PREVALENCE OF BREAST CANCER IN INDIVIDUALS WITH ATM MISSENSE OR LOSS-OF-FUNCTION VARIANTS

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Background

• The risk of breast cancer (BC) associated with heterozygous ATM pathogenic/likely pathogenic variants (PV/LPV) has been difficult to quantify.
• Studies have asserted that certain ATM missense variants may confer a higher risk of BC than loss-of-function (LOF) variants. However, except for ATM c.7271T>G, p.Val2424Gly (V2424G), evidence confirming this differential risk has been limited.
• Here we compared the prevalence of BC and age at first BC diagnosis among carriers of different types of ATM (PV/LPV).

Methods

• We retrospectively reviewed all heterozygous ATM (PV/LPV) carriers identified through multi-gene hereditary cancer panel testing.
• Included carriers had testing for at least BRCA1/2, CHEK2, and PALB2, were females over 18 years old, had no other (PV/LPV) in a gene associated with BC, and were the first person in their family meeting these criteria tested at this laboratory.
• Variants were categorized into four groups: LOF (nonsense-mediated decay (NMD) predicted); V2424G; other missense; and NMD=No (truncating, deletion/duplications, and in-frame splice variants with no NMD predicted).
• Chi-square, t-test, and ANOVA analyses were performed to compare BC prevalence and age at diagnosis.

Results

• A total of 546 ATM (PV/LPV) carriers were identified (Figure 1). LOF variants were the most common (390/546, 71.4%).
• A personal diagnosis of BC was reported in 377 carriers (69%).
• Mean age at BC diagnosis of all carriers combined was 48.2 years.
• We did not find a significant difference in the prevalence of BC between V2424G and other missense variant carriers (p=1.00) (Figure 2). Comparison to LOF variants or across all groups was limited due to insufficient power.
• Affected V2424G carriers appeared to have a lower age at BC diagnosis compared to carriers of other variants, but the difference was not statistically significant (45.1 years vs 48.5 years, p=0.14) (Figure 3).

Conclusions

• We did not find a significant difference in the prevalence of BC in ATM V2424G carriers compared to other missense variants.
• Due to the small number of V2424G and other missense variant carriers, we were not powered to compare BC prevalence between other variant groups.
• The age at first BC diagnosis appeared younger in ATM V2424G carriers compared to carriers of other ATM variants, but the difference did not reach statistical significance.
• Further work including a larger cohort and segregation studies may help elucidate differences in BC risk associated with different types of ATM variants.

References