Heterogeneity of Pancreatic Cancer Risk Across Germline Susceptibility Genes and Sex

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Objectives

Germline pathogenic variants (PVs) in *ATM, BRCA1, BRCA2, PALB2,* and *CDKN2A* confer risk for pancreatic ductal adenocarcinoma (PDAC), yet precise estimates of age-, sex-, and gene-specific penetrance vary and remain limited. We quantified PDAC risk across these genes, stratified by sex, in a large clinical cohort undergoing multigene panel testing for cancer susceptibility.

Methods

We analyzed data from 28,480 carriers of *BRCA1/2*, *ATM*, *PALB2*, and *CDKN2A* PVs, including 908 with PDAC, tested through Ambry Laboratories. Clinical status was obtained from ICD10-coded data (n=) and/or manually curated pathology and medical records (n=). Hazard ratios (HRs) were estimated via Cox proportional hazard models for time to PDAC diagnosis, by gene and sex (*BRCA2* as reference), without family history adjustment and exclusion of carriers with non-PDAC cancers.

Results

Relative to *BRCA2*, *BRCA1* carriers had significantly lower PDAC risk (HR=0.59; 95% CI 0.41-0.86; p=0.005). *CDKN2A* carriers had higher risk (HR=2.29; 95% CI 1.7-3.2; p=6.7×10^{-7}). *ATM* carriers showed suggestive difference from *BRCA2* (HR = 1.26; 95% CI 0.99–1.61; p=0.059), and *PALB2* carriers were not different (HR = 1.03; 95% CI 0.73-1.46; p = 0.86). Sex remained a significant independent predictor, with males experiencing higher risk (HR=2.00; 95% CI 1.57–2.53; p=1.0×10^{-8}). No significant gene-by-sex interactions were observed.

Conclusions

This large clinical testing cohort demonstrates heterogeneity in PDAC penetrance by gene and sex among PDAC-susceptible individuals. Relative to *BRCA2*, *BRCA1* carriers have substantially reduced risk of PDAC, *PALB2* carriers have similar risk, *CDKN2A* carriers have more than a twofold increase, and *ATM* carriers show a modest but significant elevated risk. Male carriers have higher risk than females, though this may reflect differential testing or

competing cancers ascertainment. These penetrance estimates refine gene- and sex-specific risk and may inform future PDAC surveillance and early detection strategies.