Heterogeneity of Pancreatic Cancer Risk Across Germline Susceptibility Genes and Sex

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Summary

We estimated pancreatic ductal adenocarcinoma (PDAC) risk across patients with germline pathogenic variants in ATM, BRCA1/2, PALB2, and CDKN2A in a large clinical cohort undergoing multigene panel testing for cancer susceptibility. More precise risk estimates for genetically predisposed individuals may inform targeted prevention and early detection strategies.

Objectives

Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of 11.5% with 50% of patients already metastatic at diagnosis.[1] Identification of modifiable and non-modifiable risk factors provides opportunities for prevention and early intervention. Germline pathogenic variants (PVs) in ATM, BRCA1/2, PALB2, and CDKN2A confer risk for PDAC, yet precise estimates of age-, sex-, and gene-specific penetrance are variable and limited. Large scale multi-ethnic clinical genetic datasets evaluating PDAC risk are sparse.

Our dataset comprises individuals with germline PVs in ATM, BRCA1/2, PALB2, and CDKN2A, which are the most prevalent high-penetrance PDAC susceptibility genes, accounting for up to 10% of PDAC cases.[2] We aim to generate precise gene-, age-, and sex-specific risk estimates for PDAC across these genes.

Results

PV Carrier	Hazard Ratio (95% CI)	p-value
BRCA2	1.00	–
ATM	1.26 (0.99-1.61)	0.059
BRCA1	0.59 (0.41-0.86)	0.005
CDKN2A	2.29 (1.7-3.2)	6.7×10^{-7}
PALB2	1.03 (0.73-1.46)	0.86

Table 1A. Main analysis with unaffected controls: hazard ratios from Cox proportional hazards model (with BRCA2 as reference).

PV Carrier	Hazard Ratio (95% CI)	p-value
BRCA2	1.00	–
ATM	1.56 (1.23-1.99)	0.0003
BRCA1	0.51 (0.35-0.74)	0.0004
CDKN2A	3.33 (2.42-4.58)	1.7×10^{-13}
PALB2	0.90 (0.63-1.29)	0.56

Table 1B. Sensitivity analysis with controls either unaffected or affected with other cancers: hazard ratios from Cox proportional hazards model (with BRCA2 as reference).

Conclusion

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

Next steps are to develop a SNP-based genomic risk stratification strategy among PV carriers to further improve risk stratification among high-risk individuals.

Methods

We analyzed data from 28,480 carriers of ATM, BRCA1/2, PALB2, and CDKN2A PVs, including 908 with PDAC, tested through Ambry Laboratories. Clinical status was obtained from ICD10-coded data (n=19437) and/or manually curated pathology and medical records (n=9043). 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. As a sensitivity analysis, we expanded the control group to include both unaffected controls and controls with other cancers.

	Clinical Cohort (% across rows), N = 28480				
	Total	**Cases Curated**	**Controls Curated**	**Cases ICD10**	**Controls ICD10**
Sex					
Female	23032	149 (1)	7624 (33)	247 (1)	15012 (65)
Male	5448	169 (3)	1101 (20)	343 (6)	3835 (70)
Gene					
ATM	6077	80 (1)	1341 (22)	246 (4)	4410 (73)
BRCA1	7746	43 (1)	2782 (36)	68 (1)	4853 (63)
BRCA2	10497	127 (1)	3294 (31)	162 (2)	6914 (66)
CDKN2A	1258	47 (4)	449 (36)	58 (5)	704 (56)
PALB2	3143	24 (1)	937 (30)	69 (2)	2113 (67)
Ethnicity					
African American/Black	2143	21 (1)	898 (42)	37 (2)	1187 (55)
Ashkenazi Jewish	1702	14 (1)	540 (32)	18 (1)	1130 (66)
Asian	2143	21 (1)	898 (42)	37 (2)	1187 (55)
Caucasian	1141	12 (1)	461 (40)	13 (1)	655 (57)
Hispanic	15964	193 (1)	4894 (31)	374 (2)	10503 (66)
Other	2511	40 (2)	1026 (41)	38 (2)	1407 (56)
Age					
Ages ≤ 39	7083	7 (0)	2175 (31)	17 (0)	4884 (69)
Ages 40-59	12058	100 (1)	3977 (33)	154 (1)	7827 (65)
Ages 60-79	8577	191 (2)	2432 (28)	365 (4)	5589 (65)
Ages ≥ 80	639	20 (3)	139 (22)	54 (8)	426 (67)

Table 2. Demographics of clinical cohort, by gene, sex, age, and ethnicity.

	Female, N = 23032			Male, N = 5448		
	Case	Unaffected Controls (No Cancer)	Affected Controls (Other Cancer)	Case	Unaffected Controls (No Cancer)	Affected Controls (Other Cancer)
Total	396	10649	11987	512	2990	1946
ATM	150	2311	2406	176	535	499
BRCA1	36	2897	3482	75	952	304
BRCA2	120	3889	4237	169	1183	899
CDKN2A	55	488	454	50	125	86
PALB2	44	1144	1502	49	225	179

Table 3. PV carriers by sex, PDAC status (with controls divided into those unaffected by cancer and those affected by cancer other than PDAC); blue indicates the main comparison used (cases vs. unaffected controls).

References

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