# Germline Mutation Prevalence in Consecutive, Unselected Individuals with Pancreatic Adenocarcinoma

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**Background**
Approximately 10% of pancreatic adenocarcinoma (PC) is hereditary. Knowledge of mutation status is increasingly important given it may direct PC treatment. Current NCCN guidelines for genetic testing in individuals with PC are limited, focusing on hereditary breast and ovarian cancer (HBOC). Most studies ascertaining the prevalence of inherited mutations in individuals with PC involve selected populations. This study aims to determine germline mutation prevalence in consecutive, unselected individuals with PC.

**Methods**
Participants were recruited from 3 sites over one year. Adults <90 years with pathologically-confirmed PC diagnosed within 12 weeks were eligible. Demographics, medical histories, and 3-generation pedigrees were collected. Participants provided DNA for analysis of 32 cancer susceptibility genes.

**Results**
Genetic testing was completed for 298 individuals. See Table 1 for patient characteristics. As shown in Table 2, 25 individuals (8.4%) had pathogenic mutations in a PC-susceptibility gene, one of whom also had a mutation in a non-PC gene (RAD50). Ten carriers (40%) did not meet NCCN testing guidelines for HBOC. The 2 probands with mismatch repair gene mutations did not meet Bethesda guidelines or Amsterdam criteria. Eleven individuals had pathogenic mutations in genes not currently associated with PC (10 CHEK2, 1 BARD1).

**Conclusions**
In an unselected population, 8.4% of individuals with PC were found to have germline mutations in a PC-susceptibility gene. Forty percent of individuals with mutations in PC-susceptibility genes did not meet NCCN HBOC testing guidelines. Our results suggest that broader testing guidelines targeted to the PC patient are needed.

Table 1: Study Participant Characteristics

| Characteristic | Number of Participants (n=298) |
|---|---|
| **Age** | Mean: 68.5 years<br>Range: 33-89 years |
| **Gender** | Male: 160 (53.7%)<br>Female: 138 (46.3%) |
| **Race/Ethnicity** | Caucasian: 238 (79.9%)<br>Ashkenazi Jewish: 28 (9.4%)<br>Other/Unknown: 32 (10.7%) |
| **PC Stage** | Stage I: 23 (7.7%)<br>Stage II: 128 (42.9%)<br>Stage III: 36 (12.1%)<br>Stage IV: 87 (29.2%)<br>Unknown: 24 (8.1%) |
| **Personal history of cancer**[i] | Yes: 61 (20.5%)<br>No: 217 (72.8%) |
| **Family history of any cancer**[ii] | First-degree relative: 221 (74.2%)<br>Only second-degree relative or higher: 47 (15.8%)<br>None: 23 (7.7%) |
| **Family history of pancreatic cancer** | First degree relative: 23 (7.7%)<br>Only second-degree relative or higher: 30 (10.1%)<br>None: 245 (82.2%) |

Table 2: Characteristics of Participants with Mutations in Pancreatic Cancer-Associated Genes

| Gene | Pathogenic Mutation/ Likely Pathogenic Variant | Gender | Age of PC diagnosis | Other Cancers (Age of Diagnosis) | Fulfills NCCN genetic testing guidelines[iii] |
|---|---|---|---|---|---|
| APC | c.3920T>A[iv] | F | 83 | None | Yes |
| APC | c.3920T>A[b] | F | 69 | Breast (47) | Yes |
| ATM | c.5932G>T | M | 59 | None | No |
| ATM | c.7630-2A>C | F | 67 | Melanoma (27)<br>Leukemia (61) | No |
| ATM | c.4093delC | M | 64 | None | No |
| ATM | c.7240C>T | F | 81 | Melanoma (81) | Yes |
| ATM | c.6725delC | M | 50 | None | Yes |
| ATM | c.4741dupA | M | 75 | None | No |
| ATM | c.1027_1030delGAAA | M | 58 | None | Yes |
| ATM | c.1564_1565delGA | F | 68 | None | Yes |
| ATM | c.3245_3247delATCinsTGAT | F | 59 | None | Yes |
| ATM<br>RAD50 | c.6027C>G<br>c.1052-2A<C | F | 75 | Melanoma (70) | No |
| BRCA1 | c.5266dupC | F | 70 | Breast (55)<br>Kidney (68) | Yes |
| BRCA1 | c.181T>G | M | 61 | None | Yes |
| BRCA1 | c.181T>G | M | 83 | Prostate (68)<br>Bladder (81) | Yes |
| BRCA1 | c.68_69delAG | M | 68 | None | Yes |
| BRCA2 | c.1237delC | M | 74 | Left breast (54)<br>Prostate (64)<br>Right breast (66) | Yes |
| BRCA2 | c.7341_7342delTA | F | 63 | None | Yes |
| BRCA2 | c.1444delC | M | 89 | None | No |
| BRCA2 | 5'UTR_3'UTRdel | M | 67 | None | No |
| CDKN2A | c.-34G>T | M | 66 | None | No |
| MSH6 | c.2230dupG | M | 50 | None | No |
| PALB2 | c.1240C>T | M | 75 | None | Yes |
| PMS2 | c.2174+1G>A | M | 85 | None | Yes |
| TP53 | c.909_911delCCT | M | 50 | Rhabdomyosarcoma (4)<br>Skin (33)<br>Vestibular schwannoma (43)<br>Chondroblastoma (50) | No |

[i] Excludes non-melanoma skin cancer and cervical cancer
[ii] Excludes non-melanoma skin cancer, cervical cancer, and unknown cancers
[iii] NCCN Guidelines for Breast and Ovarian Cancer Genetic/Familial High-Risk Assessment version 2.2017
[iv] Moderate risk allele (p.I1307K)