Hereditary Cancer Genetic Testing Among Patients with Pancreatic Cancer

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BACKGROUND

- Pancreatic cancer is typically diagnosed at a late, untreatable stage, with a 5-year survival rate of approximately 8%.
- Genetic testing for individuals with pancreatic cancer may aid in therapy decisions, as those with a pathogenic variant (PV) in a DNA-repair gene may benefit from PARP inhibitors.
- In addition, genetic testing for unaffected family members can identify high-risk individuals who may be appropriate for surveillance trials.

OBJECTIVE

- We evaluated several possible risk factors for pancreatic cancer using results of multi-gene panel testing among individuals with a personal history of pancreatic cancer.

METHODS

COHORT

- 1,676 individuals with a personal history of pancreatic cancer who underwent multi-gene panel testing at a single laboratory between September 2013 and November 2018 were included.
- Individuals were excluded if they had prior hereditary cancer genetic testing or if they were from states with laws preventing the use of de-identified genetic data.

GENETIC TESTING

- The panel included 25-29 cancer-susceptibility genes: ***APC***, ***ATM***, *BARD1*, ***BMPR1A***, ***BRCA1***, ***BRCA2***, *BRIP1*, *CDH1*, ***CDK4***, ***CDKN2A*** (**p16INK4a** and **p14ARF**), *CHEK2*, ***EPCAM***, *GREM1*, *HOXB13*, ***MLH1***, ***MSH2***, ***MSH6***, *MUTYH*, *NBN*, ***PALB2***, ***PMS2***, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, ***SMAD4***, ***STK11***, and ***TP53*** (genes associated with pancreatic cancer are **bolded**).

DATA ANALYSIS

- Clinical characteristics were obtained from provider-completed test request forms.
- The distribution of PVs among patients with pancreatic cancer was assessed by gene.
- Personal cancer history, family cancer history, age at diagnosis, and ancestry were assessed for individuals with a PV.

RESULTS

- Overall, 12.6% (212/1,676) of individuals with a personal history of pancreatic cancer carried a PV (Table 1).
  - PVs were more prevalent in men and for individuals who had a personal history of additional cancer(s).
  - Age at pancreatic cancer diagnosis did not influence the PV positive rate.
  - The PV positive rate was highest among those with Asian ancestry or White/Non-Hispanic ancestry.
- 84% of PVs were in genes associated with pancreatic cancer, most commonly in *BRCA2*, *ATM*, *PALB2*, and Lynch Syndrome-associated genes (Figure 1).

Table 1. Patient Characteristics

Characteristic	Total Tested	PV Carriers
Full Cohort, N (%)	1,676 (100)	212 (12.6)
Gender, N (%)		
Men	542 (32.3)	83 (15.3)
Women	1,134 (67.7)	129 (11.4)
Cancer Diagnosis, N (%)		
Pancreatic Cancer Only	958 (57.2)	108 (11.3)
Pancreatic and Other Cancer(s)	718 (42.8)	104 (14.5)
Age at Pancreatic Cancer Diagnosis (years)*		
Median (IQR)	63 (55, 71)	62 (54, 69)
≤50, N (%)	265 (15.8)	34 (12.8)
>50, N (%)	1,278 (76.3)	167 (13.1)
Ancestry, N (%)		
White/Non-Hispanic	978 (58.9)	142 (14.4)
Black/African	118 (7.0)	12 (10.2)
Hispanic/Latino	95 (5.7)	7 (7.4)
Ashkenazi Jewish	78 (4.7)	10 (12.8)
Asian	32 (1.9)	6 (18.8)
Native American	13 (0.8)	1 (7.7)
Middle Eastern	11 (0.7)	1 (9.1)
Other	7 (0.4)	2 (28.6)
Multiple Ancestries	116 (6.9)	10 (8.6)
None Specified	219 (13.1)	21 (9.6)

*The age at pancreatic cancer diagnosis was missing for 133 individuals.

Figure 1. Distribution of PVs Among Carriers (N=207)*

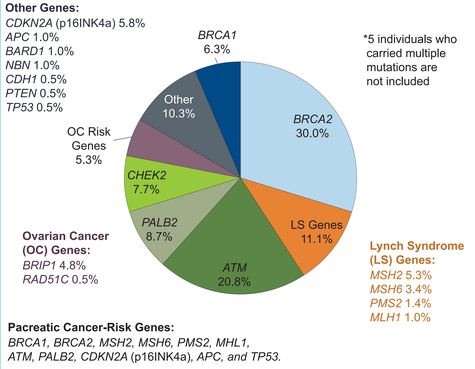
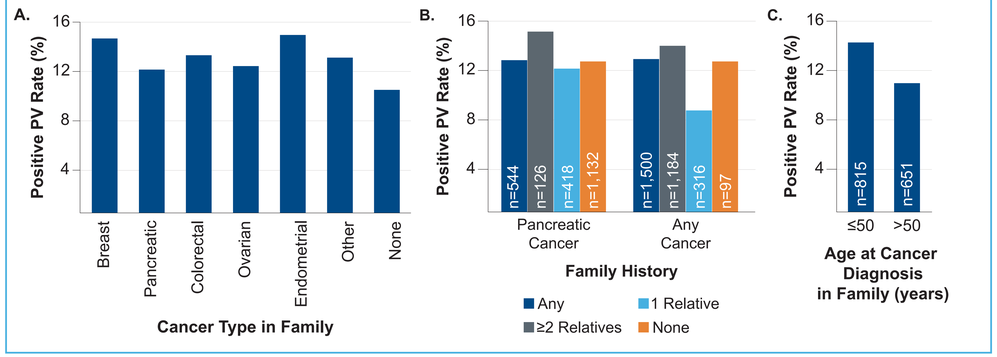


Figure 2. Positive PV Rate According to Family Cancer History according to (A) Cancer Type (B) Number of Affected Relatives and (C) Age at Diagnosis



- The PV positive rate remained high (>10%) regardless of nearly all family history characteristics evaluated, including the absence of any family history (Figure 2).
  - The PV positive rate was >10% for those with a family history of cancer, regardless of cancer type (Figure 2A).
  - The PV positive rate was elevated among individuals with pancreatic cancer and ≥2 relatives with pancreatic cancer (15.1%) and for individuals whose relatives had cancer at an early age (14.2%; Figure 2B, C).
- 10.3% (10/97) of individuals with a personal history of pancreatic cancer and no family history of cancer carried a PV, including 5 individuals with a PV in *BRCA2* (Table 2).

Table 2. Characteristics of PV Carriers with no Family History of Cancer (n=10)

Cancer Diagnosis	Genes
Pancreatic Cancer Only (n=2)	*BRCA2* (n=1), *ATM* (n=1)
Pancreatic and Breast Cancer (n=6)	*BRCA2* (n=4), *BRIP1* (n=1), *and BARD1* (n=1)
Pancreatic, Breast, and Additional Cancers (n=1)	*ATM (n=1)*
Pancreatic and Ovarian Cancer (n=1)	*BARD1 (n=1)*

Table 3. Characteristics of Individuals with a PV in CDKN2A (p16INK4a) or PALB2

Characteristic	*CDKN2A* (p16INK4a) (n=13)*	*PALB2* (n=20)**
Median Age at Diagnosis (years)†	68.0	62.5
Personal Cancer Diagnosis		
Pancreatic Cancer Only	2	14
Pancreatic and Other Cancer(s)‡	11	6
Family Cancer Diagnosis§		
Breast	10	10
Pancreatic	7	5
Colorectal	4	5
Ovarian	2	5
Endometrial	2	1
Melanoma	8	1
Other Cancer‖	3	13

*CDKN2A (p16INK4a) is associated with Familial Atypical Multiple Mole-Melanoma (FAMMM). **PALB2 is associated with hereditary breast cancer. †The age at pancreatic cancer diagnosis was missing for 2 individuals with PVs in *PALB2*. ‡Includes breast, colon, colon polyps, melanoma, ovarian and prostate cancer. §Rows are not exclusive. ‖Includes brain, colon (polyps), gastric, and prostate.

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- 11/13 *CDKN2A* (p16INK4a) PV carriers had an additional cancer diagnosis (including melanoma in 7 individuals; Table 3).
- 6/20 *PALB2* PV carriers had an additional cancer diagnosis, including breast cancer in 5 individuals (Table 3).

CONCLUSIONS

- A substantial proportion (>10%) of individuals with a personal history of pancreatic cancer carried a PV, regardless of age at diagnosis, history of other cancer, or family cancer history.
- >80% of PVs were detected in known pancreatic cancer-risk genes.
- NCCN guidelines recommend genetic testing for patients with pancreatic cancer, regardless of age at diagnosis or family cancer history.[1] A PV was found in >10% of individuals with a personal history of pancreatic cancer and no family history of cancer, with a PV in *BRCA2* observed in 50% of these cases.
- Multi-gene panel testing for patients with pancreatic cancer may help facilitate hereditary cancer risk assessment, especially for the early detection of hereditary cancers in at-risk family members.

REFERENCE: 1. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V 3.2019. January 18.

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