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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Familial pancreatic cancer risk: a population-based study in Utah

Divyanshoo R. Kohli[1,5] · Ken Robert Smith[2,3,4] · Jathine Wong[2,3,4] · Zhe Yu[2,3,4] · Kenneth Boucher[2,3,4] · Douglas O. Faigel[1] · Rahul Pannala[1] · Randall W. Burt[2,3,4] · Karen Curtin[2,3,4] · N. Jewel Samadder[1]

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Abstract

Introduction Pancreas adenocarcinoma (PC) has an undefined hereditary component. We quantified the familial risk of PC among relatives of patients diagnosed with PC and stratified it based on anatomic location of PC and age and sex of the proband.

Methods This is a retrospective, population-based, case–control study of PC diagnosed in Utah between 1980 and 2011. The Utah population database and cancer registry were used to identify index patients with PC. The risk of PC in first-degree relatives (FDRs), second-degree relatives (SDRs), and first cousins (FCs) of probands was compared with randomly selected sex- and age-matched population controls.

Results A total of 4,095 patients and 40,933 controls were identified. The relative risk (RR) of PC was 1.76 (95% CI 1.35–2.29) in FDRs, 1.42 (95% CI 1.18–1.7) in SDRs and 1.08 (95% CI 0.95–1.23) in FCs of probands compared to relatives of PC-free controls. The RR were elevated in FDRs (1.96, 95% CI 1.45–2.65), SDRs (1.54, 95% CI 1.19–1.98) and FCs (1.18, 95% CI 1.0–1.64) of female probands. Among probands diagnosed as < 65 years, RR was 2.12 (95% CI 1.37–3.28) in FDRs, 1.94 (95% CI 1.44–2.62) in SDRs, and 1.28 (95% CI 1.0–1.64) in FCs. Overall, the RR for PC was elevated in FDRs regardless of the anatomic location of PC.

Discussion There is an increased risk of PC in FDR and more distant relatives of patients with PC. Relatives of female patients with PC and patients diagnosed at age < 65 years are at a significantly increased risk of PC.

Keywords Pancreatic cancer · Familial · Hereditary cancer

Abbreviations

PC	Pancreas adenocarcinoma
UCR	Utah cancer registry
UPDB	Utah population database
FDR	First-degree relative (parent, child, sibling)
SDR	Second-degree relative (aunt/uncle, niece/nephew, grandparent/grandchild)
FC	First cousin
RR	Relative risk

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✉ N. Jewel Samadder
Samadder.jewel@mayo.edu

[1] Division of Gastroenterology and Hepatology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, USA

[2] Department of Medicine (Gastroenterology), Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[3] Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[4] Department of Medicine (Genetic Epidemiology), Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[5] Division of Gastroenterology and Hepatology, Kansas City Veterans Affairs Medical Center, Kansas City, MO, USA

Introduction

Pancreas adenocarcinoma (PC) is a leading cause of cancer-related mortality with an overall 5-year survival of 8% and is often detected at a late stage. Efforts have been made to risk-stratify patients and identify modifiable and non-modifiable factors which may predispose clinically asymptomatic individuals to PC [1, 2]. Family history of PC, including the number of family members and proximity of relationship, may increase the risk of PC. While expert consensus suggests that individuals with multiple first-degree relatives (FDRs) are at increased risk of PC and should undergo screening, the quantification of risk for second-degree relatives (SDRs), and first cousins (FCs) remains unknown [3]. The effect of gender, age of diagnosis and tumor site on the familial risk of PC also remain unknown. Further, the genes responsible for familial clustering remain to be fully investigated [4].

In this study, we quantified the risk of PC in FDRs, SDRs and FCs of patients with histologically proven PC using a population-based case–control study. We compared the risk of cancers in relatives of index cases who received a diagnosis of PC to the risk in relatives of cancer-free controls. We also explored the effect of tumor site, gender and age of diagnosis on familial PC risk.

Methods

Study design

This is a retrospective, population-based, case–control study of pancreas adenocarcinoma diagnosed in the state of Utah from 1980 to 2011, and recorded in the Utah Cancer Registry (UCR). This time period was selected since endoscopy and advanced imaging was widely available in the state and would closely reflect present-day practice and minimize misclassification bias [5]. De-identified medical information on these patients was merged with family structure in the Utah Population Database (UPDB) genealogies to investigate the descriptive characteristics and familial aggregation.

Description of databases

Information from two databases, the UCR and UPDB, was used perform the study. The UPDB is a unique database which combines the genealogies from the family history libraries to linked data from statewide resources including UCR, statewide inpatient discharge and ambulatory surgery records, driver license data, as well as birth and death certificates. Genealogies are from the Genealogical Society of Utah, dating back to the early 1800′s and are linked to the UPDB. There are currently nearly 8 million unique individuals in the database and the Utah family histories represent pedigrees that may span as many as 12 generations. It includes diagnostic records about cancer and has access to information on more than 8 million individuals [5, 6]. Previous demographic and genetic analyses have shown that the population recorded in the database is genetically representative of US white and Northern European populations with a low level of inbreeding [7].

The UCR is a statewide, population-based cancer registry which was established in 1966 and became part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program in 1973. By state law, all incident cancer diagnoses must be reported to the UCR [4]. Given an ongoing and accurate assessment of family history of cancer that does not depend on self-report, the UPDB provides a valuable resource for a thorough analysis of the familial nature of PC.

Cases and controls

Patients with histologically proven PC diagnosed between 1980 and 2011 were identified using the histological and International Classification of Disease-9 coding for malignant neoplasm of the pancreas (C25.0–C25.9). The cancers were subdivided based on the location of the tumor: head of pancreas (C25.0), body of pancreas (C25.1), tail of pancreas (C25.2), and Pancreas 'not-otherwise-specified' and overlapping/other sites (C25.3, 25.4, 25.7, 25.8, 25.9).

Population controls were selected randomly from the UPDB and individually matched to cases by gender and birth year in a 10:1 ratio. Controls were sampled without replacement and had to satisfy the following, previously reported, inclusion criteria [8]:

(a) Absence of any pancreas cancers (C25.0–25.9). Study controls were selected as not having PC to compare the prevalence and relative risk of this malignancy in their relatives.
(b) Follow-up at least as long as their respective matched case [9]. Follow-up was based on the most recent date an individual had an event recorded in Utah from vital records (deaths, births, adoptions, marriages, and divorces, Utah driver's license registrations and renewals, voter registrations, and statewide inpatient and ambulatory surgeries).

Statistics

The incidence of PC was calculated in first-degree relatives (FDRs), second-degree relatives (SDRs), and first cousins

(FCs) of patients with PC. This incidence was compared with the FDRs, SDRs and FCs of matched population controls to assess the relative risk for PC. FDRs were defined as parent, child or sibling. SDRs were defined as aunt, uncle, nephew, niece, grandparent or grandchild.

Using software developed specifically for UPDB kinship analysis, the magnitude of familial risk was estimated by Cox proportional hazard regression models to assess the relative risk of cancer incidence for FDRs, SDRs, and FCs of patients who received a diagnosis of PC. This analysis corrects for family clustering, as individuals in families may be analyzed multiple times due to more than one occurrence of PC within the family. Because observations within families are non-independent, the Huber–White sandwich estimator of variance for clustered data was used because it accounts for departures from standard statistical assumptions. This analysis corrects for any families that were analyzed multiple times because of multiple PC cases with in the family. Statistical methodology applied in this paper is provided in detail in prior publication from our group involving colorectal cancers [10].

The patients with PC were further stratified by the site of cancer within the pancreas. The relative risk of PC in FDRs, SDRs and FCs was calculated based on the probands' gender, age group at the time of diagnosis (< 65 and ≥ 65 years; < 50 and ≥ 50 years) and site of PC. A P value of < 0.05 was considered statistically significant. The study protocol was approved by the University of Utah institutional review board.

Results

Four thousand and ninety-five patients who met the inclusion criteria and had PC were identified. The mean age at diagnosis was 69.6 years (range 18–100; Table 1) and 68% of the cohort was ≥ 65 years of age. Just under half (48.3%) were female. Adenocarcinoma was identified in the head of the pancreas in half of the cohort. The presence of distant metastasis was diagnosed in 45% of the overall cohort. However, distant metastasis was present at the time of diagnosis in 35% of patients with cancer in the head of the pancreas, 58% in the body of pancreas and 70% in the tail of the pancreas. A median of 6 FDRs per subject, 15 SDRs per subject and 23 FCs per subject was evaluated using the UPDB family registry. A total of 40,933 age- and gender-matched controls were selected. The median number of FDRs, SDRs and FCs per control was 6, 17 and 24, respectively and was similar between cases and controls (supplementary table 1).

Overall, PC was present in 112 of the 20,104 FDRs of cases compared to 633 of the 196,710 FDRs of the controls [relative risk (RR) 1.76; 95% CI 1.35–2.29; $P < 0.0001$; Table 2]. The relative risk for PC among SDRs of cases compared to controls was 1.42; 95% CI 1.18–1.7 ($P = 0.0002$) and for FCs was 1.08; 95% CI 0.95–1.23 ($P = 0.16$).

The familial risk of PC was stratified based on the location of the tumor and compared with controls. The RR for FDRs of patients with cancer of the head of the pancreas was 1.62; 95% CI 1.15–2.3 ($P = 0.006$). The corresponding RR was 1.4 (95% CI 1.08–1.82; $P = 0.01$) for SDRs and 0.98 (95% CI 0.82–1.17; $P = 0.82$) for FCs (Table 3a).

Among relatives of patients with cancer of the body of pancreas, the RR for FDRs was 2.82 (95% CI 1.3–6.1), SDRs was 1.42 (95% CI 0.75–2.69) and FCs was 1.74 (95% CI 1.19–2.53) compared to relatives of controls (Table 3b). Similarly, among relatives of patients with cancer of the tail of the pancreas, the RR for FDRs was 2.33 (95% CI 1.24–4.38), SDRs was 0.99 (95% CI 0.49–1.98) and FCs was 0.91 (95% CI 0.62–1.35) compared to relatives of controls (Table 3c).

The familial risk of PC was stratified by gender and age of the index patient with PC. The RR of PC in FDRs of male cases was 1.55 (95% CI 1.07–2.26) and female cases was 1.96 (95% CI 1.45–2.65; Table 4). The RR in SDRs and FCs relatives was also elevated.

Among FDRs of cases diagnosed with pancreas adenocarcinoma at age < 65 years, the RR was 2.12 (95% CI 1.37–3.28). The corresponding RR for SDRs and FCs was 1.94 (95% CI 1.44–2.62) and 1.28 (95% CI 1.0–1.64), respectively (Table 4). In comparison, among FDRs of PC cases ≥ 65 years old, the RR for pancreas adenocarcinoma was 1.65 (95% CI 1.22–2.24) and those for SDRs was 1.21 (95% CI 0.96–1.53) and FCs was 1.03 (95% CI 0.90–1.18). Similar results were seen when the analysis was performed with an age cut-off of 50 years (supplementary table 2). Due to small number of PC diagnosed in relatives of the probands (eight cases in FDR of proband with PC > 50), the results fail to reach statistical significance but consistently show the trend of higher risk with young onset PC diagnosis.

Discussion

PC is a leading cause of cancer-related mortality with an average survival of less than 5 years. Since early detection of PC in susceptible individuals may be potentially curable and life-saving, screening and evaluation of high-risk individuals has been suggested [3]. A family history of PC is a well-known risk factor for development of PC but the risk has not been well quantified [11, 12]. In this large, population-based case–control study, the familial risk of PC was assessed based on kinship, sex, age and tumor site

Table 1 Characteristics of index patients with pancreas cancer by tumor subsite

Characteristics	All cases		Head		Body		Tail		Other sites[a]	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	4095	100	2043	49.89	302	7.37	436	10.66	1314	32.08
Age at diagnosis										
Mean	69.66		69.96		67.99		65.94		70.79	
Range	18–100		25–98		18–97		20–97		18–100	
Age group at diagnosis										
< 65 years old	1311	32.02	632	30.93	113	37.41	188	43.11	378	28.77
≥ 65 years old	2784	67.99	1411	69.07	189	62.58	248	56.88	936	71.23
Sex										
Female	1,977	48.28	1032	50.51	137	45.36	191	43.81	617	46.96
Male	2,118	51.72	1011	49.49	165	54.64	245	56.19	697	53.04
Known Church affiliation										
LDS Active	971	23.71	515	25.21	58	19.20	93	21.33	305	23.21
LDS Inactive	602	14.70	295	14.44	41	13.58	57	13.07	209	15.91
Non-LDS	2,522	61.59	1233	60.35	203	67.22	286	65.60	800	60.88
Stage of pancreas adenocarcinoma										
Localized	339	8.28	216	10.57	30	9.93	35	8.03	58	4.41
Regional	555	13.55	381	18.65	46	15.23	35	8.03	93	7.08
Regional with LN	587	14.33	416	20.36	31	10.26	45	10.32	95	7.23
Distant metastasis	1,866	45.57	716	35.05	175	57.95	310	70.10	665	50.61
Unknown stage	748	18.27	314	15.37	20	6.62	11	2.52	403	30.67

[a]Includes overlapping sites and not otherwise specified

LDS Church of Jesus Christ of Latter-day Saints, *LN* lymphadenopathy

Table 2 Risk for pancreatic cancer in relatives of all pancreas adenocarcinoma cases

Relationship	Index case		Controls		RR	95% CI	*P* value
	Affected	Unaffected	Affected	Unaffected			
FDRs	112	19,992	633	196,077	**1.76**	**1.35–2.29**	**< 0.0001**
SDRs	126	55,810	896	555,275	**1.42**	**1.18–1.7**	**0.0002**
FCs	306	62,794	2768	617,998	1.08	0.95–1.23	0.158

RR relative risk, *FDR* first-degree relative; parent, child, sibling, *SDR* second-degree relative; aunt/uncle, niece/nephew, grandparent/grandchild, *FC* first cousin

in patients with PC. To our knowledge, this is the largest such study to stratify the familial risk for PC among FDRs, SDRs and FCs.

The main tool to assess risk of PC in an individual remains the family history [3, 13]. Most of the published studies rely on case–control studies where the family history is ascertained by self-administered or interviewer-administered questionnaires [11, 14–17]. The PACIFIC study used two healthcare plans to compare patients with PC, and age- and sex-matched controls. The study demonstrated an odds ratio of 2.79 for risk of PC in FDRs. However, detailed analyses based on age and gender were not provided. Similarly, a pooled analysis from the pancreatic cancer cohort consortium analyzed 1183 cases of PC and 1205 controls from 11 different study cohorts. Using a self-administered written questionnaire, the authors concluded that family history of pancreatic cancer in a FDRs was associated with an increased risk of PC (odds ratio of 1.76). None of these studies assessed the risk in more distant relatives (i.e. SDRs and FCs) nor by sex of the proband or tumor site within the pancreas. A meta-analysis of seven case–control and two cohort studies involving 6,568 patients concluded that having an affected relative increased the risk of PC by 80%. However, the study was limited by the possible publication bias based on the marginally significant Begg–Mazumdar test, recall and selection bias inherent in questionnaire-based studies, and sparse data, especially for assessing risk in SDRs [14].

Very few studies have evaluated the risk of PC in SDRs of affected patients [17, 18]. In a hospital-based, case–

Table 3 Risk for pancreas adenocarcinoma in relatives of patients

Relationship	Index case		Controls		RR	95% CI	*P* value
	Affected	Unaffected	Affected	Unaffected			
(a) Pancreatic head cancer							
FDR	52	10,007	311	96,355	**1.62**	**1.15–2.3**	**0.0064**
SDR	65	28,121	453	273,412	**1.40**	**1.08–1.82**	**0.0106**
FC	141	31,841	1364	304,286	0.98	0.82–1.17	0.816
(b) Pancreatic body cancer							
FDR	8	1,502	30	15,049	**2.82**	**1.30–6.11**	**0.00861**
SDR	9	3,969	69	40,850	1.42	0.75–2.69	0.278
FC	31	4,679	180	46,362	**1.74**	**1.19–2.53**	**0.0042**
(c) Pancreatic tail cancer							
FDR	14	2,203	55	21,164	**2.33**	**1.24–4.38**	**0.0084**
SDR	9	5,664	91	55,444	0.99	0.49–1.98	0.9704
FC	26	6,170	274	62,730	0.91	0.62–1.35	0.6443

FDR first-degree relative; parent, child, sibling, *SDR* second-degree relative; aunt/uncle, niece/nephew, grandparent/grandchild, *FC* first cousin

Table 4 Risk for pancreas adenocarcinoma stratified by sex and age of the index case

Relationship	Sex				Age (years)			
	Male		Female		< 65		≥ 65	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
FDR	**1.55**	**1.07–2.26**	**1.96**	**1.45–2.65**	**2.12**	**1.37–3.28**	**1.65**	**1.22–2.24**
SDR	**1.31**	**1.01–1.71**	**1.54**	**1.19–1.98**	**1.94**	**1.44–2.62**	1.21	0.96–1.53
FC	0.99	0.83–1.17	**1.18**	**1.0–1.4**	**1.28**	**1.0–1.64**	1.03	0.90–1.18

FDR first-degree relative; parent, child, sibling, *SDR* second-degree relative; aunt/uncle, niece/nephew, grandparent/grandchild, *FC* first cousin

control study which assessed family history and modifiable risk factors such as smoking and alcohol use, Hassan and colleagues reported that SDRs had an adjusted odds ratio of 2.9 for developing PC. The study utilized questionnaires and interviews to assess the risk factors and the authors acknowledged that the accuracy of reporting PC was likely lower in SDRs compared to FDRs. Further, more than half of the SDRs were deceased grandparents in whom confirmation of the diagnosis of PC was not possible [17]. The accuracy of family history of cancer is often sub-optimal for SDRs and FCs which in turn can make quantification of the risk less accurate [19]. To the best of our knowledge, no study has accurately assessed the familial risk in more distant third-degree relatives (i.e. FCs).

We stratified the familial risk of PC based on location of the tumor within the pancreas. Our study confirms that PC is typically a disease of relatively older men and women, and often presents at a late stage with regional lymphadenopathy or distant metastasis. PC of the head often presents at an earlier stage compared to the tail and body of the pancreas [20]. It is notable, however, that the familial risk of PC was greatest in relatives of probands with tumors in the body or tail compared to the head of the organ. The clinical importance of these results needs to be interpreted with caution since the number of affected relatives was relatively low in body and tail PC subgroups compared to PC of the head and the confidence intervals overlap. Similarly, the risk was statistically significant in FCs of patients with body PC but not in the SDRs. The presence of only nine SDRs among the cases may have precluded robust statistical analysis.

The familial risk of PC was also stratified based on age and sex of the index case. The familial risk of PC was greater in relatives of patients who were diagnosed at an age < 65 years compared to those diagnosed at age ≥ 65 years. This is consistent with prior studies where the risk of hereditary PC was higher in relatives of cases diagnosed before age 50 years [21]. A study from the National Familial Pancreas Tumor Registry also observed that a younger age of onset for PC in patients with familial PC confers an added risk in their relatives [22]. The study also demonstrates that relatives of female patients with PC may be at a higher relative risk for PC. The biological plausibility of this is uncertain. We speculate that women are less

likely to be exposed to environmental triggers for PC such as alcohol and smoking. Hence, the relative impact of genetic predisposition may be greater in women compared to environmental triggers.

Our data from the state of Utah add to the literature published from other centers. Similar data from Japan demonstrate that patients with PC were more likely to have an FDR with PC than controls (odds ratio 2.5, $P = 0.02$). The risk factor increased significantly in the presence of concomitant current smoking and diabetes mellitus. The odds increased up to tenfold if the patients were positive for these three factors [23]. Data from the national familial pancreas tumor registry, based at the Johns Hopkins University, also assessed the risk of developing PC based on the presence of kindreds with PC. The study demonstrated that the risk of PC increases with increasing numbers of affected FDRs [24]. Similarly, data from European Study into Digestive Illnesses and Genetics (PanGenEU) estimate that the risk of PC increases in the presence of a positive family history of PC (odds ratio 2.68), especially if two FDRs had PC (odds ratio: 3.88; $P = 0.033$) [25].

This study has multiple strengths. The large size of the study, based on state-wide genealogy records and cancer registry, provides it with the statistical power to quantify the risk in FDRs as well as distant relatives. The study design does not rely on questionnaires which avoid referral, and recall bias both for the cancer diagnosis and kinship levels [5]. Further, it stratifies the familial risk based on the location of the PC as well as age and sex of the index patient. This is one of the very few studies which calculate risk for SDRs and the only study to assess the risks in FCs.

A similar study by Shirts and colleagues published in 2010 used the same database [4] to describe the familial clustering of pancreas cancer. However, that study was restricted to 1411 patients and assessed the familial risk of pancreas cancer only in FDR and SDR. The current study has a larger group of cases which provide more precise statistical estimates of risk and allows for a stratified analysis based on sex and tumor subsite. Further, the risks are calculated in FDR, SDR, as well as FC.

Our study is limited to the family history of patients and controls, and does not assess the impact of factors such as smoking, excessive alcohol use, obesity, diabetes mellitus, or chronic pancreatitis which increases the risk of PC and may be traits which are shared by family members. A significant proportion of patients in the study were affiliated to the Church of Jesus Christ of Latter-day Saints and hence may have lower prevalence of smoking and alcohol abuse. This limits generalizability to other populations but may reduce risk of confounding from unmeasured alcohol and tobacco exposure [5, 8]. The databases used in the study are representative of Caucasian populations and hence the results may not be applicable to ethnic minorities. There is also a possibility for ascertainment bias since relatives of patients with PC may be more likely to be evaluated for pancreatic disorders.

Since screening of high-risk individuals may identify early PC and allow early intervention [26, 27], quantification of the risk becomes imperative to facilitate appropriate counselling of patients and their families. The International Cancer of the Pancreas Screening consortium does not make recommendations about the risk of PC in SDRs and FCs [3]. There is an unmet need to assess the risk of PC in distant relatives. Our study provides data to quantify the risk in this cohort of patients.

In conclusion, this large population-based study used comprehensive genealogy and cancer records to quantify the familial risk of PC in FDRs, SDRs and FCs, and stratified the risk based on the age, sex and tumor site of the proband. We found an elevated risk of PC in FDRs and more distant relatives of patients with PC which may impact surveillance strategies in high-risk families. Clinicians will find the study useful while counselling patients with PC and their family members.

Author contributions Drs. Samadder and Curtin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: RWB, KC, NJS; acquisition, analysis and interpretation of data: GM, KS, DK, KC, JW, RP, KB, LP, RWB, NJS; drafting of the manuscript: DK, KC, and NJS; critical revision of the manuscript for important intellectual content: DK, GM, KC, KS, HS, DA, DF, RP, RWB; statistical analysis: JW, KC, LP; obtained funding: NJS and RWB.

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Compliance with ethical standards

Conflict of interest NJS is a consultant for Cook Medical, Cancer Prevention Pharmaceuticals and Janssen Research and Development. No other authors have a conflict of interest to disclose.

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