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Risk of Different Cancers Among First-degree Relatives of Pancreatic Cancer Patients: Influence of Probands' Susceptibility Gene Mutation Status

Samuel O. Antwi, Sarah E. Fagan, Kari G. Chaffee, William R. Bamlet, Chunling Hu, Eric C. Polley, Steven N. Hart, Hermela Shimelis, Jenna Lilyquist, Rohan D. Gnanaolivu, Robert R. McWilliams, Ann L. Oberg, Fergus J. Couch, Gloria M. Petersen

Affiliations of authors: Department of Health Sciences Research (SOA, KGC, WRB, ECP, SNH, JL, RDG, ALO, FJC, GMP), Department of Laboratory Medicine and Pathology (CH, HS, FJC), and Department of Medical Oncology (RRM), Mayo Clinic, Rochester, MN; Department of Epidemiology, Tulane University, New Orleans, LA (SEF)

Correspondence to: Gloria M. Petersen, Mayo Clinic, 200 First Street SW, BB 5-78, Rochester, MN 55905 (e-mail: petersen.gloria@mayo.edu).

Abstract

Background: Increased risk of malignancies other than pancreatic cancer (PC) has been reported among first-degree relatives (FDRs) of PC patients; however, the roles of susceptibility gene mutations are unclear. We assessed risk for 15 cancers among FDRs of unselected PC probands.

Methods: Data on 17 162 FDRs, with more than 336 000 person-years at risk, identified through 2305 sequential PC probands enrolled at Mayo Clinic (2000–2016) were analyzed. Family history data were provided by the probands. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated, comparing malignancies observed among the FDRs with that expected using Surveillance, Epidemiology, and End Results (SEER) data. Genetic testing was performed among a subset of probands (n = 2094), enabling stratified analyses among FDRs based on whether the related proband tested positive or negative for inherited mutation in 22 sequenced cancer susceptibility genes. All statistical tests were two-sided.

Results: Compared with SEER, PC risk was twofold higher among FDRs of PC probands (SIR = 2.04, 95% CI = 1.78 to 2.31, $P < .001$). Primary liver cancer risk was elevated among female FDRs (SIR = 2.10, 95% CI = 1.34 to 3.12, $P < .001$). PC risk was more elevated among FDRs of mutation-positive probands (SIR = 4.32, 95% CI = 3.10 to 5.86) than FDRs of mutation-negative probands (SIR = 1.77, 95% CI = 1.51 to 2.05, between-group $P < .001$). FDR PC risk was higher when the related proband was younger than age 60 years at diagnosis and mutation-positive (SIR = 5.24, 95% CI = 2.93 to 8.64) than when the proband was younger than age 60 years but mutation-negative (SIR = 1.76, 95% CI = 1.21 to 2.47, between-group $P < .001$). Breast (SIR = 1.29, 95% CI = 1.01 to 1.63) and ovarian (SIR = 2.38, 95% CI = 1.30 to 4.00) cancers were elevated among FDRs of mutation-positive probands.

Conclusions: Our study substantiates twofold risk of PC among FDRs of PC patients and suggests increased risk for primary liver cancer among female FDRs. FDRs of susceptibility mutation carriers had substantially increased risk for PC and increased risk for breast and ovarian cancers.

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Pancreatic cancer (PC) is a rapidly fatal malignancy with established risk factors that include tobacco smoking, long-standing diabetes, chronic pancreatitis, obesity, and positive family history of PC (1–3). In general, family history of cancer is important for accurate cancer risk stratification toward primary prevention, early detection, and timely intervention. Studies have shown that certain cancers tend to cluster in families due in part to inherited susceptibility and shared environmental exposures (4,5). Some genetic syndromes have a pleiotropic effect and are characterized by the presence of different cancer types among mutation carriers in the family, presumably because the underlying susceptibility variants target multiple tissues (4–6). For example, inherited mutations in *CDKN2A* (*p16*) can predispose to malignant melanoma or PC, and mutations in *BRCA1*, *BRCA2*, or *PALB2* predispose to breast cancer, ovarian cancer, or PC, whereas mutations in *TP53* can predispose to leukemia, breast cancer, brain cancer, or soft tissue sarcoma (4,6–8). Reliable estimates for the risk of different cancers in families of PC patients who have been tested for susceptibility genes are not available.

Individuals with PC often have multiple first-degree relatives (FDRs) affected with cancers other than PC (7,9–11), but most studies have focused primarily on the PC risk (reviewed in [12]). In 2005, we examined the occurrence of 14 common malignancies among 3335 FDRs of 426 incident PC cases diagnosed at Mayo Clinic and compared the observed number of cases of each cancer type with those expected based on data from the Surveillance, Epidemiology, and End Results (SEER) Program (11). The study, which included more than 130 000 person-years at risk, found higher than expected risks of PC and liver cancer and lower than expected risks of bladder, lung, lymphoma, prostate, and breast cancers among the FDRs, compared with the SEER reference population. In 2009, Wang et al. examined risk of death from extrapancreatic malignancies among 8564 FDRs of 1328 PC probands (13). Comparing deaths from 17 cancers among FDRs with more than 200 000 person-years of follow-up with the expected number of deaths for each cancer based on SEER data, they reported an increased risk of death from breast, liver, ovarian, and bile duct cancers among the FDRs (13). When stratified by familial vs sporadic kindreds, deaths from breast, liver, ovarian, and bile duct cancers remained increased in the familial kindreds, but only bile duct cancer deaths were elevated in the sporadic kindreds (13).

Broader insight into the pattern and scope of aggregation of cancers among relatives of PC probands can be gained with large sample sizes and evaluation of the role of inherited mutations. In the present study, we extend our previous work (11) using a larger sample size, including the data from our previous work, and additionally examined the influence of germline mutation status of PC probands on FDRs' cancer risk. Specifically, we examined the risk of 15 common malignancies among these FDRs, investigating whether risk differed by FDRs' kinship status, the FDRs' smoking history, or the probands' age at diagnosis. In a subset of probands who were tested for germline mutations in 22 cancer predisposition genes, we compared cancer risk among FDRs of mutation-positive probands with FDRs of mutation-negative probands.

Methods

Study Population

The prospective Mayo Clinic Biospecimen Resource for Pancreas Research is a registry of PC probands that utilizes an ultrarapid case ascertainment process for patient recruitment, with a participation rate of approximately 70% (14,15). The main reasons for nonparticipation in the registry are the severely debilitating nature of PC and its rapidly fatal course (14). Included in the present study were data reported on 17 162 FDRs (parents, siblings, and children) of 2305 unselected, consecutively enrolled PC probands in the registry between October 2000 and June 2016. For validation analyses described below, we used self-reported personal history of cancer provided by FDRs, who themselves enrolled in a separate familial PC study (16). Informed consent was obtained from each proband and each FDR in the familial PC study. The study was approved by the Mayo Clinic Institutional Review Board.

Data Collection

The PC probands completed structured risk factor questionnaires at enrollment that sought information on each FDR, including cancer diagnosis, age at diagnosis, dates of diagnosis, birth, and death (if applicable), and smoking history. We compared reported cases of 15 common malignancies among the FDRs with the expected number of cases for each cancer using data from the SEER 9 registries (1973–2013) (17), aligning with our previous study (11). The cancers of interest were primary bladder, brain, breast, colorectal, gastric, head and neck, leukemia, liver, lung, lymphoma, melanoma, multiple myeloma, ovary, pancreas, and prostate carcinomas. Analyses of brain, liver, and lung cancers were restricted to instances where each was the only cancer reported in an FDR (hereafter referred as primary liver, brain, or lung cancer). Because these 15 malignancies rarely occur in persons younger than age 20 years, we restricted the analyses to FDRs who were age 20 years or older. Detailed pedigrees were constructed based on family history information provided by the probands.

Germline mutations in 22 cancer predisposition genes were assessed by sequencing leukocyte DNA obtained from the PC probands. Genetic testing was performed among probands who provided blood samples (2094 of 2305 probands). Among the genes tested, 144 unique mutations determined to be deleterious (excluding variants of uncertain significance) were detected in 19 of the cancer predisposition genes: *APC*, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDKN2A*, *CHEK2*, *FANCC*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PRSS1*, *RAD51C*, *RAD51D*, and *TP53*. None of the probands carried a mutation in *CDH1*, *PTEN*, or *EPCAM* (18). The FDRs were classified as belonging to mutation-positive or mutation-negative pedigrees based on whether the related proband tested positive for a mutation in any of the tested genes (n = 1465; 198 pedigrees) or tested negative for all 22 genes (n = 14 168; 1896 pedigrees). Risk analyses were performed also among full siblings of probands who were mutation-positive (n = 636; 182 pedigrees) vs mutation-negative (n = 5663; 1728 pedigrees).

Statistical Analyses

Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were used to estimate the risk of the 15 malignancies among the FDRs. The SIRs were calculated for each cancer as the ratio of the observed to the expected number of cases. The expected number of cases was calculated from SEER data (17) based on five-year age group–specific and sex-specific incidence of each cancer multiplied by person-years at risk (17). SIRs were calculated for the overall sample as well as for males and

females separately. Three subanalyses were performed based on 1) FDRs' kinship status to the proband (mother, father, sibling, and parents plus siblings), 2) FDRs' personal smoking history (never vs ever), and 3) age of the proband at diagnosis of PC (<60 vs ≥60 years). Additionally, SIRs were calculated among FDRs of mutation-positive vs FDRs of mutation-negative probands and stratified by age of the proband at diagnosis (<60 years vs ≥60 years) in each group, and among full siblings of mutation-positive vs mutation-negative probands. Stratified analyses by sex were performed for each of these analyses.

Because of incomplete data on some of the FDRs, date of birth was imputed for 4135 FDRs (24.1%) and date of death was imputed for 1748 (10.2%), as was done previously (Supplementary Methods, available online) (11). While PC diagnoses among all probands were pathologically (>95%) or clinically confirmed, this level of verification among the FDRs was not feasible in the present study. Therefore, we relied on probands' report of cancer diagnosis in an FDR, which has been shown to have an accuracy rate ranging between 60% and 80% (19,20). In validation analyses, we assessed the accuracy of probands' report of cancer diagnosis in an FDR by comparing the proband report with the specified FDR's report of personal history of cancer. We used a subset of data extracted from the familial PC study (16), wherein 480 FDRs (both affected and unaffected) completed the same questionnaires administered to the probands; their responses were used to validate the probands' report. All statistical tests were two-sided and performed with SAS v9.4 (SAS Institute, Cary, NC). *P* values for statistical difference between SIRs were calculated assuming binomial distribution, as described in detail (21). See the Supplementary Methods (available online) for more details. *P* values less than .05 or confidence intervals that do not include 1.00 were considered statistically significant (22,23).

Results

The analyses included 17 162 FDRs, with more than 336 000 person-years at risk, identified through 2305 incident PC probands (Supplementary Methods, available online). The FDRs consisted of 4610 parents, 6920 siblings, and 5632 offspring. There were roughly equal proportions of male (50.6%) and female (49.3%) FDRs, and 43.2% of the FDRs had ever smoked. Overall, there were 3376 reported cases of cancer among the FDRs. Carcinomas of the breast (n = 463), colon and rectum (n = 338), prostate (n = 338), lung (n = 302), and pancreas (n = 233) were the most frequently reported malignancies.

The age- and sex-adjusted SIRs showed a twofold excess risk of PC among the FDRs (SIR = 2.04, 95% CI = 1.78 to 2.31, $P < .001$) as compared with the SEER reference population (Table 1). Incidence ratios for bladder, breast, colorectal, gastric, head and neck, leukemia, lung, lymphoma, melanoma, multiple myeloma, and prostate carcinomas were lower than expected among the FDRs compared with the SEER population. PC risk was elevated among both male and female FDRs. Among male FDRs only, gastric, head and neck, leukemia, melanoma, and prostate carcinomas were lower than expected; among female FDRs, breast cancer was lower (SIR = 0.77, 95% CI = 0.70 to 0.84, $P < .001$), but primary liver cancer was higher (SIR = 2.10, 95% CI = 1.34 to 3.12, $P < .001$) than expected. In subgroup analyses, we observed an excess risk of PC among the FDRs regardless of their relation to the proband, their smoking status, or the proband's age at diagnosis (Supplementary Table 1, available online). The results from the subgroup analyses are similar to those reported in Table 1, with a few notable findings. The magnitude of PC risk for FDRs of young-onset PC probands (before age 60 years) was somewhat higher (SIR = 2.39, 95% CI = 1.82 to 3.09) than that of FDRs of older-onset probands (SIR = 1.94, 95% CI = 1.66 to 2.25) (Supplementary Table 1, available online). FDRs who had ever smoked had higher PC risk (SIR = 2.40, 95% CI = 1.98 to 2.89) than nonsmoking FDRs (SIR = 1.64, 95% CI = 1.32 to 2.00). Primary liver cancer was higher among mothers of the probands (SIR = 3.38, 95% CI = 1.89 to 5.58) and among FDRs who had ever smoked (SIR = 1.74, 95% CI = 1.18 to 2.47).

A subset of probands was tested for inherited mutations in 22 cancer predisposition genes; 9.4% (198/2094) carried a mutation in at least one of 19 genes (Supplementary Table 2, available online). Among FDRs of mutation-positive probands, we observed 4.32 (95% CI = 3.10 to 5.86) times as many cases of PC as expected in the SEER reference population; the magnitude of PC risk was lower among FDRs of mutation-negative probands (SIR = 1.77, 95% CI = 1.51 to 2.05, between-group difference, $P < .001$) (Table 2). Risks of breast (SIR = 1.29, 95% CI = 1.01 to 1.63) and ovarian (SIR = 2.38, 95% CI = 1.30 to 4.00) cancers were higher among FDRs of mutation-positive probands; while among FDRs of mutation negative probands, breast cancer risk was lower than expected (SIR = 0.64, 95% CI = 0.58 to 0.71), and there was no association for ovarian cancer. These results are very similar to those observed among full siblings of the probands (Table 3), such that PC risk was 4.09 (95% CI = 2.42 to 6.46) times higher than expected among siblings of mutation-positive probands, while it was 1.52 (95% CI = 1.16 to 1.94) higher than expected among siblings of mutation-negative probands (between-group difference, $P = .001$). Further, breast (SIR = 1.63, 95% CI = 1.17 to 2.22) and ovarian (SIR = 2.52, 95% CI = 1.01 to 5.20) cancers were elevated among siblings of mutation-positive probands. Among siblings of mutation-negative probands, breast cancer risk was lower than expected (SIR = 0.65, 95% CI = 0.55 to 0.76), and no association was found for ovarian cancer. Similar results were obtained from the sex-stratified analyses (Supplementary Tables 3 and 4, available online). Moreover, FDRs of young-onset, mutation-positive probands had much higher PC risk (SIR = 5.24, 95% CI = 2.93 to 8.64) than FDRs of young-onset probands who were mutation-negative (SIR = 1.76, 95% CI = 1.21 to 2.47, between-group difference, $P < .001$) (Table 4). Similarly, FDRs of mutation-positive, older-onset probands had higher PC risk (SIR = 3.93, 95% CI = 2.56 to 5.75) than FDRs of mutation-negative, older-onset probands (SIR = 1.77, 95% CI = 1.48 to 2.09, between-group difference, $P = .001$) (Table 5; Supplementary Table 6, available online).

To assess the accuracy of reporting by the probands, we compared probands' report of a history of cancer in an FDR with the FDR's self-report among those with available data (n = 480). For PC, 98.5% (473/480) of reports were concordant. For the other cancers, 94% (434/462) of reports were concordant (Supplementary Methods, available online).

Discussion

We examined the risk of 15 common malignancies among FDRs of PC probands by comparing numbers of each cancer type observed among the FDRs with those expected using data from SEER. We observed a twofold higher than expected risk of PC among FDRs of the PC probands. Risk estimates for PC were consistently increased among parents and siblings of the probands, and suggest a potential aggregation of PC with primary liver cancer among female FDRs. Further analyses showed that the

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Table 1. Standardized incidence ratios* for cancer risk among first-degree relatives of pancreatic cancer probands, stratified by sex of the relatives; the Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2016

	Overall (n = 17 162)				Male (n = 8692)				Female (n = 8470)			
Cancer type	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)
Bladder	82	200.7	685 085	0.41 (0.32 to 0.51)†	58	176.4	339 152	0.33 (0.25 to 0.43)†	24	45.0	345 932	0.53 (0.34 to 0.79)†
Brain‡	57	52.3	687 624	1.09 (0.83 to 1.41)	32	31.7	340 889	1.01 (0.69 to 1.42)	25	21.5	346 735	1.16 (0.75 to 1.72)
Breast	463	655.4	680 553	0.71 (0.64 to 0.77)†	1	5.4	339 754	0.18 (0.00 to 1.02)	462	599.1	340 798	0.77 (0.70 to 0.84)†
Breast, Female	462	599.1	340 798	0.77 (0.70 to 0.84)†	n/a	n/a	n/a	n/a	462	599.1	340 798	0.77 (0.70 to 0.84)†
Colorectal	338	516.3	682 944	0.65 (0.59 to 0.73)†	178	299.9	338 134	0.59 (0.51 to 0.69)†	160	227.2	344 810	0.70 (0.60 to 0.82)†
Gastric	66	86.4	685 681	0.76 (0.59 to 0.97)†	37	61.5	339 554	0.60 (0.42 to 0.83)†	29	29.4	346 127	0.99 (0.66 to 1.42)
Head and neck	102	160.7	686 862	0.63 (0.52 to 0.77)†	71	125.6	340 451	0.57 (0.44 to 0.71)†	31	43.3	346 411	0.72 (0.49 to 1.02)
Leukemia	86	118.2	686 932	0.73 (0.58 to 0.90)†	53	77.9	340 344	0.68 (0.51 to 0.89)†	33	45.1	346 588	0.73 (0.50 to 1.03)
Liver‡	50	44.0	687 767	1.14 (0.84 to 1.50)	26	35.1	340 967	0.74 (0.48 to 1.08)	24	11.4	346 800	2.10 (1.34 to 3.12)†
Lung‡	302	600.1	686 657	0.50 (0.45 to 0.56)†	189	406.7	340 329	0.46 (0.40 to 0.54)†	113	221.0	346 328	0.51 (0.42 to 0.61)†
Lymphoma	103	194.5	684 761	0.53 (0.43 to 0.64)†	57	117.3	338 983	0.49 (0.37 to 0.63)†	46	81.3	345 778	0.57 (0.41 to 0.76)†
Melanoma	115	160.2	684 679	0.72 (0.59 to 0.86)†	62	99.0	339 121	0.63 (0.48 to 0.80)†	53	67.4	345 558	0.79 (0.59 to 1.03)
Myeloma	21	56.2	685 946	0.37 (0.23 to 0.57)†	13	34.7	339 706	0.38 (0.20 to 0.64)†	8	23.2	346 240	0.34 (0.15 to 0.68)†
Ovary	83	69.1	345 411	1.20 (0.96 to 1.49)	n/a	n/a	n/a	n/a	83	69.1	345 411	1.20 (0.96 to 1.49)
Pancreas	233	114.5	685 426	2.04 (1.78 to 2.31)†	118	65.9	339 502	1.79 (1.48 to 2.15)†	115	50.5	345 924	2.28 (1.88 to 2.73)†
Prostate	338	697.7	336 398	0.48 (0.43 to 0.54)†	338	697.7	336 398	0.48 (0.43 to 0.54)†	n/a	n/a	n/a	n/a

*Compared the observed with the expected number of cases based on data from the Surveillance, Epidemiology, and End Results program (nine registries, 1973–2013). CI = confidence interval; SIR = standardized incidence ratio.
†Statistically significant association.
‡Where each was the only primary site reported, thereby excluding metastatic cases.

Table 2. Standardized incidence ratios* for cancer risk among first-degree relatives of pancreatic cancer probands, stratified by mutation status of the probands; the Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2016

	FDRs of mutation-positive probands†,‡ (n = 1465; from 198 pedigrees)				FDRs of mutation-negative probands†,‡ (n = 14 168; from 1896 pedigrees)			
Cancer type	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)
Bladder	12	16.6	56 741	0.72 (0.37 to 1.26)	65	165.9	566 204	0.39 (0.30 to 0.50)§
Brain‖	4	4.3	57 092	0.92 (0.25 to 2.36)	50	43.2	568 247	1.16 (0.86 to 1.53)
Breast	70	54.2	56 268	1.29 (1.01 to 1.63)§	348	541.8	562 646	0.64 (0.58 to 0.71)§
Breast, Female	70	50.6	28 795	1.38 (1.08 to 1.75)§	347	494.9	281 504	0.70 (0.63 to 0.78)§
Colorectal	38	42.7	56 431	0.89 (0.63 to 1.22)	268	426.8	564 592	0.63 (0.55 to 0.71)§
Gastric	5	7.2	56 875	0.70 (0.22 to 1.63)	55	71.4	566 629	0.77 (0.58 to 1.00)
Head and neck	9	13.3	56 992	0.67 (0.31 to 1.28)	87	132.8	567 589	0.66 (0.52 to 0.81)§
Leukemia	9	9.8	57 001	0.92 (0.42 to 1.74)	73	97.6	567 697	0.75 (0.59 to 0.94)§
Liver‖	6	3.7	57 054	1.64 (0.60 to 3.58)	42	36.4	568 390	1.15 (0.83 to 1.56)
Lung‖	19	49.8	56 949	0.38 (0.23 to 0.60)§	247	496.0	567 532	0.50 (0.44 to 0.56)§
Lymphoma	9	16.1	56 796	0.56 (0.25 to 1.06)	87	160.7	565 853	0.54 (0.43 to 0.67)§
Melanoma	11	13.3	56 718	0.83 (0.41 to 1.48)	93	132.4	565 881	0.70 (0.57 to 0.86)§
Myeloma	2	4.7	56 908	0.43 (0.05 to 1.55)	17	46.5	566 851	0.37 (0.21 to 0.59)§
Ovary	14	5.9	29 389	2.38 (1.30 to 4.00)§	62	57.0	285 083	1.09 (0.83 to 1.39)
Pancreas	41	9.5	56 807	4.32 (3.10 to 5.86)§	167	94.6	566 497	1.77 (1.51 to 2.05)§
Prostate	33	56.4	27 205	0.58 (0.40 to 0.82)§	278	577.2	278 322	0.48 (0.43 to 0.54)§

*Compared the observed with the expected number of cases based on data from the Surveillance, Epidemiology, and End Results program (nine registries, 1973–2013). CI = confidence interval; FDR = first-degree relative; SIR = standardized incidence ratio.

†Does not sum to 2305 pedigrees because not all families had an individual included in the mutation testing study.

‡Probands who tested positive or negative for inherited mutation in *APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDKN2A, CHEK2, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PRSS1, RAD51C, RAD51D*, and *TP53*.

§Statistically significant association.

‖Where each was the only primary site reported, thereby excluding metastatic cases.

increased PC risk was higher among FDRs who had ever smoked than among nonsmoking FDRs, and the magnitude of the SIR for PC was higher among FDRs of young-onset probands than among FDRs of older-onset probands. We also observed lower than expected risk of bladder, breast, colorectal, gastric, head and neck, leukemia, lung, lymphoma, melanoma, multiple myeloma, and prostate carcinomas among the FDRs compared with the SEER reference population.

Familial aggregation of certain cancers may be due to shared genetic susceptibility and/or shared etiologic risk factors, or chance alone (24). For PC, inherited genetic factors account for 5% to 10% of cases, while tobacco smoking accounts for 20% to 25% of cases (2,25). A nested case–control study found that shared tobacco smoking behavior is an independent risk for familial aggregation of PC (26). Our results are consistent with independent reports (9,12,26–30) and with our previous smaller study (11), in which we observed a nearly twofold increase in PC risk among FDRs of PC probands (SIR = 1.88, 95% CI = 1.51 to 4.46) (11). Ghadirian et al. reported a fivefold increased risk among FDRs of PC probands compared with FDRs of noncancer controls and a twofold higher PC risk among FDRs of young-onset probands (10). Klein and colleagues reported a ninefold excess risk of PC among FDRs of PC probands compared with SEER; and consistent with our findings, they found higher PC risk among FDRs who had ever smoked (SIR = 19.2, 95% CI = 7.7 to 39.5) than among nonsmoking FDRs (SIR = 6.25, 95% CI = 1.70 to 16.0) (31).

Compared with the FDRs of 1896 PC probands who did not carry a mutation in any of the cancer genes tested, PC risk was statistically significantly higher among FDRs of probands who tested positive for a mutation; this would be expected based on Mendelian law probability that 50% of the full siblings likely carry the mutation(s) detected in their related mutation-positive proband. Ovarian and breast cancers were elevated among FDRs, particularly siblings, of PC probands who were mutation-positive. Moreover, SIRs for PC were much higher among FDRs of young-onset probands who carry a susceptibility gene mutation than among FDRs of young-onset probands who were mutation-negative, or FDRs of older-onset probands regardless of proband's mutation status.

Because the liver, brain, and lung are common metastatic sites, we restricted reported cancer cases for each of these sites to instances where they were reported as the only primary site (ie, liver only, lung only, or brain only). Thus, the increased risk of liver cancer observed among female FDRs, which concurs with our earlier findings (11), is potentially less prone to confounding by metastatic cases. Wang et al. (13) reported excess risk of death from liver cancer among FDRs of PC probands (standardized mortality ratio [SMR] = 1.91, 95% CI = 1.07 to 3.14), with a stronger trend toward increased risk among female FDRs (SMR = 2.38, 95% CI = 0.94 to 4.98) than among male FDRs (SMR = 1.65, 95% CI = 0.74 to 53.18) (13). Ghadirian et al. (10) also observed a statistically nonsignificant increased risk of liver cancer among FDRs of PC probands (relative risk = 1.89). While the sample sizes were small in these reports, these findings together suggest aggregation of PC with liver cancer that may be due to suggest the existence of a yet-to-be-identified pleiotropic genetic variant associated with both conditions, shared environmental risk factors among family members, or a combination of these factors. Further research involving pathologically confirmed primary liver cancers is needed before firm conclusions can be drawn about the familial aggregation of PC with liver cancer.

Table 3. Standardized incidence ratios* for cancer risk among siblings of pancreatic cancer probands, stratified by mutation status of the proband; the Mayo Clinic Biospecimen Resource for Pancreas Research Registry, 2000–2016

	All siblings (n = 6920)				Siblings of mutation-positive probands†,‡ (n = 636; from 182 pedigrees)				Siblings of mutation-negative probands†,‡ (n = 5663; from 1728 pedigrees)			
Cancer type	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)
Bladder	35	88.7	302 654	0.39 (0.27 to 0.55)§	5	7.7	26 302	0.65 (0.21 to 1.51)	28	72.9	248 785	0.38 (0.26 to 0.56)§
Brain‖	24	23.1	303 711	1.04 (0.67 to 1.55)§	2	2.0	26 486	0.99 (0.11 to 3.59)	19	19.0	249 598	1.00 (0.60 to 1.56)
Breast	213	289.7	300 853	0.74 (0.64 to 0.84)§	41	25.1	26 068	1.63 (1.17 to 2.22)§	154	238.3	247 450	0.65 (0.55 to 0.76)§
Breast, female	213	258.6	147 081	0.82 (0.72 to 0.94)§	41	23.8	13 535	1.72 (1.24 to 2.34)§	154	211.8	120 461	0.73 (0.62 to 0.85)§
Colorectal	118	228.3	302 015	0.52 (0.43 to 0.62)§	15	19.8	26 187	0.76 (0.42 to 1.25)	93	187.7	248 327	0.50 (0.40 to 0.61)§
Gastric	18	38.2	303 022	0.47 (0.28 to 0.75)§	2	3.3	26 400	0.60 (0.07 to 2.17)	14	31.4	249 025	0.45 (0.24 to 0.75)§
Head and neck	43	71.0	303 476	0.61 (0.44 to 0.82)§	5	6.2	26 458	0.81 (0.26 to 1.88)	35	58.4	249 363	0.60 (0.42 to 0.83)§
Leukemia	34	52.2	303 529	0.65 (0.45 to 0.91)§	2	4.5	26 438	0.44 (0.05 to 1.59)	30	42.9	249 476	0.70 (0.47 to 1.00)
Liver‖	17	19.4	303 814	0.87 (0.51 to 1.40)	4	1.7	26 448	2.36 (0.64 to 6.05)	12	16.0	249 698	0.75 (0.39 to 1.31)
Lung‖	135	265.2	303 377	0.51 (0.43 to 0.60)§	6	23.1	26 451	0.26 (0.09 to 0.56)§	112	217.9	249 320	0.51 (0.42 to 0.62)§
Lymphoma	43	85.9	302 602	0.50 (0.36 to 0.67)§	3	7.5	26 369	0.40 (0.08 to 1.17)	38	70.6	248 648	0.54 (0.38 to 0.74)§
Melanoma	59	70.7	302 337	0.83 (0.63 to 1.08)	7	6.1	26 271	1.14 (0.46 to 2.35)	44	58.2	248 577	0.76 (0.55 to 1.02)
Myeloma	7	24.9	303 124	0.28 (0.11 to 0.58)§	0	2.2	26 414	to	6	20.4	249 112	0.29 (0.11 to 0.64)§
Ovary	38	29.8	149 004	1.28 (0.90 to 1.75)	7	2.8	13 863	2.52 (1.01 to 5.20)§	29	24.4	121 823	1.19 (0.80 to 1.71)
Pancreas	89	50.6	302 897	1.76 (1.41 to 2.17)§	18	4.4	26 354	4.09 (2.42 to 6.46)	63	41.6	248 955	1.52 (1.16 to 1.94)§
Prostate	152	316.2	152 447	0.48 (0.41 to 0.56)§	12	25.8	12 449	0.46 (0.24 to 0.81)§	127	261.0	125 856	0.49 (0.41 to 0.58)§

*Compared the observed with the expected number of cases based on data from the Surveillance, Epidemiology, and End Results program (nine registries, 1973–2013). CI = confidence interval; FDR = first-degree relative; SIR = standardized incidence ratio.

†Does not sum to 2305 pedigrees because not all families had an individual included in the mutation testing study.

‡Probands who tested positive or negative for inherited mutation in *APC*, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDKN2A*, *CHEK2*, *FANCC*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PRSS1*, *RAD51C*, *RAD51D*, and *TP53*.

§Statistically significant association.

‖Where each was the only primary site reported, thereby excluding metastatic cases.

Table 4. Standardized incidence ratios* for cancer risk among first-degree relatives of pancreatic cancer probands who were younger than age 60 years at diagnosis, stratified by probands' mutation status; the Mayo Clinic Biospecimen Resource for Pancreas Research Registry, 2000–2016

	FDRs of probands age < 60 y at diagnosis							
	FDRs of mutation-positive probands†,‡ (n = 493; from 72 pedigrees)				FDRs of mutation-negative probands†,‡ (n = 3331; from 494 pedigrees)			
Cancer type	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)
Bladder	6	5.0	17 114	1.20 (0.44 to 2.60)	11	32.9	112 158	0.33 (0.17 to 0.60)§
Brain‖	2	1.3	17 281	1.52 (0.17 to 5.50)	8	8.6	112 617	0.93 (0.40 to 1.84)
Breast	22	16.4	17 026	1.34 (0.84 to 2.03)	82	107.4	111 509	0.76 (0.61 to 0.95)§
Breast, Female	22	15.3	8703	1.44 (0.90 to 2.18)	81	99.8	56 793	0.81 (0.64 to 1.01)
Colorectal	15	12.9	17 043	1.16 (0.65 to 1.92)	58	84.6	111 960	0.69 (0.52 to 0.89)§
Gastric	2	2.2	17 180	0.92 (0.10 to 3.34)	7	14.2	112 332	0.49 (0.20 to 1.02)
Head and neck	3	4.0	17 214	0.74 (0.15 to 2.18)	6	26.3	112 444	0.23 (0.08 to 0.50)§
Leukemia	4	3.0	17 258	1.35 (0.36 to 3.45)	19	19.4	112 583	0.98 (0.59 to 1.53)
Liver‖	2	1.1	17 278	1.81 (0.20 to 6.53)	7	7.2	112 669	0.97 (0.39 to 2.00)
Lung‖	6	15.1	17 227	0.40 (0.15 to 0.87)§	49	98.3	112 519	0.50 (0.37 to 0.66)§
Lymphoma	2	4.9	17 176	0.41 (0.05 to 1.48)	21	31.8	112 065	0.66 (0.41 to 1.01)
Melanoma	5	4.0	17 120	1.25 (0.40 to 2.91)	27	26.2	112 136	1.03 (0.68 to 1.50)
Myeloma	1	1.4	17 191	0.71 (0.01 to 3.95)	4	9.2	112 337	0.43 (0.12 to 1.11)
Ovary	5	1.8	8866	2.82 (0.91 to 6.58)	11	11.5	57 447	0.97 (0.58 to 1.58)
Pancreas	15	2.9	17 142	5.24 (2.93 to 8.64)§	33	18.7	112 249	1.76 (1.21 to 2.47)§
Prostate	15	17.0	8204	0.88 (0.49 to 1.45)	66	112.3	54 156	0.59 (0.45 to 0.75)§

*Compared the observed with the expected number of cases based on data from the Surveillance, Epidemiology, and End Results program (nine registries, 1973–2013). CI = confidence interval; FDR = first-degree relative; SIR = standardized incidence ratio.
†Does not sum to 2305 pedigrees because not all families had an individual included in the mutation testing study.
‡Probands who tested positive or negative for inherited mutation in *APC*, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDKN2A*, *CHEK2*, *FANCC*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PRSS1*, *RAD51C*, *RAD51D*, and *TP53*.
§Statistically significant association.
‖Where each was the only primary site reported, thereby excluding metastatic cases.

Table 5. Standardized incidence ratios* for cancer risk among first-degree relatives of pancreatic cancer probands who were age 60 years or older at diagnosis, stratified by probands' mutation status; the Mayo Clinic Biospecimen Resource for Pancreas Research Registry, 2000–2016

	FDRs of probands who were age ≥ 60 y at diagnosis							
	FDRs of mutation-positive probands†,‡ (n = 972; from 126 pedigrees)				FDRs of mutation-positive probands†,‡ (n = 10 837; from 1402 pedigrees)			
Cancer type	No. observed	No. expected	Person-years at risk	SIR (95% CI)	No. observed	No. expected	Person-years at risk	SIR (95% CI)
Bladder	6	11.6	39 627	0.52 (0.19 to 1.12)	54	133.0	454 046	0.41 (0.30 to 0.53)§
Brain‖	2	3.0	39 811	0.66 (0.07 to 2.39)	42	34.6	455 630	1.21 (0.87 to 1.64)
Breast	48	37.8	39 241	1.27 (0.94 to 1.68)	266	434.4	451 137	0.61 (0.54 to 0.69)§
Breast, Female	48	35.3	20 092	1.36 (1.01 to 1.80)§	266	395.0	224 710	0.67 (0.59 to 0.76)§
Colorectal	23	29.8	39 387	0.77 (0.49 to 1.16)	210	342.2	452 632	0.61 (0.53 to 0.70)§
Gastric	3	5.0	39 695	0.60 (0.12 to 1.75)	48	57.2	454 297	0.84 (0.62 to 1.11)
Head and neck	6	9.3	39 779	0.64 (0.24 to 1.40)	81	106.5	455 144	0.76 (0.60 to 0.95)§
Leukemia	5	6.8	39 744	0.73 (0.24 to 1.71)	54	78.3	455 114	0.69 (0.52 to 0.90)§
Liver‖	4	2.5	39 776	1.57 (0.42 to 4.02)	35	29.2	455 721	1.20 (0.84 to 1.67)
Lung‖	13	34.7	39 722	0.37 (0.20 to 0.64)§	198	397.7	455 013	0.50 (0.43 to 0.57)§
Lymphoma	7	11.3	39 619	0.62 (0.25 to 1.28)	66	128.9	453 787	0.51 (0.40 to 0.65)§
Melanoma	6	9.3	39 598	0.65 (0.24 to 1.41)	66	106.2	453 745	0.62 (0.48 to 0.79)§
Myeloma	1	3.3	39 717	0.31 (0.00 to 1.71)	13	37.3	454 514	0.35 (0.19 to 0.60)§
Ovary	9	4.1	20 523	2.19 (1.03 to 4.16)§	43	45.5	227 635	0.94 (0.68 to 1.27)
Pancreas	26	6.6	39 665	3.93 (2.56 to 5.75)§	134	75.9	454 247	1.77 (1.48 to 2.09)§
Prostate	18	39.4	19 001	0.46 (0.27 to 0.72)§	212	464.9	224 167	0.46 (0.40 to 0.52)§

*Compared the observed with the expected number of cases based on data from the Surveillance, Epidemiology, and End Results program (nine registries, 1973–2013). CI = confidence interval; FDR = first-degree relative; SIR = standardized incidence ratio.
†Does not sum to 2305 pedigrees because not all families had an individual included in the mutation testing study.
‡Probands who tested positive or negative for inherited mutation in APC, *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDKN2A*, *CHEK2*, *FANCC*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PRSS1*, *RAD51C*, *RAD51D*, and *TP53*.
§Statistically significant association.
‖Where each was the only primary site reported, thereby excluding metastatic cases.

Strengths of the study include the use of an extensive risk factor questionnaire that allowed for uniform collection of data on multiple malignancies, the very large sample size, and the availability of cancer susceptibility mutation status on probands. A major limitation of this study is the reliance on probands' reports of cancer diagnosis in an FDR as pathologic or clinical verification of cancer in the FDRs was not feasible in this study. In our subanalysis of FDRs from whom we had collected self-reported data, we found 98% agreement in the reporting of family history of PC between the probands and the FDRs and 94% agreement for reporting of other malignancies. This suggests that the potential impact of misclassification of cancer in the FDRs is likely minimal. However, there is the possibility that the PC probands may have had a greater awareness of a family history of PC than family history of other cancers, which may explain the observed lower than expected risk of some cancers among the FDRs as compared with the SEER population. Thus, underreporting of cancers other than PC has potential impact on the lower than expected risk observed for some cancers. Our study is limited also in its generalizability by race; 97% of the probands were White. We imputed missing data on dates of birth and death for some FDRs to ensure that the analysis reflects the population of FDRs in our registry to the fullest extent possible. Imputations were done a priori while blinded to the cancer status of the FDRs; thus, potential misclassification would be nondifferential by cancer status and would tend to attenuate effect estimates toward the null (19,32).

Our study substantiates a twofold risk of PC among FDRs of PC patients. It further suggests aggregation of PC with liver cancer among female FDRs. We found fourfold increased risk of PC and elevated risk of breast and ovarian cancer in FDRs of susceptibility gene mutation carriers, suggesting a potential role of inherited mutations in familial cancer risk. Younger age at the proband's PC diagnosis was also associated with increased PC risk in the FDRs. Our findings enable more refined cancer risk estimation for genetic counseling and inform cancer screening recommendations for FDRs of PC probands.

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