Supplementary Methods

Imputation of dates of birth and death

Because of incomplete data on some of the first-degree relatives (FDRs), date of birth was imputed for 4,135 (24%) of the FDRs and date of death was imputed for 1,748 (10%) of the FDRs in order to calculate SIRs. Dates of birth were imputed based on the proband's date of birth, using estimated age for appropriate FDR as was done previously (12). For example, we added 20 years to a proband's age to impute age for a parent with missing age; or subtracted 20 years from a proband's age to impute age for an offspring; and used birth order as provided by the proband to impute age for a sibling with missing age, with 2-year age intervals between siblings according to birth order. Dates of death were imputed for FDRs who died with a diagnosis of cancer by adding two years to the date of diagnosis. For deceased FDRs who did not have a diagnosis of cancer, we used data on life expectancy (76 years for males and 78 for females) to impute age at death. Among FDRs with cancer diagnosis whose age at diagnosis was not known (919 of 2,338), two methods were used to impute mean age at diagnosis for each cancer. We used data from the enterprise-wide Mayo Clinic Tumor Registry on cases enrolled between January 1, 1993, and November 31, 2015, to impute sex- and cancer-specific mean age for 725 of the 919 participants. For the remaining 194 participants, we subtracted two years from their chronological age and used that value as their age at diagnosis because their chronological age was younger than the mean age of cancer diagnosis in the Tumor Registry.

Characteristics of the pancreatic cancer probands & FDRs

Data on 17,162 FDRs were derived from 2,305 unselected, sequentially enrolled pancreatic cancer (PC) probands. The majority of the probands were White (97.8%), few were African American (1%), and the remaining were multiracial (0.5%), Asian/Asian American (0.4%), American Indian/Alaskan Native (0.2%), Native Hawaiian/Pacific Islander (<0.1%) or other (<0.1%), and most of the probands were male (55.2%). Analyses were performed among FDRs of the PC probands (n=17,162), including stratified

analyses among mothers (n=2,305), fathers (n=2,305), and siblings (n=6,920) of the probands. No subanalysis was performed among offspring only due to low numbers of cancers reported among the offspring of the probands.

Assessment of accuracy of probands' report of family history of cancer

To assess the accuracy of reporting by the probands, we used available data among unselected subset of subjects to compare probands' report of a history of cancer diagnosis in a FDR with the respective FDR's self-report of personal history of cancer (i.e., the "gold standard"). Reports on non-melanoma skin cancer were excluded from the validation analysis. The study questionnaire included two separate questions: one specific to PC and another specific to other cancers. The questionnaire was completed by both affected and unaffected FDRs. The proband and FDR both needed to answer the question in order for the data to be included in the analysis. In all, 480 proband-FDR pairs reported on PC and 462 proband-FDR pairs reported on other cancers; therefore, the denominator for other cancer types decreased by 18 responses. For PC, we found 98.5% (473/480) concordant reports between the probands and the FDRs, with between-reports sensitivity of 0.75 and specificity of 0.99. Of the seven discordant reports, four FDRs reported a personal history of PC while the related proband did not—all of which were explained by the fact that the questionnaires were completed by the probands before cancer diagnosis in the respective FDR (i.e., at the time of the questionnaire completion, the FDR did not have a diagnosis of cancer). For the remaining three discordant reports for PC, the probands reported a history of PC in a FDR while the related FDRs did not report a personal history of PC. If we eliminate the four discordant reports that were due to differences in the time between questionnaire completion and cancer diagnosis, the concordance rate for PC would increase to 99% (473/476), with sensitivity of 1 and specificity of 0.99. For other cancer types, we found 94% (434/462) concordant report between the probands and the FDRs, with sensitivity of 0.81 and specificity of 0.98. Among the 28 discordant reports for other cancer types, there were seven instances where reports by the probands and the FDRs did not

match the cancer type. In fourteen instances, the FDRs reported personal history of a specific cancer, but the probands did not report any cancer history; six of these were explained by the fact that the proband completed the questionnaire before the FDR was diagnosed with cancer. For the remaining seven discordant reports, the probands reported a family history of specific cancers, while the FDR did not. Here also, if we exclude the six reports that were due to differences in the time between questionnaire completion and cancer diagnosis from the denominator, concordant reports for other cancers increases to 95% (434/456), with between-reports sensitivity of 88 and specificity of 0.98.

Statistical analyses

Confidence intervals for standardized incidence ratios (SIRs) were calculated as described in detail by Breslow and Day [21] and Rothman and Boice [22], and were considered statistically significant if they did not include the value 1. Between-group comparisons were considered statistically significantly different if the confidence intervals for one group did not overlap the other [31, 32]. Furthermore, we calculated p-values for statistical difference between SIRs assuming binomial distribution as has been previously described in detail by Altman *et al*. [20].

Supplementary Table 1. Standardized incidence ratios (SIRs)* for cancer risk among first-degree relatives of pancreatic cancer probands, stratified by relation to the proband, smoking status of the relatives, and probands' age at diagnosis; the Mayo Clinic Biospecimen Resource for Pancreas Research Registry, 2000-2016.

Cancer type	Mothers only (n =2,305)	Fathers only (n =2,305)	Parents and siblings (n=11,530)	FDRs who ever smoked(n =6,651)	FDRs who never smoked(n =8,901)	Proband age < 60 years (n =4,285)	Proband age ≥ 60 years (n =12,877)
Bladder	0.63 (0.32–1.13)	0.56 (0.39–0.78)‡	0.50 (0.40–0.62)‡	0.59 (0.44–0.79)‡	0.31 (0.21–0.44)‡	0.40 (0.23–0.64)‡	0.41 (0.32–0.52)‡
Brain †	1.44 (0.74–2.52)	1.22 (0.66–2.04)	1.17 (0.87–1.54)	1.09 (0.69–1.63)	1.12 (0.75–1.61)	0.90 (0.43–1.66)	1.14 (0.84–1.52)
Breast	0.91 (0.79–1.04)	0.51 (0.01–2.82)	0.79 (0.72–0.87)‡	0.62 (0.52–0.72)‡	0.84 (0.75–0.95)‡	0.86 (0.71–1.03)	0.67 (0.60–0.74)‡
Breast, F	0.91 (0.79–1.04)	n/a	0.86 (0.78–0.95)‡	0.92 (0.78–1.07)	0.74 (0.66–0.83)‡	0.92 (0.76–1.10)	0.73 (0.66–0.81)‡
Colorectal	1.12 (0.91–1.36)	1.04 (0.86–1.25)	0.78 (0.70–0.87)‡	0.75 (0.64–0.88)‡	0.64 (0.54–0.74)‡	0.72 (0.57–0.90)‡	0.64 (0.56–0.72)‡
Gastric	1.93 (1.21–2.93)‡	1.17 (0.76–1.71)	0.94 (0.72–1.19)	0.80 (0.53–1.16)	0.68 (0.45–0.97)‡	0.55 (0.26–1.00)	0.82 (0.62–1.07)
Head and neck	1.01 (0.59–1.62)	0.83 (0.59–1.15)	0.75 (0.61–0.91)‡	1.15 (0.91–1.45)	0.25 (0.15–0.39)‡	0.35 (0.18–0.62)‡	0.71 (0.57–0.87)‡
Leukemia	1.15 (0.70–1.77)	0.99 (0.66–1.43)	0.85 (0.68–1.05)	0.94 (0.69–1.26)	0.61 (0.43–0.85)‡	1.04 (0.68–1.52)	0.64 (0.49–0.83)‡
Liver †	3.38 (1.89–5.58)‡	1.26 (0.72–2.04)	1.33 (0.98–1.77)	1.74 (1.18–2.47)‡	0.78 (0.45–1.25)	0.96 (0.44–1.83)	1.18 (0.85–1.60)
Lung †	0.64 (0.48–0.84)‡	0.74 (0.61–0.89)‡	0.61 (0.54–0.68)‡	1.07 (0.94–1.21)	0.10 (0.07–0.15)‡	0.53 (0.42–0.68)‡	0.49 (0.43–0.56)‡
Lymphoma	0.70 (0.44–1.06)	0.68 (0.46–0.98)‡	0.59 (0.48–0.72)‡	0.56 (0.41–0.75)‡	0.55 (0.41–0.72)‡	0.61 (0.39–0.90)‡	0.51 (0.40–0.64)‡
Melanoma	0.65 (0.38–1.04)	0.50 (0.30–0.79)‡	0.72 (0.58–0.88)‡	0.66 (0.48–0.90)‡	0.86 (0.66–1.08)	1.06 (0.74–1.47)	0.63 (0.50–0.78)‡
Myeloma	0.56 (0.18–1.30)	0.40 (0.13–0.93)‡	0.37 (0.22–0.59)‡	0.44 (0.21–0.81)‡	0.32 (0.15–0.61)‡	0.50 (0.18–1.10)	0.34 (0.19–0.56)‡
Ovary	1.57 (1.13–2.13)‡	n/a	1.42 (1.12–1.76)‡	1.03 (0.64–1.58)	1.34 (1.01–1.73)‡	1.82 (1.20–2.65)‡	1.03 (0.78–1.34)
Pancreas	3.48 (2.70–4.41)‡	2.93 (2.29–3.71)‡	2.43 (2.12–2.77)‡	2.40 (1.98–2.89)‡	1.64 (1.32–2.00)‡	2.39 (1.82–3.09)‡	1.94 (1.66–2.25)‡
Prostate	n/a	0.72 (0.62–0.83)‡	0.59 (0.52–0.65)‡	0.54 (0.47–0.63)‡	0.46 (0.38–0.55)‡	0.61 (0.49–0.75)‡	0.45 (0.40–0.51)‡

***** Compared the observed with the expected number of cases based on data from the Surveillance Epidemiology and End Results (SEER) Program; 9 registries, 1973–2013.
†Where each was the only primary site reported, thereby excluding metastatic cases.
‡Statistically significant result

Supplementary Table 2. A total of 144 unique germline mutations were found in 19 of 22 cancer susceptibility genes among 198 of 2,305 tested pancreatic cancer probands; the Mayo Clinic Biospecimen Resource for Pancreas Research Registry, 2000-2016.

Gene	Mutation	Frequency	Percent	Cumulative Frequency*
APC	exon4-16 deletion	1	0.49	1
ATM	c.1333delC	1	0.49	2
ATM	c.1564_1565delGA	2	0.98	4
ATM	c.170G>A_p.Trp57X	1	0.49	5
ATM	c.1978delA	1	0.49	6
ATM	c.2023C>T_p.Gln675X	1	0.49	7
ATM	c.2250G>A_p.=	2	0.98	9
ATM	c.2502dupA	1	0.49	10
ATM	c.2880delC	1	0.49	11
ATM	c.3245_3247delinsTGAT	4	1.96	15
ATM	c.3802delG	3	1.47	18
ATM	c.3993+1G>A	1	0.49	19
ATM	c.3994-2A>G	1	0.49	20
ATM	c.467G>A_p.Trp156X	1	0.49	21
ATM	c.5623C>T_p.Arg1875X	2	0.98	23
ATM	c.5674G>T_p.Glu1892X	1	0.49	24
ATM	c.5712dupA	1	0.49	25
ATM	c.5932G>T_p.Glu1978X	1	0.49	26
ATM	c.6013delinsAA	1	0.49	27
ATM	c.6100C>T_p.Arg2034X	2	0.98	29
ATM	c.7000_7003delTACA	1	0.49	30
ATM	c.7327C>T_p.Arg2443X	1	0.49	31
ATM	c.741dupT	1	0.49	32
ATM	c.7463G>A_p.Cys2488Tyr	1	0.49	33
ATM	c.7570G>C_p.Ala2524Pro	1	0.49	34
ATM	c.7630-2A>C	5	2.45	39
ATM	c.7638_7646del9_p.Arg2547_Ser2549del	2	0.98	41
ATM	c.790delT	2	0.98	43
ATM	c.8264_8268del5	1	0.49	44
ATM	c.8264dupA	1	0.49	45
ATM	c.8321delT	1	0.49	46
ATM	c.8732C>T_p.Thr2911Ile	1	0.49	47
ATM	c.8737_8738delGA	1	0.49	48
ATM	c.9021dupA	1	0.49	49
ATM	c.9040C>T_p.Gln3014X	1	0.49	50
ATM	exon 2-15 deletion	1	0.49	51
ATM	exon 39-63 deletion	1	0.49	52
ATM	exon 57-63 deletion	1	0.49	53
BARD1	c.632T>A_p.Leu211X	1	0.49	54
BRCA1	c.1556delA	1	0.49	55
BRCA1	c.212+1G>A	1	0.49	56
BRCA1	c.2709_2710delTG	1	0.49	57
BRCA1	c.3481_3491del11	1	0.49	58
BRCA1	c.4065_4068delTCAA	1	0.49	59
BRCA1	c.4689C>G_p.Tyr1563X	1	0.49	60
BRCA1	c.5096G>A_p.Arg1699Gln	1	0.49	61
BRCA1	c.514delC	1	0.49	62
BRCA1	c.5266dupC	2	0.98	64
BRCA1	c.5503C>T_p.Arg1835X	1	0.49	65
BRCA2	c.1813dupA	2	0.98	67

Supplementary Table 2 (continued).

Gene	Mutation	Frequency	Percent	Cumulative Frequency*
BRCA2	c.26delC	1	0.49	68
BRCA2	c.2830A>T_p.Lys944X	1	0.49	69
BRCA2	c.3407_3408insAlu	1	0.49	70
BRCA2	c.3744_3747delTGAG	2	0.98	72
BRCA2	c.3847_3848delGT	1	0.49	73
BRCA2	c.4478_4481delAAAG	1	0.49	74
BRCA2	c.4965C>G_p.Tyr1655X	1	0.49	75
BRCA2	c.5213_5216delCTTA	1	0.49	76
BRCA2	c.5350_5351delAA	2	0.98	78
BRCA2	c.5621_5624delTTAA	1	0.49	79
BRCA2	c.5645C>A_p.Ser1882X	2	0.98	81
BRCA2	c.5722_5723delCT	1	0.49	82
BRCA2	c.5864C>A_p.Ser1955X	1	0.49	83
BRCA2	c.5946delT	2	0.98	85
BRCA2	c.6037A>T_p.Lys2013X	1	0.49	86
BRCA2	c.6275_6276delTT	2	0.98	88
BRCA2	c.6373dupA	1	0.49	89
BRCA2	c.6761_6762delTT	2	0.98	91
BRCA2	c.7025_7026delAA	1	0.49	92
BRCA2	c.7069_7070delCT	4	1.96	96
BRCA2	c.7435+2T>A	1	0.49	97
BRCA2	c.7558C>T_p.Arg2520X	1	0.49	98
BRCA2	c.7976+1G>A	1	0.49	99
BRCA2	c.8167G>C_p.Asp2723His	2	0.98	101
BRCA2	c.8243G>A_p.Gly2748Asp	1	0.49	102
BRCA2	c.8247_8248delGA	1	0.49	103
BRCA2	c.8594dupT	1	0.49	104
BRCA2	c.9004G>A_p.Glu3002Lys	1	0.49	105
BRCA2	c.9117G>A_p.=	1	0.49	106
BRCA2	c.9403delC	1	0.49	107
BRCA2	c.961C>T_p.Gln321X	1	0.49	108
BRCA2	c.9867delT	1	0.49	109
BRIP1	c.133G>T_p.Glu45X	1	0.49	110
BRIP1	c.2133delT	1	0.49	111
BRIP1	c.2392C>T_p.Arg798X	1	0.49	112
BRIP1	c.2400C>G_p.Tyr800X	1	0.49	113
CDKN2A	c.-34G>T	1	0.49	114
CDKN2A	c.240_253del14	1	0.49	115
CDKN2A	c.286delG	1	0.49	116
CDKN2A	c.457G>T_p.Asp153Tyr	1	0.49	117
CDKN2A	c.47T>G_p.Leu16Arg	2	0.98	119
CDKN2A	c.71G>C_p.Arg24Pro	1	0.49	120
CHEK2	c.1100delC	15	7.35	135
CHEK2	c.1111_1127dup17	1	0.49	136
CHEK2	c.1283C>T_p.Ser428Phe	1	0.49	137
CHEK2	c.1427C>T_p.Thr476Met	3	1.47	140
CHEK2	c.349A>G_p.Arg117Gly	2	0.98	142
CHEK2	c.444+1G>A	2	0.98	144
FANCC	c.1162G>T_p.Gly388X	1	0.49	145
FANCC	c.1642C>T_p.Arg548X	2	0.98	147
FANCC	c.284_293del10	1	0.49	148
FANCC	c.67delG	2	0.98	150
FANCC	c.844-1G>C	1	0.49	151
FANCC	c.992_995dupAGCA	1	0.49	152

Supplementary Table 2 (continued).

Gene	Mutation	Frequency	Percent	Cumulative Frequency*
MLH1	c.1489dupC	1	0.49	153
MLH1	c.1852_1854delAAG_p.Lys618del	1	0.49	154
MLH1	c.677+3A>G	1	0.49	155
MLH1	exon 9-12 duplication	1	0.49	156
MSH2	c.1046C>T_p.Pro349Leu	1	0.49	157
MSH6	c.1094G>A_p.Trp365X	1	0.49	158
MSH6	c.1306_1307dupTA	1	0.49	159
MSH6	c.3261dupC	1	0.49	160
MSH6	c.3804dupA	1	0.49	161
MSH6	c.3939_3957dup19	1	0.49	162
MSH6	c.3959_3962delCAAG	1	0.49	163
MSH6	c.467C>G_p.Ser156X	1	0.49	164
NBN	c.2160delA	1	0.49	165
NBN	c.657_661del5	3	1.47	168
PALB2	c.1424dupC	1	0.49	169
PALB2	c.1653T>A_p.Tyr551X	1	0.49	170
PALB2	c.2718G>A_p.Trp906X	1	0.49	171
PALB2	c.3113G>A_p.Trp1038X	1	0.49	172
PALB2	c.3116delA	1	0.49	173
PALB2	c.3350+4A>G	1	0.49	174
PALB2	c.3456dupA	1	0.49	175
PALB2	c.3549C>A_p.Tyr1183X	1	0.49	176
PALB2	c.509_510delGA	1	0.49	177
PALB2	c.948delC	1	0.49	178
PALB2	del exon 13	1	0.49	179
PMS2	c.1687C>T_p.Arg563X	1	0.49	180
PMS2	c.1831dupA	2	0.98	182
PMS2	c.2175-1G>A	1	0.49	183
PMS2	c.903G>T_p.Lys301Asn	2	0.98	185
PRSS1	c.365G>A_p.Arg122His	2	0.98	187
PRSS1	c.47C>T_p.Ala16Val	7	3.43	194
RAD51C	c.224dupA	2	0.98	196
RAD51C	c.397C>T_p.Gln133X	1	0.49	197
RAD51C	exon 9 deletion	1	0.49	198
RAD51D	exon 3 deletion	1	0.49	199
TP53	c.1009C>T_p.Arg337Cys	1	0.49	200
TP53	c.374C>T_p.Thr125Met	1	0.49	201
TP53	c.686_687delGT	1	0.49	202
TP53	c.743G>T_p.Arg248Leu	1	0.49	203
TP53	c.850_860del11	1	0.49	204

*****The cumulative frequency is 204 because six of the 198 mutation-positive probands had mutations in multiple genes.

Supplementary Table 3. Standardized incidence ratios (SIRs)***** for cancer risk by sex 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.

Cancer type	FDRs of mutation-positive probands† *N* = 1,465 (from 198 pedigrees)								FDRs of mutation-negative probands† *N* =14,168 (from 1,896 pedigrees)							
	Male				Female				Male				Female			
	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)
Bladder	7	14.3	27,409	0.49 (0.20–1.01)	5	3.8	29,332	1.31 (0.42–3.06)	49	145.9	280,628	0.34 (0.25–0.44)§	16	37.1	285,575	0.43 (0.25–0.70)§
Brain ‡	3	2.6	27,574	1.17 (0.24–3.42)	1	1.8	29,518	0.55 (0.01–3.04)	28	26.2	282,097	1.07 (0.71–1.54)	22	17.7	286,150	1.24 (0.78–1.88)
Breast	0	0.4	27,472	—	70	50.6	28,795	1.38 (1.08–1.75)§	1	4.5	281,142	0.22 (0.00–1.24)	347	494.9	281,504	0.70 (0.63–0.78)§
Breast, F	n/a	n/a	n/a	n/a	70	50.6	28,795	1.38 (1.08–1.75)§	n/a	n/a	n/a	n/a	347	494.9	281,504	0.70 (0.63–0.78)§
Colorectal	19	24.2	27,240	0.79 (0.47–1.23)	19	19.2	29,191	0.99 (0.59–1.54)	141	248.3	279,876	0.57 (0.48–0.67)§	127	187.6	284,716	0.68 (0.56–0.81)§
Gastric	2	5.0	27,450	0.40 (0.05–1.45)	3	2.5	29,425	1.20 (0.24–3.50)	32	50.9	280,979	0.63 (0.43–0.89)§	23	24.3	285,650	0.95 (0.60–1.42)
Head and neck	5	10.2	27,530	0.49 (0.16–1.15)	4	3.7	29,462	1.09 (0.29–2.78)	61	104.0	281,718	0.59 (0.45–0.75)§	26	35.7	285,870	0.73 (0.48–1.07)
Leukemia	3	6.3	27,518	0.48 (0.10–1.39)	6	3.8	29,484	1.57 (0.57–3.41)	49	64.5	281,668	0.76 (0.56–1.00)	24	37.2	286,029	0.65 (0.41–0.96)§
Liver ‡	3	2.8	27,551	1.06 (0.21–3.09)	3	1.0	29,502	3.08 (0.62–9.00)	22	29.1	282,182	0.76 (0.47–1.15)	20	9.4	286,208	2.12 (1.29–3.27)§
Lung ‡	13	32.8	27,481	0.40 (0.21–0.68)§	6	18.8	29,469	0.32 (0.12–0.69)§	150	336.7	281,735	0.45 (0.38–0.52)§	97	182.3	285,796	0.53 (0.43–0.65)§
Lymphoma	4	9.5	27,413	0.42 (0.11–1.08)	5	6.9	29,382	0.72 (0.23–1.69)	50	97.0	280,450	0.52 (0.38–0.68)§	37	67.1	285,403	0.55 (0.39–0.76)§
Melanoma	4	8.0	27,420	0.50 (0.13–1.28)	7	5.7	29,298	1.23 (0.49–2.52)	52	81.9	280,598	0.63 (0.47–0.83)§	41	55.6	285,283	0.74 (0.53–1.00)
Myeloma	1	2.8	27,470	0.36 (0.00–1.99)	1	2.0	29,438	0.51 (0.01–2.82)	10	28.7	281,110	0.35 (0.17–0.64)§	7	19.1	285,741	0.37 (0.15–0.75)§
Ovary	n/a	n/a	n/a	n/a	14	5.9	29,389	2.38 (1.30–4.00)§	n/a	n/a	n/a	n/a	62	57.0	285,083	1.09 (0.83–1.39)
Pancreas	19	5.3	27,449	3.57 (2.15–5.57)§	22	4.3	29,358	5.13 (3.22–7.77)§	86	54.5	280,939	1.58 (1.26–1.95)§	81	41.7	285,557	1.94 (1.54–2.41)§
Prostate	33	56.4	27,205	0.58 (0.40–0.82)§	n/a	n/a	n/a	n/a	278	577.2	278,322	0.48 (0.43–0.54)§	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 (SEER) Program; 9 registries, 1973–2013.

†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*.

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

§Statistically significant result

—Zero count was observed; therefore, incidence ratio could not be estimated

Abbreviations: Obs., observed, Expct., expected.

Supplementary Table 4. Standardized incidence ratios (SIRs)* for cancer risk by sex among siblings of pancreatic cancer probands, stratified by mutation status of the probands; the Mayo Clinic Biospecimen Resource for Pancreas Research, 2000-2016.

Cancer type	Siblings of mutation-positive probands† *N* = 636 (from 182 pedigrees)								Siblings of mutation-negative probands† *N* = 5,663 (from 1,728 pedigrees)							
	Male				Female				Male				Female			
	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)
Bladder	2	6.5	12,513	0.31 (0.03–1.11)	3	1.8	13,789	1.67 (0.34–4.89)	19	65.9	126,772	0.29 (0.17–0.45)§	9	15.9	122,013	0.57 (0.26–1.08)
Brain‡	2	1.2	12,567	1.71 (0.19–6.18)	0	0.9	13,918	—	14	11.8	127,360	1.18 (0.65–1.98)	5	7.6	122,238	0.66 (0.21–1.54)
Breast	0	0.2	12,533	—	41	23.8	13,535	1.72 (1.24–2.34)§	0	2.0	126,989	—	154	211.8	120,461	0.73 (0.62–0.85)§
Breast, F	n/a	n/a	n/a	n/a	41	23.8	13,535	1.72 (1.24–2.34)§	n/a	n/a	n/a	n/a	154	211.8	120,461	0.73 (0.62–0.85)§
Colorectal	9	11.0	12,416	0.82 (0.37–1.55)	6	9.1	13,771	0.66 (0.24–1.44)	43	112.3	126,615	0.38 (0.28–0.52)§	50	80.2	121,713	0.62 (0.46–0.82)§
Gastric	1	2.3	12,519	0.44 (0.01–2.46)	1	1.2	13,881	0.85 (0.01–4.72)	9	23.0	126,916	0.39 (0.18–0.74)§	5	10.4	122,108	0.48 (0.16–1.12)
Head and neck	2	4.6	12,570	0.43 (0.05–1.56)	3	1.7	13,887	1.73 (0.35–5.05)	26	46.9	127,228	0.55 (0.36–0.81)§	9	15.3	122,135	0.59 (0.27–1.12)
Leukemia	0	2.9	12,533	—	2	1.8	13,905	1.11 (0.12–3.99)	21	29.1	127,222	0.72 (0.45–1.10)	9	15.9	122,254	0.57 (0.26–1.08)
Liver‡	3	1.3	12,541	2.32 (0.47– 6.79)	1	0.5	13,907	2.18 (0.03–12.12)	7	13.1	127,424	0.53 (0.21–1.10)	5	4.0	122,273	1.24 (0.40–2.89)
Lung‡	4	15.0	12,551	0.27 (0.07–0.68)§	2	8.9	13,900	0.23 (0.03–0.81)§	64	152.0	127,215	0.42 (0.32–0.54)§	48	77.9	122,104	0.62 (0.45–0.82)§
Lymphoma	0	4.3	12,533	—	3	3.3	13,836	0.92 (0.19–2.70)	23	43.8	126,666	0.52 (0.33–0.79)§	15	28.7	121,982	0.52 (0.29–0.86)§
Melanoma	3	3.6	12,483	0.82 (0.17–2.40)	4	2.7	13,788	1.49 (0.40–3.81)	28	37.0	126,678	0.76 (0.50–1.09)	16	23.8	121,899	0.67 (0.38–1.09)
Myeloma	0	1.3	12,533	—	0	0.9	13,881	—	4	13.0	126,980	0.31 (0.08–0.79)§	2	8.2	122,132	0.24 (0.03–0.88)§
Ovary	n/a	n/a	n/a	n/a	7	2.8	13,864	2.52 (1.01–5.20)§	n/a	n/a	n/a	n/a	29	24.4	121,823	1.19 (0.80–1.71)
Pancreas	6	2.4	12,529	2.47 (0.90–5.37)	12	2.0	13,825	5.95 (3.07–10.39)§	33	24.6	126,904	1.34 (0.92–1.88)	30	17.8	122,051	1.68 (1.14–2.40)§
Prostate	12	25.8	12,449	0.46 (0.24–0.81)§	0	n/a	n/a	n/a	127	261.0	125,856	0.49 (0.41–0.58)§	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 (SEER) Program; 9 registries, 1973–2013.

†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*.

‡Where each was the only primary site reported.

§Statistically significant result

—Zero count was observed; therefore, incidence ratio could not be estimated

Supplementary Table 5. Standardized incidence ratios (SIRs)***** for cancer risk among first-degree relatives (FDRs) of pancreatic cancer probands who were younger than 60 years at diagnosis, stratified by probands' mutation status for each sex; the Mayo Clinic Biospecimen Resource for Pancreas Research, 2000-2016.

FDRs of Probands who were < 60 years at diagnosis

Cancer type	FDRs of Probands who tested positive for susceptibility gene mutation† *N* =493 (from 72 pedigrees)								FDRs of Probands who were negative for mutation† *N* = 3,331 (from 494 pedigrees)							
	Male				Female				Male				Female			
	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)
Bladder	4	4.3	8,293	0.93 (0.25–2.37)	2	1.1	8,821	1.74 (0.20–6.30)	9	28.4	54,543	0.32 (0.14–0.60)§	2	7.5	57,615	0.27 (0.03–0.96)§
Brain ‡	2	0.8	8,366	2.57 (0.29–9.28)	0	0.6	8,915	—	4	5.1	54,881	0.78 (0.21–2.01)	4	3.6	57,736	1.12 (0.30–2.86)
Breast	0	0.1	8,323	—	22	15.3	8,703	1.44 (0.90–2.18)	1	0.9	54,716	1.14 (0.01–6.36)	81	99.8	56,793	0.81 (0.64–1.01)
Breast, F	n/a	n/a	n/a	n/a	22	15.3	8,703	1.44 (0.90–2.18)	n/a	n/a	n/a	n/a	81	99.8	56,793	0.81 (0.64–1.01)
Colorectal	8	7.3	8,249	1.09 (0.47–2.15)	7	5.8	8,794	1.21 (0.48–2.49)	32	48.3	54,508	0.66 (0.45–0.93)§	26	37.9	57,452	0.69 (0.45–1.01)
Gastric	0	1.5	8,323	—	2	0.8	8,857	2.66 (0.30–9.59)	5	9.9	54,705	0.50 (0.16–1.18)	2	4.9	57,627	0.41 (0.05–1.47)
Head and neck	3	3.1	8,343	0.97 (0.20–2.85)	0	1.1	8,870	—	3	20.2	54,757	0.15 (0.03–0.43)§	3	7.2	57,687	0.42 (0.08–1.22)
Leukemia	1	1.9	8,343	0.52 (0.01–2.91)	3	1.2	8,915	2.59 (0.52–7.56)	12	12.6	54,873	0.95 (0.49–1.67)	7	7.5	57,710	0.93 (0.37–1.92)
Liver ‡	1	0.9	8,367	1.16 (0.02–6.46)	1	0.3	8,911	3.40 (0.4–18.92)	4	5.7	54,910	0.71 (0.19–1.81)	3	1.9	57,760	1.57 (0.32–4.60)
Lung ‡	3	10.0	8,348	0.30 (0.06–0.88)§	3	5.7	8,879	0.53 (0.11–1.55)	33	65.5	54,816	0.50 (0.35–0.71)§	16	36.8	57,703	0.43 (0.25–0.71)§
Lymphoma	1	2.9	8,314	0.35 (0.00–1.93)	1	2.1	8,862	0.48 (0.01–2.67)	9	18.9	54,542	0.48 (0.22–0.91)§	12	13.5	57,523	0.89 (0.46–1.55)
Melanoma	1	2.4	8,318	0.41 (0.01–2.29)	4	1.7	8,802	2.33 (0.63–5.97)	15	15.9	54,590	0.94 (0.53–1.55)	12	11.2	57,546	1.07 (0.55–1.87)
Myeloma	1	0.8	8,320	1.18 (0.02–6.56)	0	0.6	8,870	—	2	5.6	54,706	0.36 (0.04–1.29)	2	3.9	57,632	0.52 (0.06–1.87)
Ovary	n/a	n/a	n/a	n/a	5	1.8	8,866	2.82 (0.91–6.58)	n/a	n/a	n/a	n/a	19	11.5	57,447	1.65 (0.98–2.58)
Pancreas	7	1.6	8,319	4.34 (1.74–8.94)§	8	1.3	8,823	6.21 (2.67–12.24)§	22	10.6	54,643	2.08 (1.30–3.14)§	11	8.4	57,607	1.31 (0.65–2.34)
Prostate	15	17.0	8,204	0.88 (0.49–1.45)	0	n/a	n/a	n/a	66	112.3	54,156	0.59 (0.45–0.75)§	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 (SEER) Program; 9 registries, 1973–2013.

†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*.

‡Where each was the only primary site reported.

§Significant association

—Zero count was observed; therefore, standardized incidence ratio was not estimable

Supplementary Table 6. Standardized incidence ratios (SIRs)* for cancer risk among first-degree relatives (FDRs) of pancreatic cancer probands who were 60 years or older at diagnosis, stratified by probands' mutation status for each sex; the Mayo Clinic Biospecimen Resource for Pancreas Research, 2000-2016.

FDRs of Probands who were ≥ 60 years at diagnosis																
Cancer type	FDRs of Probands who tested positive for susceptibility gene mutation† *N* = 972 (from 126 pedigrees)								FDRs of Probands who were negative for mutation† *N* = 10,837 (from 1,402 pedigrees)							
	Male				Female				Male				Female			
	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)	No. Obs.	No. Expt.	Person-yrs.	SIR (95% CI)
Bladder	3	9.9	19,116	0.30 (0.06–0.88)§	3	2.7	20,511	1.13 (0.23–3.29)	40	117.6	226,085	0.34 (0.24–0.46)§	14	29.6	227,960	0.47 (0.26–0.79)§
Brain ‡	1	1.8	19,208	0.56 (0.01–3.11)	1	1.3	20,603	0.78 (0.01–4.36)	24	21.1	227,216	1.14 (0.73–1.69)	18	14.2	228,414	1.27 (0.75–2.01)
Breast	0	0.3	19,149	—	48	35.3	20,092	1.36 (1.00–1.80)	0	3.6	226,426	—	266	395.0	224,710	0.67 (0.59–0.76)§
Breast, F	n/a	n/a	n/a	n/a	48	35.3	20,092	1.36 (1.00–1.80)	n/a	n/a	n/a	n/a	266	395.0	224,710	0.67 (0.59–0.76)§
Colorectal	11	16.8	18,991	0.65 (0.33–1.17)	12	13.4	20,397	0.89 (0.46–1.56)	109	199.9	225,369	0.55 (0.45–0.66)§	101	149.8	227,263	0.67 (0.55–0.82)§
Gastric	2	3.5	19,127	0.58 (0.06–2.09)	1	1.7	20,568	0.57 (0.01–3.18)	27	41.0	226,274	0.66 (0.43–0.96)§	21	19.4	228,023	1.08 (0.67–1.66)
Head and neck	2	7.1	19,187	0.28 (0.03–1.02)	4	2.6	20,592	1.55 (0.42–3.98)	58	83.7	226,961	0.69 (0.53–0.90)§	23	28.5	228,183	0.81 (0.51–1.21)
Leukemia	2	4.4	19,175	0.46 (0.05–1.64)	3	2.7	20,568	1.12 (0.23–3.28)	37	51.9	226,795	0.71 (0.50–0.98)§	17	29.7	228,319	0.57 (0.33–0.92)§
Liver ‡	2	2.0	19,185	1.01 (0.11–3.65)	2	0.7	20,591	2.94 (0.33–10.63)	18	23.4	227,273	0.77 (0.46–1.22)	17	7.5	228,448	2.26 (1.31–3.61)§
Lung ‡	10	22.9	19,133	0.44 (0.21–0.80)§	3	13.1	20,589	0.23 (0.05–0.67)§	117	271.2	226,919	0.43 (0.36–0.52)§	81	145.5	228,093	0.56 (0.44–0.69)§
Lymphoma	3	6.6	19,099	0.45 (0.09–1.33)	4	4.8	20,521	0.83 (0.22–2.12)	41	78.2	225,908	0.52 (0.38–0.71)§	25	53.6	227,879	0.47 (0.30–0.69)§
Melanoma	3	5.6	19,102	0.54 (0.11–1.57)	3	4.0	20,496	0.75 (0.15–2.19)	37	66.0	226,008	0.56 (0.39–0.77)§	29	44.4	227,736	0.65 (0.44–0.94)§
Myeloma	0	2.0	19,149	—	1	1.4	20,568	0.73 (0.01–4.04)	8	23.1	226,404	0.35 (0.15–0.68)§	5	15.3	228,110	0.33 (0.11–0.76)§
Ovary	n/a	n/a	n/a	n/a	9	4.1	20,523	2.19 (1.00–4.16)	n/a	n/a	n/a	n/a	43	45.5	227,635	0.94 (0.68–1.27)
Pancreas	12	3.7	19,130	3.23 (1.67–5.65)§	14	3.0	20,535	4.67 (2.55–7.84)§	64	43.9	226,297	1.46 (1.12–1.86)§	70	33.3	227,951	2.10 (1.64–2.66)§
Prostate	18	39.4	19,001	0.46 (0.27–0.72)§	n/a	n/a	n/a	n/a	212	464.9	224,167	0.46 (0.40–0.52)§	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 (SEER) Program; 9 registries, 1973–2013.

†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*.

‡Where each was the only primary site reported.

§ Significant association

—Zero count was observed; therefore, standardized incidence ratio was not estimable