cases of breast cancer cases have a hereditary component[1]
- Risk reducing strategies:
  - Risk reducing mastectomy (RRM)
  - Salpingo-oophorectomy
  - Risk-reducing medications,
  - Surveillance
- NCCN guidelines: discussion of RRM for *BRCA1* and *BRCA2* mutation carriers[2]
- Less known about utility of RRM in patients with moderate penetrance mutations, therefore fewer guidelines

Objective

Compare risk-reducing decision-making patterns in patients with non-BRCA genetic mutations

Methods



Results

Table 1. Patient characteristics.

	All Patients (N=528)	Study Group: BRCA Mutation (N=350)	Study Group: High Penetrance Mutation (N=44)	Study Group: Moderate Penetrance Mutation (N=134)	*P*
Age at Genetic Testing (Years) – Median (IQR)	41.9 (32.0 - 55.1)	39.8 (30.3 - 52.1)	41.9 (33.1 - 57.9)	46.9 (36.7 - 60.4)	<0.001
Race/Ethnicity					0.05
Non-Hispanic White	418 (79.2%)	283 (80.9%)	30 (68.2%)	105 (78.4%)	
Non-Hispanic Black	37 (7%)	20 (5.7%)	6 (13.6%)	11 (8.2%)	
Non-Hispanic Other	19 (3.6%)	13 (3.7%)	2 (4.5%)	4 (3%)	
Hispanic or Latino	18 (3.4%)	9 (2.6%)	5 (11.4%)	4 (3%)	
Sexual Orientation					<0.001
Heterosexual	346 (65.5%)	205 (58.6%)	29 (65.9%)	112 (83.6%)	
Homosexual	5 (0.9%)	4 (1.1%)	0 (0%)	1 (0.7%)	
Bisexual	3 (0.6%)	1 (0.3%)	1 (2.3%)	1 (0.7%)	
Unknown	174 (33%)	140 (40%)	14 (31.8%)	20 (14.9%)	
Marital Status					0.08
Married/Partner	330 (62.5%)	215 (61.4%)	27 (61.4%)	88 (65.7%)	
Separated/Divorced	45 (8.5%)	26 (7.4%)	2 (4.5%)	17 (12.7%)	
Single	103 (19.5%)	76 (21.7%)	10 (22.7%)	17 (12.7%)	
Widowed	16 (3%)	9 (2.6%)	3 (6.8%)	4 (3%)	
Insurance					<0.001
Private	328 (62.1%)	206 (58.9%)	34 (77.3%)	88 (65.7%)	
Government	95 (18%)	55 (15.7%)	10 (22.7%)	30 (22.4%)	
None Reported	105 (19.9%)	89 (25.4%)	0 (0%)	16 (11.9%)	
History of Any Cancer					0.03
No	364 (68.9%)	243 (69.4%)	23 (52.3%)	98 (73.1%)	
Yes	164 (31.1%)	107 (30.6%)	21 (47.7%)	36 (26.9%)	
Family History of Cancer					0.002
No	5 (0.9%)	0 (0%)	0 (0%)	5 (3.7%)	
Yes	521 (98.7%)	349 (99.7%)	44 (100%)	128 (95.5%)	
Family History of Breast Cancer					0.002
No	125 (23.7%)	67 (19.1%)	16 (36.4%)	42 (31.3%)	
Yes	401 (75.9%)	282 (80.6%)	28 (63.6%)	91 (67.9%)	

No statistically significant difference found based on smoking status, contraceptive use, comorbidities, BMI, number of pregnancies

Figure 1. Risk-reduction strategy by mutation type (BCRA vs high penetrance vs moderate penetrance

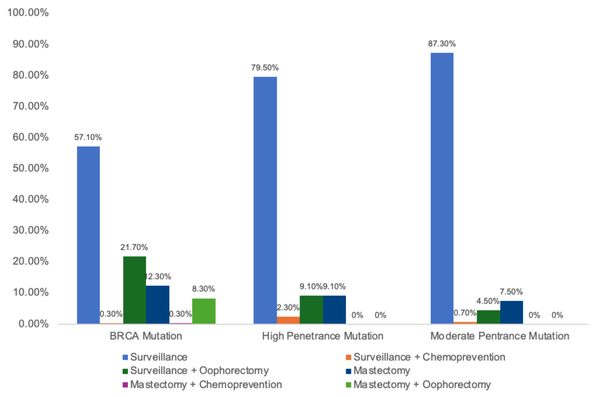


Figure 2. Progression to malignancy by mutation type (BCRA vs high penetrance vs moderate penetrance

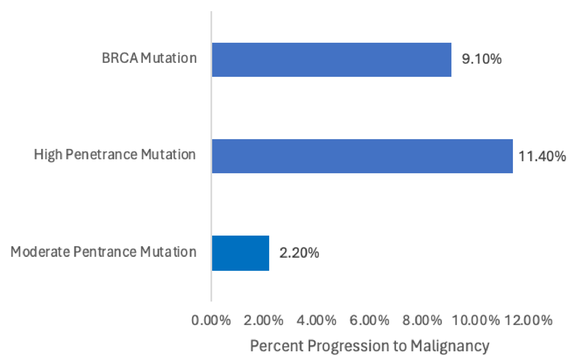


Table 2. Patient characteristics by mastectomy receipt for patients with a moderate penetrance mutation

	All Patients (N=134)	Mastectomy (N=10)	Non-Mastectomy (N=124)	*P*
Age at Genetic Testing (Years) – Median (IQR)	46.9 (36.7 - 60.4)	39.4 (31.7 - 46.4)	47.5 (37.1 - 61.2)	0.03
Race/Ethnicity				0.78
Non-Hispanic Caucasian or White	105 (78.4%)	9 (90%)	96 (77.4%)	
Non-Hispanic Black or African American	11 (8.2%)	0 (0%)	11 (8.9%)	
Non-Hispanic Other	4 (3%)	0 (0%)	4 (3.2%)	
Hispanic or Latino	4 (3%)	0 (0%)	4 (3.2%)	
Insurance				0.51
Private	88 (65.7%)	7 (70%)	81 (65.3%)	
Government	30 (22.4%)	1 (10%)	29 (23.4%)	
None Reported	16 (11.9%)	2 (20%)	14 (11.3%)	
BMI – Median (IQR)	26.5 (23.3 - 30.6)	27.7 (23.3 - 28.4)	26.5 (23.4 - 30.6)	0.81
Number of Pregnancies – Median (IQR)	2 (0 - 3)	2 (0 - 4)	2 (0 - 3)	0.42
Family History of Cancer				1.00
No	5 (3.7%)	0 (0%)	5 (4%)	
Yes	128 (95.5%)	10 (100%)	118 (95.2%)	
Number of Family Members with Cancer – Median (IQR)	4 (2 - 5)	5 (4 - 5)	4 (2 - 6)	0.52
Family History of Breast Cancer				0.13
No	42 (31.3%)	1 (10%)	41 (33.1%)	
Yes	91 (67.9%)	9 (90%)	82 (66.1%)	
Number of Family Members with Breast Cancer – Median (IQR)	1 (0 - 2)	2 (2 - 2)	1 (0 - 2)	0.05
Progression to Breast Malignancy				0.62
No	131 (97.8%)	10 (100%)	121 (97.6%)	
Yes	3 (2.2%)	0 (0%)	3 (2.4%)	

Data Highlights

Patient Characteristics across mutation type

- Moderate penetrance mutation associated with older age at genetic testing, private health insurance, and less personal or family history of cancer

Risk Reduction Strategy by mutation type

- Smaller portion of patients with moderate penetrance mutation undergoing RRM compared to those with high penetrance or BRCA mutation (7.5% vs 9.1% vs 20.9%)

Progression to malignancy by mutation type

- Smaller portion of patients with moderate penetrance mutation progressing compared to those with high penetrance or BRCA mutation (2.2% vs 11.4% vs 9.1%)

Characteristics associated with mastectomy receipt in moderate penetrance

- High portion of patients who underwent RRM were younger at age of genetic testing (39y v 47y) and had more family members with breast cancer (2 vs 1) amongst patients with moderate penetrance mutations

Conclusions

- Patients with moderate penetrance mutations are much less frequently undergoing RRM when compared to patients with BRCA mutations or high penetrance mutations.
- Age and family members with breast cancer may influence RRM decision in moderate penetrance mutation carriers
- Still a need for more information on the clinical utility of identifying moderate penetrance mutations, and on RRM in this patient populations

References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast Cancer Statistics, 2022. CA Cancer J Clin. 2022;72(6):524-41.
2. Daly MB, Pilarski R, Yurgelun MB, Berry MP, Buys SS, Dickson P, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020. Journal of the National Comprehensive Cancer Network. 2020;18(4):380-91.

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