Real-world clinical characteristics and management of breast cancer in patients with germline pathogenic variants in *ATM*, *CHEK2*, and *PALB2*

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BACKGROUND

- Breast cancer is the most common type of cancer in women.
- While breast cancer risks and clinical characteristics with *BRCA1* and *BRCA2* variants are well-defined, the characteristics associated with germline pathogenic variants (PVs) in the moderate penetrant genes, *ATM*, *CHEK2*, and *PALB2*, are less clear.
- We describe the clinical characteristics and management decisions associated with germline moderate penetrant PVs in a large real-world clinical cohort.

METHODS

COHORT

- We conducted a retrospective, observational analysis across seven clinical sites of patients with a current or prior breast cancer diagnosis and a PV or likely PV in either *ATM*, *CHEK2*, or *PALB2*. Patients were grouped into cohorts based on the gene variant (*ATM*, *CHEK2*, *PALB2*) or whether multiple variants were identified.

STATISTICAL ANALYSIS

- Chi-square testing was performed to assess differences between categorical variables when patient counts for single cells within the results tables were greater than or equal to 5. Fisher's exact test was used when the distribution could not be assumed with chi-square testing.

RESULTS

- The cohort consisted of 506 patients who met testing eligibility criteria. The cohort was largely female (99.2%), White (self-reported; 80.8%), with median breast cancer diagnosis at 48 years (range 19, 82).
- The cohort frequency of PVs varied by gene: *ATM* 26.9% (n=136), *CHEK2* 48.2% (n=244), and *PALB2* 22.9% (n=116).
- Ten individuals (2%) had multiple variants within the three genes.
- The distribution of disease stage, clinical characteristics, medical management decision and disease recurrence was not significantly different between individuals with *ATM*, *CHEK2,* or *PALB2* variants for a majority of the variables assessed.
  - However, the frequency of triple negative breast cancer (5.1% of all individuals) significantly varied by gene PV cohort (p<0.0001) and was highest in patients with *PALB2* PVs (*ATM*, 0.7%; *CHEK2*, 3.3%; *PALB2*, 13.8%) (Figure 1).
- Across all PV cohorts, individuals most frequently had stage 1A breast cancer (31.6%), ductal history (77.1%), grade 2 disease (39.9%), and/or HER2 negative disease (60.7%).
- Though not mutually exclusive, the most common patient management decisions included adjuvant hormonal therapy (76.1%, p=0.003; lowest in individuals with *PALB2* PVs), radiation (56.3%, no significant difference by gene PV), bilateral mastectomy (49.6%, no significant difference by gene PV) (Table1), and adjuvant chemotherapy (not shown).

Figure 1. *ATM*, *CHEK2*, *PALB2*, and multiple mutation pathogenic variants in patients who had Triple Negative Breast Cancer (N=26)

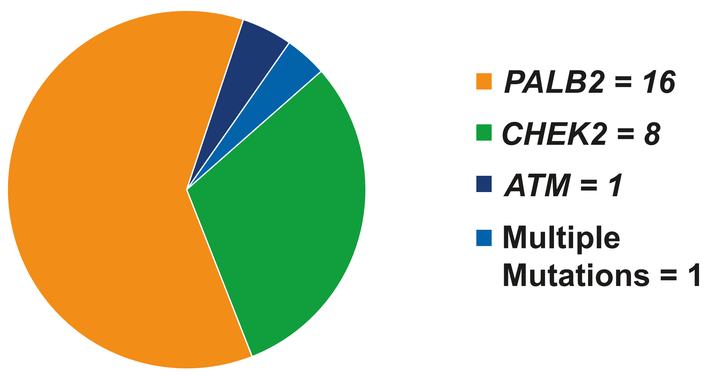

Table 1. Patient Characteristics and Management Decisions

Variable	Overall N=506	*ATM* N=136	*CHEK2* N=244	*PALB2* N=116	Multiple Mutations N=10	P-value
Gender						
Female	502 (99.2)	136 (100.0%)	242 (99.2%)	114 (98.3%)	10 (100.0%)	0.324
Male	4 (0.8%)	0 (0.00%)	2 (0.8%)	2 (1.7%)	0 (0.00%)	
Age at Diagnosis						
Mean	49.8	48.8	50.9	49	46.7	0.275
Adjuvant Hormonal Therapy						
Yes	385 (76.1%)	108 (79.4%)	196 (80.3%)	73 (62.9%)	8 (80.0%)	0.003
No	121 (23.9%)	28 (20.6%)	48 (19.7%)	43 (37.1%)	2 (20.0%)	
Adjuvant Radiation Therapy						
Yes	285 (56.3%)	80 (58.8%)	144 (59.0%)	58 (50.0%)	3 (30.0%)	0.061
No	217 (42.9%)	55 (40.4%)	98 (40.2%)	58 (50.0%)	6 (60.0%)	
Not Documented	4 (0.8%)	1 (0.7%)	2 (0.8%)	0 (0.00%)	1 (10.0%)	
Surgery Course						
Mastectomy	123 (24.3%)	33 (24.3%)	55 (22.5%)	34 (29.3%)	1 (10.0%)	0.42
Lumpectomy	205 (40.5%)	55 (40.4%)	103 (42.2%)	44 (37.9%)	3 (30.0%)	0.801
Bilateral Mastectomy	251 (49.6%)	65 (47.8%)	123 (50.4%)	57 (49.1%)	6 (60.0%)	0.875

CONCLUSIONS

- In this real-world clinical cohort of patients with germline PVs in *ATM*, *CHEK2,* or *PALB2*, the majority of patient and clinical characteristics and treatment decisions did not significantly differ by gene.
- Triple negative breast cancer was more common in those with *PALB2* PVs and may drive future management and prevention strategies.