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Research Article

Cancer Prevention Research

High Prevalence of Hereditary Cancer Syndromes and Outcomes in Adults with Early-Onset Pancreatic Cancer

Sarah A. Bannon[1,*], Maria F. Montiel[2,*], Jennifer B. Goldstein[3,*], Wenli Dong[4], Maureen E. Mork[1], Ester Borras[2], Merve Hasanov[5], Gauri R. Varadhachary[3], Anirban Maitra[6], Matthew H. Katz[7], Lei Feng[4], Andrew Futreal[8], David R. Fogelman[3], Eduardo Vilar[1,2,3], and Florencia McAllister[1,2,3]

Abstract

Introduction: We aimed to determine the prevalence and landscape of germline mutations among patients with young-onset pancreatic ductal adenocarcinoma (PDAC) as well as their influence in prognosis.

Methods: Patients from two cohorts were studied, the high-risk cohort (HRC), which included 584 PDAC patients who received genetic counseling at The University of Texas MD Anderson Cancer Center, and a general cohort (GC) with 233 metastatic PDAC patients. We defined germline DNA sequencing on 13 known pancreatic cancer susceptibility genes. The prevalence and landscape of mutations were determined, and clinical characteristics including survival were analyzed.

Results: A total of 409 patients underwent genetic testing (277 from HRC and 132 from GC). As expected, the HRC had higher prevalence of germline mutations compared with the GC: 17.3% versus 6.81%. The most common mutations in both cohorts were in BRCA1/2 and mismatch-repair (MMR) genes. Patients younger than 60 years old had significantly higher prevalence of germline mutations in both the HRC [odds ratios (OR), 1.93 $\pm$ 1.03–3.70, $P = 0.039$] and GC (4.78 $\pm$ 1.10–32.95, $P = 0.036$). Furthermore, PDAC patients with germline mutations in the GC had better overall survival than patients without mutations (HR, 0.44; 95% CI of HR, 0.25–0.76, $P = 0.030$).

Discussion: Germline mutations are highly prevalent in patients with PDAC of early onset and can be predictive of better outcomes. Considering emerging screening strategies for relatives carrying susceptibility genes as well as impact on therapy choices, genetic counseling and testing should be encouraged in PDAC patients, particularly those of young onset. *Cancer Prev Res; 11(11); 679–86. ©2018 AACR.*

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the eleventh most common cancer in incidence and the third leading cause of cancer-related deaths in the United States (1). The majority of PDACs are sporadic; however, 5% to 10% may have a hereditary cause (2). PDAC is considered a disease of the elderly, and most diagnoses are made in individuals over the age of 65, with a median age at diagnosis of 70 years (3). Individuals diagnosed with PDAC under the age of 60 are considered to be young onset and potentially at high risk for a genetic predisposition. Although pancreatic cancer is typically associated with environmental and lifestyle factors such as smoking, obesity, and diabetes (4–7), inherited germline mutations confer a significantly elevated lifetime risk for PDAC. Germline mutations in a growing number of genes have been associated with increased risk of PDAC, including

[1]Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, Houston, Texas. [2]Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, Texas. [3]Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas. [5]Internal Medicine Department, The University of Texas Health Science Center at Houston, Houston, Texas. [6]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [7]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [8]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

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*S.A. Bannon, M.F. Montiel, and J.B. Goldstein contributed equally to this article.

Corresponding Author: Florencia McAllister, Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, 1515 Holcombe, Unit 1360, Houston, TX 77030. Phone: 713-745-0914; Fax: 713-834-6350; E-mail: fmcallister@mdanderson.org

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ATM, *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PALB2*, *STK11*, and *PRSS1* (2, 8–11).

Familial pancreatic cancer (FPC) is defined as a family with at least two first-degree relatives (FDR) with pancreatic cancer without an identifiable syndrome or genetic mutation in the family. Relatives meeting FPC criteria have an empirically increased risk to develop PDAC over the general population; these individuals can be even further stratified depending on their degree of relationship with the affected relative(s) (12). The standard incidence rates to develop PDAC in individuals with one FDR, two FDRs, or three or more FDRs are 3 to 4, 5 to 7, and 17 to 32, respectively (3, 13).

Germline mutations confer an elevated lifetime risk for PDAC (2, 8–11). Typically, germline mutations associated with higher risk for PDAC have been suggested by kindreds with multiple generations of pancreatic or related cancers (breast, ovarian, colon, etc.), early cancer diagnoses, individuals with multiple primary tumors, and/or Ashkenazi Jewish ethnicity (13).

Recent studies have found that an appreciable fraction of patients with apparent sporadic pancreatic cancers have germline mutations (14, 15). In search of predictive factors for germline mutations, previous studies have looked at age of presentation, but results have been ambiguous. Grant and colleagues (16) and Holter and colleagues (17) reported 3.8% and 4.5% prevalence of germline mutations in PDAC patients, respectively, while Hu and colleagues (18) reported 9.4% prevalence of mutations in established PDAC genes and up to 13.5% total pathogenic mutations. These three studies found no differences in age with respect to mutations, but the numbers of young-onset PDAC included in the analysis were rather low. Very recently, a major study from Shindo and colleagues (15) has found slightly higher prevalence of germline mutations in younger patients. Therefore, we aimed to definitively determine if patients with germline mutations present earlier than those without mutations. Given that only 30% of individuals with PDAC are diagnosed under the age of 60 (17), we examined germline mutation prevalence in a high-risk cohort (HRC) which includes a large young-onset PDAC subpopulation during an 11-year period at the University of Texas MD Anderson Cancer Center (MDACC). As validation, we examined a general cohort (GC) of PDAC patients also seen at MDACC.

Materials and Methods

Patient selection

High-risk cohort (HRC). Included patients were referred to genetic counseling, based on established criteria (Supplementary Table S1), seen at the MDACC from 2005 to 2016. All patients diagnosed with PDAC diagnosed under the age of 60 (young-onset PDAC) met referral criteria regardless of family history. From a total of 584 patients seen in the HRC, 261 were patients with young-onset PDAC. The standard genetic counseling consultation included obtaining a pedigree of at least three generations, risk assessment, and review of the patient's personal medical history and risk factors. Genetic testing was recommended based on formal risk assessment made by a board-certified genetic counselor (S.A. Bannon and M.E. Mork). All genetic testing was performed at Clinical Laboratory Improvement Amendments-certified laboratories. The landscape of genetic testing options has dramatically evolved over the time during which these patients were seen for genetic counseling. Single-gene analysis based on personal or family history or multigene panel testing were performed. In the panels, up to 13 mutations were tested: *ATM*, *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PALB2*, *STK11*, *TP53*, and *EPCAM*.

General cohort (GC). All patients with metastatic pancreatic cancer who received first-line chemotherapy at MDACC, between January 2010 and January 2016, and consented for DNA testing, were eligible. Results were considered for research purposes only and not used to make clinical decisions. Exome capture was performed from 500 ng of genomic DNA using the KAPA library (KAPA Biosystems) and sequenced using an Illumina HiSeq 2500 instrument with 200× average coverage. Genetic variants were classified based on available public databases[Exome Aggregation Consortium Database 0.3, COSMIC release 70,72, NHLBI exome sequencing project ESP6500SI-V2, dbSNP129,138, ClinVar v20150330, Exome Variant Server (EVS), 1000 Genomes, dbVar, Human Gene Mutation Database, HGVS, and DECIPHER] accessed between January 2017 and December 2017 and *in silico* analysis (SIFT, PolyPhen-2, MutationTaster). For the present study, we have focused on analyzing the 13 same genes that were included in the multigene panel testing performed in HRC patients.

For both cohorts, clinical and pathologic data were abstracted from the Electronic Health Record. MDACC Institutional Review Board approved this study. The study was conducted in accordance with the Belmont report.

Patients diagnosed with only a pathogenic germline mutation (in both cohorts) were assigned to the hereditary group and those with a variant of uncertain significance (VUS) or no identifiable mutations were assigned to the sporadic group. Patients harboring a pathogenic gene mutation and an additional VUS were assigned to the hereditary group.

Statistical analysis

Categorical variables are reported as frequencies and percentages; continuous data are summarized as mean and standard deviation (SD). The χ^2 and Fisher exact tests were used to evaluate associations between categorical variables and mutation status. The *t* test was used to compare the distributions of continuous variables (such as age) between mutation statuses. Univariate logistic

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regression models were used to evaluate the association between the risk factor (age) and mutation status. Odds ratios (OR) and 95% confidence intervals (CI) were estimated to measure the strength of association. The recursive-partitioning method was used to select optimal cutoff point for continuous age based on mutation status using HRC. The identified optimal cutoff point for age was validated using GC. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Living patients were censored at date of the last follow-up. Kaplan–Meier curves were estimated for the survival distributions by mutation status. The log-rank test was used to test the difference in survival distributions between subgroups. Univariate Cox proportional hazard models were used to determine the effects of mutation status on OS. Hazard ratios and 95% CI were provided. All tests are two-sided. *P* values less than 0.05 are considered statistically significant. All analyses were conducted using SAS 9.4 (SAS) and S-Plus 8.0 (TIBCO Software Inc.) software.

Results

Patients

High-risk cohort. Between 2005 and 2016, 584 patients with PDAC received genetic counseling. The characteristics of this population are described in Table 1. The mean age at diagnosis was 61.44 years, and slightly more than half were female (53.8%). In terms of racial/ethnicity characteristics, the majority of patients were non-Hispanic white (82.7%), while Hispanic, black, and Asian represented 6.8%, 7.2%, and 3%, respectively. A large proportion of patients had no previous history of tobacco use (58.2%) while alcohol consumption was reported by 62.7% of patients. Importantly, 13.6% of patients had personal history of breast cancer and 4.5% had gynecologic cancer. A total of 171 patients were found to have at least one FDR with breast cancer (29.2%). With respect to family history of pancreatic cancer, 127 patients had at least one FDR (21.7%) and 111 had at least one second-degree relative (SDR) affected (19%).

From the 584 patients in the HRC, 277 underwent genetic testing for hereditary pancreatic cancer genes. We compared the clinical and pathologic characteristics of patients who underwent testing with those who did not, and we found that younger patients were more likely to be tested ($P = 0.019$). We then observed that patients with personal history of chronic pancreatitis were less likely to be tested ($P = 0.014$) and those with a personal history of breast or gynecologic cancers were more likely to undergo genetic testing ($P = 0.0001$ and $P = 0.0085$). Those with at least one FDR with breast cancer were also more likely to undergo genetic testing than those without an FDR with breast cancer ($P = 0.0047$; Supplementary Table S2). These results were expected as young patients or those with stronger personal or family history of cancer received a stronger recommendation for genetic testing at the time of genetic counseling.

Table 1. Patient demographics, personal and family history in HRC ($n = 584$)

Characteristic	HRC ($n = 584$)
Age at diagnosis (mean)	61.44 (25–89)
Sex	
Female	310 (53.1%)
Male	274 (46.9%)
Race	
White	183 (82.7%)
Hispanic	40 (6.8%)
Black	42 (7.2%)
Asian	18 (3.0%)
Unknown	1 (0.17%)
Smoking history	
Never	340 (58.2%)
Past/current	244 (41.8%)
Alcohol history	
Never	218 (37.3%)
Occasional/heavy	366 (62.7%)
History of pancreatitis	54 (9.2%)
Chronic diabetes	96 (16.4)
New-onset diabetes	79 (13.5%)
Personal history of cancer	
Breast	80 (13.6%)
Gynecologic	26 (4.45%)
Melanoma	13 (2.2%)
Colon	25 (4.2%)
Family history of cancer	
≥1 affected FDR	
Breast	171 (29.2%)
Pancreas	127 (21.7%)
≥1 affected SDR	
Breast	166 (28.4%)
Pancreas	111 (19.0%)

NOTE: Age is shown in years with range.
Abbreviations: FDR, first-degree relative; SDR, second-degree relative.

Outcomes of genetic counseling and testing in HRC

Pathogenic germline mutations were identified in 48 patients (17.32%; Fig. 1A), VUS were found on 14 patients, and 215 patients had uninformative results. Of the 277 patients who underwent clinical genetic testing in the HRC, 240 (86.7%) were tested by single-gene analysis and 37 (23.3%) by the multigene panel. Of the 130 young-onset (<60) PDAC patients, 28 (21.6%) underwent panel testing and 102 (78.4%) had single-gene testing. In the young-onset cohort, we compared the mutation detection of panel versus single-gene testing. We found no significant difference in the yield of pathogenic mutations detected with panel versus single-gene testing, 21.43% versus 22.5%, respectively ($P = 0.9$). However, panel testing identified a significantly higher number of VUS than single-gene testing, as expected (25% vs. 1.96%; $P = 0.0003$; Supplementary Fig. S1). There was significant heterogeneity in the number of patients tested for each gene, as single-gene(s) genetic testing was determined by a genetic counselor based on personal and family history risk assessment; therefore, not all patients in the HRC were tested for all genes. The most frequently mutated genes were *BRCA1* and *BRCA2* (29/128 patients with

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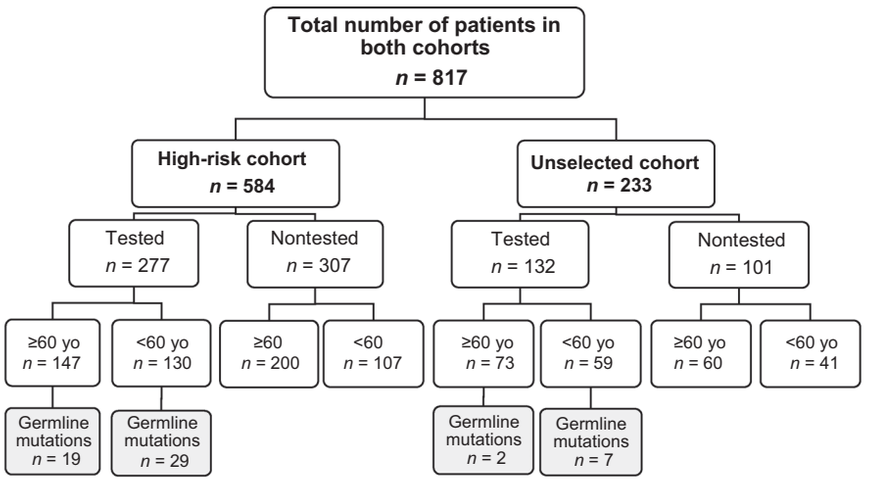
A



B

	HRC			GC		
	OR	CI	*P* value	OR	CI	*P* value
Age <60 vs. age ≥60	1.93	1.03–3.70	0.039	4.78	1.10–32.95	0.036
Age <42 vs. age ≥42	4.17	1.42–11.84	0.011	20	3.16–131.27	0.002

Figure 1.
A, Flow diagram. Mutation status by age of diagnosis in both cohorts (HRC and GC). **B,** Statistical analysis assessing the association between mutation status and age (age $\geq$ 60 years vs. < 60 years and age $\geq$ 42 years vs. < 42 years) in HRC and GC. OR, odds ratio; CI, confidence interval.

BRCA2 mutations and 5/127 with *BRCA1*, respectively), which is consistent with previous reports (17). The second most common group of mutations detected were in the MMR genes, with 2 of 33 in *MLH1*, 3 of 34 in *MSH2*, and *2 of* 33 in *MSH6*. Seven patients had germline mutations in other genes: 2 of 35 in *TP53* and *ATM* (30 tested) and 1 each in *APC* (31 tested), *CDKN2A* (37 tested) and *STK11* (33 tested; Supplementary Fig. S2A). VUS were considered as negative due to inconclusive association with PDAC predisposition. There were three patients who carried both, one pathogenic mutation and one VUS. For analysis purposes, these patients were considered in the group of patients with pathogenic mutations. Details on the pathogenic mutations found in HRC young-onset patients are listed in Supplementary Table S3.

Influence of age in HRC genetic testing results

We then looked at the influence of age in the mutation status of tested patients within the HRC, which was the main goal of the study. We found that the mean age at time of PDAC diagnosis in patients with germline mutations was significantly younger than in patients without mutations [56.6 (SD $\pm$ 10.95) vs. 61.07 (SD $\pm$ 10.95); P = 0.010; Table 2]. We then compared mutation prevalence in early-onset PDAC patients (<60 years old) with older patients ($\geq$60 years old) and found that early-onset patients had significantly higher odds of testing positive compared with older patients (OR, 1.93; 95% CI, 1.03–3.70, P = 0.039; Fig. 1A and B).

Using the recursive-partitioning method, we identified 42 years of age as the optimal cutoff that best separates age-stratified groups based on mutation status in the HRC. Patients younger than 42 years had remarkably higher odds of testing positive for a mutation than patients older than 42 years (OR, 4.17; 95% CI, 1.42–11.84, P = 0.011; Fig. 1B).

Importantly, we found that approximately half (50.1%) of the patients in the HRC met National Comprehensive Cancer Network (NCCN) 2018 *BRCA1/BRCA2* genetic testing criteria (Supplementary Table S4), and 44.6% of patients younger than 60 years met criteria, indicating that 55.4% of young-onset patients were tested solely based on indication of age. Finally, in the mutation-positive HRC, 52.1% of patients met criteria, while in the mutated younger-onset group 41.4% did (Supplementary Table S5).

Comparison of mutation-positive versus mutation-negative patients in HRC

We then assessed for the association between other potential predictive factors and mutational status, and a significant difference was seen by ethnicity, with Hispanic individuals more likely to test positive (P = 0.026; Table 2). With respect to family history, patients with at least one or more FDR with breast, gynecologic, and colon cancers were significantly more likely to harbor mutations (P = 0.021, P = 0.031, P = 0.022, respectively; Table 2). Also, patients with at least one SDR with gynecologic cancers were more likely to have germline

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Table 2. Comparison of demographical information, clinical characteristics, and family history of cancer in patients from the HRC who tested positive versus negative for mutations

Characteristic	Mutation positive ($n = 48$) *n* (%)	Mutation negative ($n = 229$) *n* (%)	*P* value
Age			
Mean (years ± SD)	56.6 (±10.95)	61.07 (±10.95)	0.010*
Sex			
Female	22 (45.8)	127 (55.5)	0.223
Male	25 (54.2)	102 (44.5)	
Race			
White	35 (72.9)	200 (87.3)	0.026*
Hispanic	8 (16.6)	11 (4.8)	
Asian	2 (4.1)	11 (4.8)	
Black	3 (6.2)	7 (3.0)	
Stage			
Localized	16 (33.3)	68 (29.7)	0.870
Borderline	7 (14.6)	33 (14.4)	
Metastatic	25 (52.1)	128 (55.9)	
Grade of differentiation			
Well	0 (0)	2 (1.3)	0.220
Moderately	18 (58.1)	115 (72.3)	
Poorly	13 (41.9)	42 (26.4)	
Smoking history			
Current	8 (16.7)	43 (18.8)	0.752
Past	11 (22.9)	42 (18.3)	
Never	29 (60.4)	144 (62.9)	
Alcohol history			
Heavy	1 (2.1)	14 (16.1)	0.244
Occasional	26 (54.2)	142 (62)	
Never	21 (43.8)	73 (31.9)	
History of pancreatitis	1 (2.1)	16 (7)	0.322
Chronic diabetes	10 (20.8)	36 (15.7)	0.386
Personal history of cancer			
Breast	13 (27.1)	43 (18.8)	0.192
Gynecologic	2 (4.2)	17 (7.4)	0.543
Melanoma	2 (4.2)	7 (3.1)	0.657
Colon	3 (6.3)	11 (4.8)	0.715
Family history of cancer			
≥1 affected FDR			
Breast	23 (56.1)	74 (36.8)	0.021*
Gynecologic	10 (34.5)	29 (17.3)	0.031*
Melanoma	5 (10.4)	16 (7)	0.379
Pancreas	11 (23.4)	52 (22.7)	0.917
Colon	12 (25)	28 (12.2)	0.022*
≥1 affected SDR			
Breast	14 (29.2)	72 (31.4)	0.756
Gynecologic	9 (18.8)	18 (7.9)	0.020*
Melanoma	1 (2.1)	11 (4.8)	0.698
Pancreas	7 (14.9)	50 (21.8)	0.284
Colon	7 (18.9)	25 (13.4)	0.385

NOTE: VUS were tabulated as negative results.
Abbreviations: FDR, first-degree relative; SDR, second-degree relative; *, $P < 0.05$.

mutations. Patients with family history contributory for pancreatic cancer in FDRs and/or SDRs were not more likely to have germline mutations than those without it (Table 2). There were no other significant differences between the two groups (with mutations vs. without mutations) regarding sex, grade of differentiation, stage, personal history of cancer, and other risk factors.

General cohort

To validate the higher prevalence of germline mutations in early-onset PDAC in a non-HRC, we analyzed a second group of patients with PDAC seen at the same institution referred to as the general cohort (GC). A total of 233 consecutive patients with metastatic PDAC receiving chemotherapy treatment at MD Anderson were enrolled, from which 132 patients had sequencing performed. The selection of patients for sequencing was randomly performed. The characteristics of the tested GC population are described in Supplementary Table S6. The mean age at diagnosis was 59.73 years, and 59.1% of the patients were male. Most of patients were non-Hispanic white (84%), and Hispanic, black, and Asian represented 4.5%, 9%, and 2.2%, respectively. A total of 11 patients were found to have at least one FDR with pancreatic cancer (8.3%), while 9 patients had at least one SDR with pancreatic cancer (6.8%).

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Genetic testing results in GC and influence of age

From the 132 patients who had sequencing, 9 were found to have a pathogenic germline mutation (6.81%; Fig. 1A). Again in this group, the most common mutations found were in *BRCA*/2 genes (Supplementary Fig. S2B). The average age of patients with germline mutations was also younger than patients without mutations [48.44 (SD ± 9.65) vs. 60.56 (SD ± 10.57; $P = 0.033$; Supplementary Table S7]. In this cohort, 59 patients presented with early-onset PDAC (<60) and 7 of them had germline mutations, which is significantly associated with higher odds of testing positive for a mutation compared with older patients (>60; OR, 4.78; 95% CI, 1.10–32.95; $P = 0.036$; Fig. 1A and B). When using the optimal cutoff of 42 years of age, determined using the HRC data set, again we found significantly higher prevalence of mutations in patients younger than 42 versus those older (OR, 20; 95% CI, 3.16–131.27, $P = 0.002$; Fig. 1B). No other factors, besides age, were associated with higher prevalence of mutations in the GC (Supplementary Table S7).

Mutational status as predictive of clinical outcomes in HRC and GC

We then performed an analysis of clinical outcomes in both cohorts. We first analyzed OS in resectable patients from the HRC, and found that patients with germline mutations had significantly better OS than patients without mutations, with a median survival of 70.4 months versus 32.6 months, respectively (HR, 0.55; 95% CI of HR, 0.33–0.91, $P = 0.03$; Fig. 2A). Adjuvant chemotherapy regimens in the resectable HRC patients were composed of single-agent gemcitabine and/or platinum-based regimens, including 5-fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX), single-agent oxaliplatin, and cisplatin. Unfortunately, we do not have enough power to detect differences in outcomes by treatment type given the limited number of patients in each chemotherapy type.

We then analyzed survival in PDAC patients from GC (all metastatic). Patients from the GC with germline mutations had significantly improved survival than patients without mutations detected with a median survival of 18.2 versus 9.2 months (HR, 0.44; 95% CI of HR, 0.25–0.76, $P = 0.03$), regardless of adjuvant chemotherapy treatment regimen (Fig. 2B). When we looked at the metastatic patients from the HRC, we did not find significant differences in survival based on their mutational status (Supplementary Fig. S3A). However, metastatic patients in the HRC, disregarding their mutational status, had significantly longer OS than patients without mutations in the GC (HR, 0.51; 95% CI of HR, 0.39–0.66, $P < 0.0001$; Supplementary Fig. S3B).

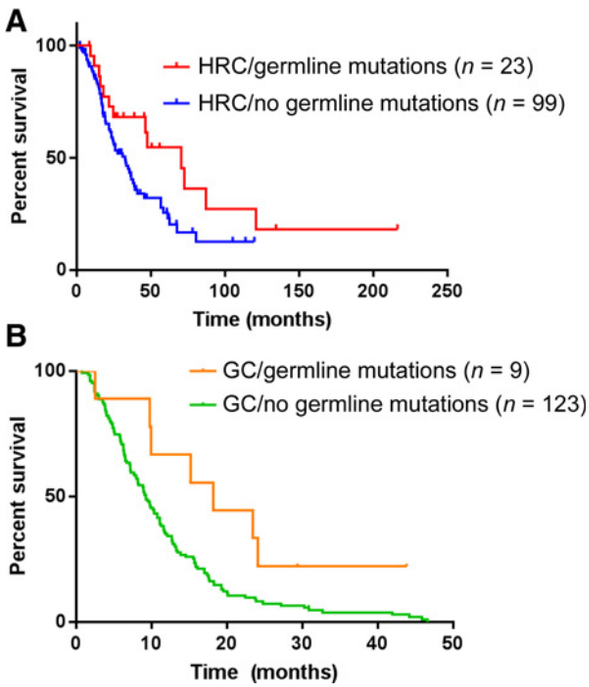

Figure 2.
Survival data. Kaplan–Meier survival curves for resectable PDAC patients by mutation status in the HRC (**A**) and for metastatic patients from GC (**B**). *N* = number of patients in each subgroup. *P* value calculated based on the log-rank test.

Discussion

This study analyzes a large HRC of patients diagnosed with pancreatic cancer at a tertiary referral center with the main goal of determining if patients with germline mutations on PDAC susceptibility genes present earlier than those with sporadic PDAC. We determined the prevalence of germline mutations and looked for predictive factors of germline mutations and used a second GC for validation purposes. A total of 17.32% of patients in the HRC were found to have pathogenic germline mutations against 6.81% in the GC, which is consistent with the previously reported prevalence of hereditary pancreatic cancer in the general pancreatic cancer population (15, 16). Interestingly, panel testing did not yield significantly increased detection of pathogenic germline mutations over single-gene(s) testing as guided by genetic counselor risk assessment. However, panel testing did significantly increase the risk of identifying VUS. This finding is significant in the clinical practice context where VUS can pose confusion and add uncertainty to individuals attempting to discern their risk to develop PDAC. Germline mutations for genes associated with increased risk of PDAC were found in 11% to 22% of PDAC patients younger than 60 years old and 44% to 50% of patients younger than 42 years old. Therefore, young age represents a strong predictive factor of germline mutations in PDAC patients. The optimal cutoff point of 42 years old found in the HRC was exploratory and tested in the unselected cohort. However, this cutoff point should be further validated in a larger scaled study in the future.

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We found that family history of breast, gynecologic, or colon cancer is actually predictive of germline mutations while family history of PDAC was not predictive, in agreement with previous reports (15, 16) while family history of PDAC was not more prevalent on patients with germline mutations. These data suggest that the germline mutations associated with familial PDAC may not be included in the panel of established PDAC susceptibility genes.

Regarding clinical outcomes, we have found that patients in the HRC without mutations had a shorter OS than those with mutations only in patients older than 60 years. An explanation for this might be that PDAC patients younger than 60 years who tested negative may still harbor a germline mutation in genes for which they were not tested. With respect to metastatic patients, only PDAC patients from the GC with germline mutations were found to have better clinical outcomes compared with those without mutations. Similar to the explanation above, patients from the HRC do not have substantial differences based on their mutational status because those with negative results may also have mutations, which have not been tested for.

The use of a discovery cohort with a large number of young-onset PDAC patients and a validation cohort with patients who were not at high risk for mutations based on personal and/or family history is strength of the study. A major limitation of this study is the use of panels with differing genes analyzed in individual patients of the HRC and not all patients were tested for all genes. The reason for this is that single-gene analysis of one to three genes was standard of care until 2013 when multigene panels became available at our institution. We compared demographic data from patients tested for individual genes or with panels and found no differences between the two groups (Supplementary Table S8), suggesting that this factor should not affect final results. Additionally, panel testing did not yield significantly higher detection of pathogenic mutations, but did significantly increase the likelihood to identify VUS. Future studies would ideally include comprehensive analysis of an entire cohort for the same set of genes to validate these findings. Similarly, variants identified in the GC cohort were subject to classification on the research platform involving public database review and *in silico* analysis but were not subjected to the stringent clinical variant interpretation as those tested via standard clinical genetic testing in the HRC cohort.

Higher detection rates of germline mutations will potentially affect therapy choices for patients with PDAC. *BRCA*-associated PDAC have been shown to have higher sensitivity to platinum therapy and poly (ADP-ribose) polymerase (PARP) inhibitors (19) while tumors with genetic defects in MMR genes have greater susceptibility to immune-checkpoint blocking agents (20). Moreover, unaffected family members may be identified and receive genetic counseling and risk assessment to enter pancreatic cancer screening programs and undergo cancer surveillance and prevention (21, 22).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.A. Bannon, M.F. Montiel, J.B. Goldstein, W. Dong, A. Maitra, M.H. Katz, E. Vilar, F. McAllister

Development of methodology: S.A. Bannon, M.F. Montiel, J.B. Goldstein, E. Vilar, F. McAllister

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.A. Bannon, M.F. Montiel, J.B. Goldstein, M.E. Mork, M. Hasanov, G.R. Varadhachary, M.H. Katz, A. Futreal, D.R. Fogelman, F. McAllister

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.A. Bannon, M.F. Montiel, J.B. Goldstein, W. Dong, E. Borras, M. Hasanov, A. Maitra, M.H. Katz, L. Feng, A. Futreal, F. McAllister

Writing, review, and/or revision of the manuscript: S.A. Bannon, M.F. Montiel, J.B. Goldstein, W. Dong, M.E. Mork, E. Borras, A. Maitra, M.H. Katz, A. Futreal, E. Vilar, F. McAllister

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.F. Montiel, J.B. Goldstein, M. Hasanov, F. McAllister

Study supervision: F. McAllister

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