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Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan)

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A family history of pancreatic cancer has consistently been associated with increased risk of pancreatic cancer. However, uncertainty remains about the strength of this association. Results from previous studies suggest a family history of select cancers (*i.e.*, ovarian, breast and colorectal) could also be associated, although not as strongly, with increased risk of pancreatic cancer. We examined the association between a family history of 5 types of cancer (pancreas, prostate, ovarian, breast and colorectal) and risk of pancreatic cancer using data from a collaborative nested case-control study conducted by the Pancreatic Cancer Cohort Consortium. Cases and controls were from cohort studies from the United States, Europe and China, and a case-control study from the Mayo Clinic. Analyses of family history of pancreatic cancer included 1,183 cases and 1,205 controls. A family history of pancreatic cancer in a parent, sibling or child was associated with increased risk of pancreatic cancer [multivariate-adjusted odds ratios (ORs) = 1.76, 95% confidence interval (CI) = 1.19–2.61]. A family history of prostate cancer was also associated with increased risk (OR = 1.45, 95% CI = 1.12–1.89). There were no statistically significant associations with a family history of ovarian cancer (OR = 0.82, 95% CI = 0.52–1.31), breast cancer (OR = 1.21, 95% CI = 0.97–1.51) or colorectal cancer (OR = 1.17, 95% CI = 0.93–1.47). Our results confirm a moderate sized association between a family history of pancreatic cancer and risk of pancreatic cancer and also provide evidence for an association with a family history of prostate cancer worth further study.

A family history of pancreatic cancer is considered an established risk factor for pancreatic cancer.[1] However, uncertainty remains about the size of the relative risk associated with a family history of pancreatic cancer in first degree relatives. Relative risks less than 2.0 were reported by the 2 largest studies to date, a US cohort study [relative risk = 1.7, 95% confidence interval (CI) 1.4–1.9][2] and a Swedish registry-based analysis (relative risk (RR) = 1.7, 95% CI 1.2–2.4).[3] However, nearly all other studies have reported relative risks of 2.0 or more. An Icelandic registry-based analysis reported a relative risk of 2.3 (90% CI = 1.8–3.0)[4] and relative risk estimates from case-control studies have ranged from 1.9 to 5.0.[5–12]

A family history of ovarian, colorectal or breast cancer has also been associated with increased risk of pancreatic cancer in some studies. Two[4,6] of 7 studies[2–4,6,8–10] that examined family history of ovarian cancer reported a statistically significant increased risk of pancreatic cancer, as did 4 (Refs. 2,4,6 and 10) of 8 studies[2–4,6,8–10,13] that examined family history of colorectal cancer. Only 1 (Ref. 10) of 8 studies[2–4,6,8–10,13] that examined family history of breast cancer found significantly increased risk, although there was some suggestion of modestly increased risk in 2 others.[6,13] A family history of prostate cancer has not been associated with increased risk of pancreatic cancers in previous studies.[2–4,6,8–10] It should be noted that with the exception of the US cohort study,[2] which included 7,306 pancreatic cancer deaths, and the Swedish registry-based analysis,[3] which included 1,254 cases of pancreatic cancer, all of these studies of family history of cancer included fewer than 1,000 cases. Given the low prevalence of a family history of each specific type of cancer, some of these studies likely had limited statistical power to detect modest associations. Identifying associations between family history of specific cancers and risk of pancreatic cancer could provide clues to both environmental and genetic factors contributing to pancreatic cancer etiology.

We pooled data from several prospective cohort studies and 1 rapid ascertainment case-control study participating in the Pancreatic Cancer Cohort Consortium (PanScan) in order

to examine the association between a family history of pancreatic and certain other cancers and risk of pancreatic cancer.

Material and Methods

Study populations

The PanScan study was assembled to conduct a genome-wide association study, and includes pancreatic cancer cases and matched controls from twelve prospective cohort studies and 1 ultra-rapid ascertainment case-control study. This analysis includes cases and controls in PanScan that were from studies that had family history data available, namely, the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study case-control study (Mayo),[14] and the following 10 cohorts: the Alpha-Tocopherol, Beta-Carotene Prevention Study (ATBC),[15] the Give Us a Clue to Cancer and Heart Disease Study (Clue II),[16] the Cancer Prevention Study Nutrition Cohort (CPS II),[17] the European Prospective Investigation into Cancer and Nutrition (EPIC),[18] the Health Professionals Follow-up Study (HPFS),[19] the Nurses' Health Study (NHS),[20] the New York University Women's Health Study (NYU-WHS),[21] the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO),[22] the Shanghai Men's and Women's Health Study (SMWHS)[23,24] and the Women's Health Initiative (WHI).[25]

Six studies (CPS-II, Clue II, Mayo, NHS, PLCO and SMWHS) had sufficient family history data to be included in analyses of all of the types of family history of cancer that we examined. Other studies could be included only in the specific analyses for which appropriate family history data was available. ATBC was included in analyses of family history of pancreatic, colorectal and prostate cancer, HPFS was included in analyses of family history of breast and prostate cancer, NYU-WHS was included in analyses of family history of breast and colorectal cancer, WHI was included in analyses of family history of ovarian, prostate, breast and colorectal cancer and specific EPIC study centers that had collected information about family history of breast cancer were included in analyses of family history of breast cancer. We did not examine family history of cancers other than pancreatic, prostate, ovarian, colorectal and breast cancer because few studies had information on family history of other cancers.

Cases from the Mayo case-control study included in this pooled analysis were included in a previous analysis of family history and pancreatic cancer.[9] In addition, most cases from the CPS-II Nutrition Cohort included in this analysis were included in a previous analysis of family history and pancreatic cancer mortality.[2] However, the previous analysis used family history information reported by CPS-II participants in 1982 whereas this analysis used more up to date family history information reported between 1997 and 2001.

The Special Studies Institutional Review Board (SSIRB) of the National Cancer Institute approved the pooled PanScan study. Each study was approved by its local institutional review board (IRB).

Case ascertainment and control selection

Cases included all incident primary pancreatic adenocarcinoma (ICD-O-3 code C250–C259 or C25.0–C25.3, C25.7–C25.9). We excluded known nonexocrine pancreatic tumors (C25.4, histology type, 8150, 8151, 8153, 8155, 8240, 8246). Cases were confirmed through cancer registries (ATBC, CPS II, EPIC, HPFS, NHS, NYU-WHS, SMWHS), death certificates (CPS II, EPIC, HPFS, NHS) or review of medical records by medical personnel (ATBC, CPS II, EPIC, HPFS, Mayo, NHS, NYU-WHS, PLCO, WHI, SMWHS).

Controls were matched in a 1:1 ratio to cases within each study on calendar year of birth ($\pm$5 years), sex and race and were alive and free of pancreatic cancer on the incidence date of the matched case. Some studies also matched on other factors including age at baseline or age at blood draw ($\pm$5 years), date/time of day of blood draw, fasting status at blood draw and smoking status.

Ascertainment of family history

Participants in all studies self-reported family history of different cancers on self-administered written questionnaires. Some studies ascertained family history only in parents and siblings (ATBC, EPIC, NHS, HPFS, NYU-WHS), others also included children (CPS II, CLUE II, Mayo, PLCO, SMWHS, WHI). The Mayo study also ascertained family history beyond first degree relatives (*e.g.*, grandparents, aunts and uncles). For this analysis, we considered only family history in first degree relatives (parents, siblings and children).

Statistical analysis

Our primary analyses were based on a dichotomous variable (yes/no) for family history of each type of cancer. We also examined family history by number of affected relatives (1 or 2 or more) and by age at diagnosis of the youngest affected relative. Age at relative's diagnosis was not ascertained in the ATBC study and was sometimes left missing by participants in other studies. Therefore, analyses by age at relative's diagnosis include considerably fewer subjects than other analyses. For family history of breast and colorectal cancer we used category cut-points of 45 and 55 years, respectively, to be able to include data from the WHI study in our analysis. The WHI questionnaire did not ask for exact age of relative's cancer diagnosis, but instead asked participants to report whether or not their relative was diagnosed before or after age 45 (for breast cancer), or before or after age 55 (for colorectal cancer).

We calculated odds ratios (ORs) and 95% CI for pancreatic cancer risk using unconditional logistic regression. We used unconditional logistic regression rather than a matched pair analysis using conditional logistic regression to avoid losing information from matched sets in which 1 subject had missing family history data. Results, however, were similar in analyses using conditional logistic regression. Unless otherwise specified, models were adjusted for age (<50, 50–54,

Table 1. Characteristics of study populations included in pancreatic cancer cohort consortium (PanScan) family history analyses

Study	References	Location	Year(s) family history data collected[1]	Cases (*n*)	Controls (*n*)	Median age at case diagnosis (years)	Male[2] (%)	Caucasian[2] (%)
ATBC	15	Finland	1991–1992	175	177	70	100	100
Clue II	16	USA	1989	39	48	74	48	100
CPS II	17	USA	1997	153	146	76	51	99
EPIC[3]	18	Europe	1992–2000	105	113	63	40	100
HPFS[3]	19	USA	1996	55	55	70	100	100
Mayo	14	USA	2000–2003	400	400	68	58	99
NHS	20	USA	1996	88	88	70	0	95
NYU-WHS[3]	21	USA	1985–1991	13	13	70	0	77
PLCO	22	USA	1993–2001	250	267	72	60	92
SMWHS	23, 24	China	1996 (women)	78	79	69	22	0
			2001 (men)					
WHI[3]	25	USA	1993–1998	267	263	72	0	86

[1]For ATBC, Clue II, CPS-II, Mayo, NHS, PLCO and SMWHS, year data on family history of pancreatic cancer were collected. For HPFS, EPIC, NYU-WHS and WHI, which did not collect data on family history of pancreatic cancer, year data on family history of breast cancer were collected. [2]Percentage among controls, percentages among cases similar due to matching on sex and race. [3]Not included in analyses of family history of pancreatic cancer. Numbers shown are cases and controls included in analyses of family history of breast cancer.

55–59, 60–64, 65–69, 70–74–75–79, ≥80), study, sex, cigarette smoking status (never, former quit ≥10 years, former quit <10 years, current <20 cigarettes/day, current 20 cigarettes/day, current >20 cigarettes/day, unknown), race (Caucasian, African, Asian, other, unknown), BMI (<25, 25 to <30, ≥30, unknown) and self-reported diabetes (yes, no, missing). Because of small numbers, models that included only 1 study (study-specific models) included the adjustment variables above except that they were not adjusted for race, and used less detailed categories for age (10 year categories) and cigarette smoking (never/former/current).

We modeled multiplicative interaction terms between a dichotomous variable for family history of each cancer and age at diagnosis (<60, ≥60), BMI (<25, ≥25), sex and cigarette smoking status (current, not current), all common and established risk factors for pancreatic cancer. We also evaluated heterogeneity across studies by fitting models with and without multiplicative interaction terms between family history and study and calculating a *p*-value for heterogeneity using the likelihood ratio statistic.[26]

Results

Demographic characteristics and numbers of cases and controls are shown by study in Table 1. The numbers of cases and controls from each study shown in Table 1 are the numbers included in analyses of family history of pancreatic cancer, or (for studies that did not collect information on family history of pancreatic cancer) the numbers that were included in analyses of family history of breast cancer. Similar numbers of cases and controls from each study were generally included in analyses of other types of family history of cancer. Most cases and controls were from the United States and were Caucasian. The overall prevalence of a family history of pancreatic cancer among controls in whom this information was available was 3.6%, although prevalence varied considerably by study, with the highest prevalence (6.9%) observed in the CPS-II Nutrition Cohort, the oldest study population in PanScan.

A family history of pancreatic cancer in a first degree relative was associated with moderately increased risk of pancreatic cancer (OR = 1.76, 95% CI = 1.19–2.61; Table 2). The population attributable fraction associated with this odds ratio is 3.0%.[27] It should be noted that the population attributable fraction for family history does not fully represent the population effect of genetic factors because higher risk genetic variants may often be present in individuals with no family history. Results adjusted only for age, sex, race and study were similar to multivariate-adjusted results (OR = 1.82, 95% CI = 1.24–2.68). Having 2 relatives with a family history of pancreatic cancer was rare, so the risk associated with having 2 affected relatives could not be assessed with precision. Results are shown by study in Figure 1. There was no evidence of heterogeneity across studies ($p = 0.27$).

A family history of prostate cancer was also associated with increased risk of pancreatic cancer (OR = 1.45, 95% CI = 1.12–1.89; Table 2). There was evidence of heterogeneity across studies in the odds ratio for family history of prostate cancer ($p = 0.03$ for heterogeneity). In analyses by study (not shown in table), a family history of prostate cancer was associated with a statistically significant increase in risk in PLCO (OR = 2.99, 95% CI = 1.28–6.98) and WHI (OR = 2.88, 95% CI = 1.48–5.59), a suggestion of increased risk in HPFS

Table 2. Risk of pancreatic cancer by family history of various cancers and by number and age at diagnosis of affected relatives[1]

Type of cancer family history	Family history in first degree relative		Number of affected first degree relatives		Age at diagnosis of youngest affected first degree relative[2]	
	No	Yes	One	Two or more	≥60	<60
Pancreatic[3]						
OR (95% CI)	1.00 (Ref.)	1.76 (1.19–2.61)	1.70 (1.14–2.53)	4.26 (0.48–37.79)	1.82 (1.05–3.13)	1.54 (0.71–3.34)
Cases/controls	1,107/1,162	76/43	70/42	6/1	38/22	20/11
Prostate[4]						
OR (95% CI)	1.00 (Ref.)	1.45 (1.12–1.89)	1.50 (1.14–1.97)	1.03 (0.44–2.40)	1.20 (0.84–1.72)	1.65 (0.67–4.04)
Cases/controls	1,354/1,420	156/115	144/104	12/11	73/64	14/8
Ovarian[5]						
OR (95% CI)	1.00 (Ref.)	0.82 (0.52–1.31)	0.84 (0.53–1.35)	–	0.43 (0.13–1.42)	1.06 (0.44–2.57)
Cases/controls	1,235/1,251	35/43	35/42	0/1	4/10	11/10
					≥55	<55
Colorectal[6]						
OR (95% CI)	1.00 (Ref.)	1.17 (0.93–1.47)	1.21 (0.95–1.53)	0.87 (0.44–1.70)	1.11 (0.84–1.46)	0.91 (0.52–1.59)
Cases/controls	1,321/1,358	191/172	173/153	18/19	119/113	25/28
					≥45	<45
Breast[7]						
OR (95% CI)	1.00 (Ref.)	1.21 (0.97–1.51)	1.17 (0.92–1.47)	1.64 (0.87–3.10)	1.29 (0.99–1.68)	1.22 (0.70–2.10)
Cases/controls	1,254/1,307	200/178	176/161	24/17	137/116	29/26

[1]Adjusted for age, sex, cohort, race, BMI, cigarette smoking and diabetes. [2]Age categories for family history of breast and colorectal cancer based on categories reported by individual studies—see Material and Methods section. [3]Family history of pancreatic cancer analyses includes 7 studies (ATBC, Clue II, CPS II, Mayo, NHS, PLCO, SMWHS). [4]Family history of prostate cancer analyses includes 9 studies (ATBC, Clue II, CPS II, HPFS, Mayo, NHS, PLCO, SMWHS, WHI). [5]Family history of ovarian cancer analyses includes 7 studies (Clue II, CPS II, Mayo, NHS, PLCO, SMWHS, WHI). [6]Family history of colorectal cancer analyses includes 10 studies (ATBC, Clue II, CPS II, HPFS, Mayo, NHS, NYU-WHS, PLCO, SMWHS, WHI). [7]Family history of breast cancer analyses includes 10 studies (CLUE II, CPS II, EPIC, HPFS, Mayo, NHS, NYU-WHS, PLCO, SMWHS, WHI).

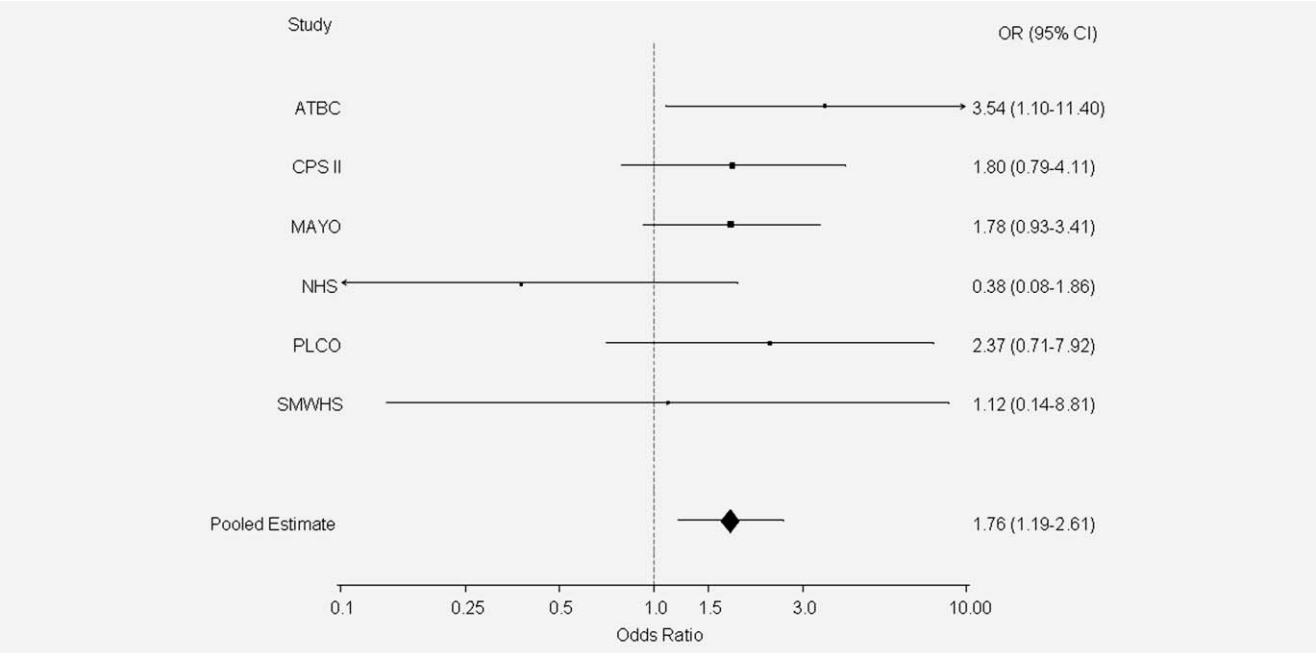

Figure 1. Odds ratios for Pancreatic cancer associated with family history of pancreatic cancer by study. Results from the Clue II study are not shown because no controls in Clue II had a family history of pancreatic cancer. Pooled estimate from logistic regression model as described in Material and Methods section.

(OR = 2.46, 95% CI = 0.88–6.92), and no suggestion of increased risk in the remaining 6 studies (ORs ranging from 0.4 to 1.2). The increase in risk of pancreatic cancer associated with a family history of prostate cancer differed by age at pancreatic cancer diagnosis ($p = 0.01$ for interaction), with a statistically significant increase in risk of pancreatic cancer diagnosed at age 60 or older (RR = 1.65, 95% CI = 1.25–2.18), but no suggestion of increased risk of pancreatic cancer diagnosed before age 60 (OR = 0.64, 95% CI = 0.29–1.44). However, numbers for this analysis were limited since relatively few pancreatic cancer cases were diagnosed before age 60. There was no evidence of particularly increased risk with having 2 affected relatives or with having a relative diagnosed with prostate cancer before age 60 (Table 2).

A family history of ovarian cancer was not associated with risk of pancreatic cancer (OR = 0.82, 95% CI = 0.52–1.31). There was a suggestion of increased risk of pancreatic cancer associated with a family history of colorectal cancer (OR = 1.17, 95% CI = 0.93–1.47) and breast cancer (OR = 1.21, 95% CI = 0.97–1.51), but neither of these associations was statistically significant.

We also examined results specifically among the cohort studies (excluding the Mayo case-control study). Among the cohort studies, ORs associated with risk of pancreatic cancer were 1.78 (95% CI = 1.07–2.97) for a family history of pancreatic cancer, 1.51 (95% CI = 1.10–2.08) for a family history of prostate cancer, 0.70 (95% CI = 0.42–1.18) for a family history of ovarian cancer, 1.10 (95% CI = 0.84–1.44) for a family history of colorectal cancer and 1.19 (95% CI = 0.92–1.55) for a family history of breast cancer. We also calculated *p*-values for heterogeneity of associations across all studies, as noted in the Material and Methods section. With the exception of family history of prostate cancer ($p = 0.03$ as noted above) we found no statistical evidence for heterogeneity across studies. *p* values for heterogeneity across studies for family history of pancreatic, ovarian, colorectal and breast cancer were 0.27, 0.35, 0.57 and 0.43, respectively.

Because we hypothesized family history associations might be substantially stronger for earlier onset pancreatic cancer (diagnosed before age 60), we examined results specifically among those diagnosed under age 60, although numbers for this analysis were limited. Odds ratios for pancreatic cancer before the age of 60 were 0.86 (95% CI = 0.25–3.00) for a family history of pancreatic cancer, 0.64 (95% CI = 0.29–1.44) for a family history of prostate cancer, 1.21(95% CI = 0.57–2.54) for a family history of breast cancer, 6.20 (95% CI = 0.69–55.54) for a family history of ovarian cancer and 1.41 (95% CI = 0.64–3.09) for a family history of colorectal cancer.

We found no statistically significant interactions between sex, smoking status or body mass index and family history of any of the cancers we examined. Odds ratios for family history of pancreatic cancer were 2.11 (95% CI = 1.15–3.85) among never smokers, 1.25 (95% CI = 0.67–2.35) among former smokers and 2.84 (95% CI = 1.06–7.59) among current smokers.

Discussion

This large pooled analysis confirms that a family history of pancreatic cancer is associated with moderately increased risk of pancreatic cancer. The size of the increase in risk we observed (OR = 1.8) is consistent with results from the 2 largest studies to date, a large US cohort study[2] and a Swedish registry based analysis,[3] which both reported relatives risk of 1.7. Our results are less consistent with the relative risk estimates of 2.5 or greater observed in some previous case-control studies.[5–8,10,11]

The association between a family history of pancreatic cancer and risk of pancreatic cancer is likely due to genetic and/or other risk factors that are shared by family members. Relatively little is known about the specific genetic factors that might contribute to associations between family history of cancer and risk of pancreatic cancer. Inherited truncating mutations in the *BRCA2* gene increase risk of pancreatic cancer,[28] but these mutations have been detected in only about 6% of pancreatic cancer patients with a family history of pancreatic cancer.[29] Inherited mutations in the DNA mismatch-repair genes responsible for hereditary nonpolyposis colorectal cancer (HNPCC) are also associated with increased risk of pancreatic cancer,[28,30] but these mutations are rare in the general population. Peutz-Jeghers syndrome (caused by an inherited mutation in *LKB1*), hereditary pancreatitis (caused by an inherited mutation in *PRSS1*) and inherited mutations in *CDKN2A* (responsible for familial atypical multiple mole melanoma syndrome), increase risk of pancreatic cancer, but are very rare.[28] In addition to these rare mutations, common polymorphisms in the *ABO* gene have recently been shown to be associated with modestly increased risk of pancreatic cancer.[31] Nongenetic risk factors that are shared between family members could also have contributed to the association we observed. However, in our analysis, adjustment for nongenetic pancreatic risk factors, including obesity, diabetes and smoking, did not attenuate the association between a family history of pancreatic cancer and risk of pancreatic cancer, indicating these risk factors are unlikely to explain the association with family history.

A family history of prostate cancer was associated with a notable increase in risk of pancreatic cancer in this analysis (OR = 1.45, 95% CI = 1.12–1.89). The magnitude of this association was unexpected, given that a family history of prostate cancer has not been associated with significant increases in risk of pancreatic cancer in 7 previous studies.[2–4,6,8–10] It should be noted, however, that previous studies do not preclude a small increase in risk associated with a family history of prostate cancer. In the 3 largest previous studies,[2–4] a family history of prostate cancer was associated with nonstatistically significant relative risks ranging between 1.06 and 1.13. In this analysis, the association between a family history of prostate cancer and risk of pancreatic cancer was most apparent in the WHI and PLCO

studies. We know of no clear explanation why results from these 2 studies with respect to a family history of prostate cancer would differ from those of other studies included in this pooled analysis. Like the WHI and PLCO cohorts, the NHS and CPS-II cohorts are composed mostly of well-educated older adults from the United States, but there was no suggestion of any association between a family history of prostate cancer and risk of pancreatic cancer in either NHS or CPS-II. Chance may be at least partly responsible for the association with a family history of prostate cancer observed in our study. Further examination of this association between a family history of prostate cancer and risk of pancreatic cancer in other large studies may be informative.

A family history of ovarian cancer was not associated with increased risk of pancreatic cancer in our analysis (OR = 0.82, 95% CI = 0.52–1.31). Our null results are similar to those from a large Swedish registry-based analysis,[3] a large US cohort study[2] and 2 US case-control studies.[8,9] However, a strong increase in risk of pancreatic cancer was observed in a US population-based case-control study (OR = 5.3, 95% CI = 1.4–20.2),[6] and in a large registry-based analysis from Iceland (RR = 1.7, 90% CI = 1.3–2.1).[4] Family history of ovarian cancer may be associated with increased risk of pancreatic cancer in the Icelandic population because Icelanders have a unusually high prevalence of BRCA2 truncating mutations,[32] which increase risk of both ovarian[33] and pancreatic cancer.[34,35]

A family history of colorectal cancer was not associated with a statistically significant increase in risk of pancreatic cancer in our study. However, our risk estimate (OR = 1.2, 95% CI = 0.9–1.5) does not preclude a weak association. Previous studies of a family history of colorectal have yielded mixed results. Significantly increased risk of pancreatic cancer was observed in 2 US case-control studies[6,10] and in a registry-based analysis from Iceland.[4] A statistically significant increase in risk was also observed in a large US cohort study, but the increase in risk appeared quite small (RR = 1.12, 95% CI = 1.01–1.23).[2] No association was observed in a large registry-based analysis from Sweden.[3] To date, the totality of epidemiologic evidence does not support an important association between a family history of colorectal cancer and risk of pancreatic cancer.

A family history of breast cancer was also not associated with a statistically significant increase in risk in our study, although our risk estimate (OR = 1.2, 95% CI = 1.0–1.5) does not preclude a weak association. A family history of breast cancer was associated with increased risk in 1 US case-control study.[10] However, the absence of increased risk in our study is consistent with results from most previous studies of family history of breast cancer.[2–4,6,8,9,13]

Strength of this analysis is its relatively large size, which is important given the low prevalence of family histories of individual types of cancer. Although not as large as a recent analysis of family history and pancreatic cancer mortality in a US cohort,[2] this pooled analysis is among the largest studies of family history to date and includes a somewhat geographically diverse population, with participants from Europe, China and the United States. Limitations of this analysis include the fact that family history of cancer was self-reported and some misclassification of family history can be expected as a result.[36] In cohort studies, which contributed most of the cases and controls in this analysis, misclassification of family history would be expected to be nondifferential with respect to later development of pancreatic cancer and would therefore contribute to underestimating the strength of associations with family history. In addition, participants in the cohort studies included in this analysis may have reported family history several years before their diagnosis date. A small proportion of participants who had no family history of a particular type of cancer at the time family history was assessed would have acquired a family history of this type of cancer during study follow-up. However, this proportion is likely to have been too small to have meaningfully influenced our relative risk estimates. An additional limitation is that numbers were limited for analyses by number and age of affected relatives.

In summary, results of this large pooled analysis indicate that a family history of pancreatic cancer is associated with moderately increased risk of pancreatic cancer. The association between family history of prostate cancer and increased risk of pancreatic cancer observed in our study should be interpreted cautiously and requires careful examination in future analyses of family history.

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