**Risk of pancreatic cancer associated with family history of cancer and of other medical conditions**

Esther Molina-Montes, PhD (1), Paulina Gomez-Rubio, PhD (1), Mirari Marquez, PhD (1), Marta Rava, PhD (1), Matthias Löhr, MD, PhD (2), Christoph W. Michalski, MD PhD (3,4), Xavier Molero, MD, PhD (5,6,7), Lucas Ilzarbe, MD (8), Antoni Farré, MD, PhD (9), José Perea, MD PhD (10), William Greenhalf, PhD (11), Michael O’Rorke, PhD (12), Adonina Tardón, MD, PhD (7,13), Thomas Gress, MD, PhD (14), Victor M. Barberà, PhD (15), Tatjana Crnogorac-Jurcevic, PhD (16), Enrique Domínguez-Muñoz, MD (17), Luís Muñoz-Bellvís, MD (18), Joaquim Balsells, MD (5,6,7), Eithne Costello, PhD (11), Jiaqui Huang, PhD (2), Mar Iglesias, MD (8), Jörg Kleeff, MD, PhD (3,11), Bo Kong, PhD (3), Josefina Mora, PhD (8), Liam Murray, PhD (12), Damian O’Driscoll, PhD (19), Pablo Peláez, MD (10), Ignasi Poves, MD (8), Aldo Scarpa, MD, PhD (20), Weimin Ye (2), Manuel Hidalgo, MD, PhD (21), Linda Sharp, PhD (19), Alfredo Carrato, MD, PhD (22), Francisco X. Real, MD, PhD (23,24), Núria Malats, MD, PhD (1) on behalf of the PanGenEU Study Investigators (25)

**Authors’ affiliations:**

1. Spanish National Cancer Research Center (CNIO), Genetic and Molecular Epidemiology Group, Madrid, Spain.
2. Karolinska Institutet and University Hospital, Gastrocentrum, Stockholm, Sweden.
3. Technical University of Munich, Department of Surgery, Munich, Germany.
4. University of Heidelberg, Department of Surgery, Heidelberg, Germany.
5. Hospital Universitari Vall d’Hebron, Exocrine Pancreas Research Unit and Vall d’Hebron Research Institute (VHIR), Barcelona, Spain.
6. Universitat Autònoma de Barcelona, Campus de la UAB, Barcelona, Spain.
7. Centro de Investigación Biomédica en Red, Enfermedades Hepáticas y Digestivas, Epidemiológica y Salud Pública (CIBEREHD and CIBERESP), Madrid. Spain.
8. Hospital del Mar—Parc de Salut Mar, Department of Gastroenterology, Barcelona, Spain.
9. Hospital de la Santa Creu i Sant Pau, Department of Gastroenterology, Barcelona, Spain.
10. University Hospital 12 de Octubre, Department of Surgery, Madrid, Spain.
11. The Royal Liverpool University Hospital, Department of Molecular and Clinical Cancer Medicine, Liverpool, UK.
12. Queen's University Belfast, Centre for Public Health, Belfast, UK.
13. Instituto Universitario de Oncología del Principado de Asturias, Department of Medicine, Oviedo, Spain.
14. University Hospital of Giessen and Marburg, Department of Gastroenterology, Marburg, Germany.
15. Hospital General Universitario de Elche, Laboratorio de Genética Molecular, Elche, Spain.
16. Barts Cancer Institute, Queen Mary University of London, Centre for Molecular Oncology, John Vane Science Centre, London, UK.
17. Hospital Clínico Universitario de Santiago de Compostela, Department of Gastroenterology, Santiago de Compostela, Spain.
18. Hospital Universitario de Salamanca, General and Digestive Surgery Department, Salamanca, Spain.
19. National Cancer Registry Ireland, Cork, Ireland, and Institute of Health & Society, Newcastle University, UK.
20. University and Hospital trust of Verona, ARC-Net centre for Applied Research on Cancer and Department of Pathology and Diagnostics, Verona, Italy.
21. Hospital Madrid-Norte-Sanchinarro, Madrid, Spain.
22. Hospital Ramón y Cajal, Department of Oncology, Madrid, Spain.
23. Spanish National Cancer Research Centre (CNIO), Epithelial Carcinogenesis Group, Madrid, Spain.
24. Universitat Pompeu Fabra, Departament de Ciències Experimentals i de la Salut, Barcelona, Spain.
25. PanGenEU Study Investigators (Supplemental Annex S1).

**Corresponding authors:**

 Núria Malats, M.D., M.P.H., Ph.D., and Esther Molina-Montes, Ph.D.

Genetic and Molecular Epidemiology Group

Spanish National Cancer Research Center (CNIO)

C/Melchor Fernandez Almagro, 3, 28029, Madrid, Spain,

Phone: +34-912-246-900 (ext.3330), Fax: +34-912-246-911

E-mail: nmalats@cnio.es and memolina@cnio.es

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**List of abbreviations:**

PC: Pancreatic ducal adenocarcinoma

BMI: Body mass index

FDR: First-degree relative

FH: Family history

FHC: Family history of cancer

FHPC: Family history of pancreatic ducal adenocarcinoma

FPC: Familial pancreatic cancer

FHD: Family history of diabetes

FHAL: Family history of allergies

FHAS: Family history of asthma

FHCF: Family history of cystic fibrosis

FHPC: Family history of chronic pancreatitis

OR: Odds ratio

HR: Hazard ratio

CI: Confidence interval

**Keywords:** pancreatic cancer, familial, epidemiology, case-control, cohort, risk.

**Abstract:**

**Background:** Pancreatic cancer (PC) has been associated with family history (FH) of pancreatic cancer (PC) and of diabetes mellitus. Our aim was to further characterize these associations and to explore PC risk associated with FH of other cancers and of PC-associated morbidities.

**Methods:** 1,431 PC cases and 1,090 controls included in the PanGenEU study provided information on the occurrence of cancer, diabetes, allergies, asthma, cystic fibrosis and chronic pancreatitis among their first-degree relatives (FDR). Logistic regression was used to evaluate PC risk associated with FH of these diseases by subsets of family members and number of affected relatives. Familial aggregation of cancer in 16,747 relatives of the cases and controls was assessed within a reconstructed cohort using Cox proportional hazard regression.

**Results:** Having FHPC was associated with an increased PC risk (OR=2.68; 95%CI: 2.27–4.06) when compared with cancer-free FH, the risk being greater when ≥2 FDRs suffered PC (OR=3.88; 95%CI: 2.96-9.73) and among current-smokers (OR=3.16, 95%CI: 2.56-5.78, interaction p-value=0.039). Cumulative risk of PC to age 75 was 2.2% in the FDR of cases and 0.7% in those of controls (HR=2.42; 95%CI: 2.16-2.71). PC risk was also significantly associated with FH of any cancer (OR=1.30; 95%CI: 1.13-1.54) and diabetes (OR=1.24; 95%CI: 1.01-1.52), but not with FH of other diseases.

**Conclusion:** Individuals with FH of cancer, PC or diabetes are more vulnerable to develop PC. Smoking notably increase the PC risk associated with FHPC. Further evaluation of these associations should be undertaken to guide prevention strategies in families at higher risk of PC.

**Introduction**

Little progress has been made in our knowledge about pancreatic cancer (PC) in recent years. PC remains therefore an incurable and devastating disease, with the lowest 5-year survival rate of all cancers (<7%),1,2 mortality rates on the rise and no immediate prospect of an improvement.3,4 Causative factors of PC include a constellation of medical conditions, such as diabetes, chronic pancreatitis, obesity, allergies and asthma, a number of lifestyle-related factors (smoking and heavy alcohol intake), non-O blood group, and family history (FH) of PC (FHPC).5 Regarding the latter, as many as 10% of all PCs are aggregated in some families, suggesting a heritable predisposition for PC development.6 Familial pancreatic cancer (FPC), defined as two or more first-degree relatives (FDRs) affected with PC, is believed to have a strong genetic component. However, genetic susceptibility explains less than 2% of all familial PCs owing to the genetic heterogeneity of this disease.7 Shared non-genetic exposures may also lead to this excess PC risk among family members.8

Findings from several epidemiological studies, including a meta-analysis8 of nine studies,9–17 support that FHPC is associated with an increased PC risk.8,18–23 Three of these earlier studies relied on population-based family data,18–20 several others were case-control studies,8,21 and fewer were prospective studies,13,22 including those participating in the PanScan consortium.23 However, a consensus on the risk estimates has not yet been achieved despite all studies’ attempts to estimate PC risk associated with FHPC, likely attributable to the inappropriate assessment of lifetime risks of PC among relatives.24,25 Concerns have been also raised regarding failure to adjust for smoking or other potential confounders in some studies.8 Not accounting for risk factors that are shared between family members could be also a source of bias. Thus, a great deal remains to be done in assessing the association between FHPC and PC risk.

In addition to PC, familial aggregation of some cancer types leading to PC has been reported for colorectal, breast and other cancers.11,19,21,23,26 Mutations in genes responsible for hereditary cancers, such as BRCA2 for breast cancer, may explain these associations,6 though they can be also attributable to other shared risk factors in the family.

Regarding other diseases, the association between FH of diabetes (FHD) and PC risk has been examined in a Swedish population-based study, reporting an increased risk in siblings of diabetics close to 3 times that of the general population,27 and in a case-control study of 654 PC cases that reported modestly weak association (OR=1.37).28 To our knowledge, no studies exist on the association between FH of other diseases and PC risk. Genetic and non-genetic factors may also explain the familial clustering of these diseases.29 On these grounds, the need for exploring PC risk associated with FH of these diseases is well warranted.

Our aim was to comprehensively analyze the association between risk of PC and FH of cancer and other diseases in FDRs within the largest and most informative study of incident PC conducted to-date, which enabled us to perform a two-way evaluation of this association in a case-control setting and a reconstructed cohort of the relatives of the cases and controls.

**Methods**

*Study population:*

This study includes individuals from the PanGenEU study, a large European case-control study. All potential eligible PC cases were recruited at first instance to overcome selection bias attributable to the rapid progression of the disease. Diagnosis of all included cases was ratified thereafter through review of medical records and physician´s assent. Eligible controls where free of PC and conditions at hospital admission unrelated to any known PC risk factor. They were selected by virtue of the characteristics of the PC cases regarding age, sex and center, i.e. the hospital´s catchments area, except in Ireland and Sweden where controls were population-based. All subjects provided written informed consent and the study was approved by the local Ethical Committees of the participating centers. More details are provided in supplementary methods and elsewhere.30

*Data collection of FH and other variables:*

Information on the occurrence of diseases (cancer, diabetes, allergies, asthma, chronic pancreatitis and cystic fibrosis) in FDRs of the cases and controls was collected through face-to-face interviews conducted by trained monitors. This information was collected separately for each family member distinguishing by the type of relative. Whenever there was a FDR with a positive history of cancer, the interviewers gathered additional information about the cancer site (up to three cancers) and age at every cancer diagnosis (Supplementary Methods). Information on age at diagnosis was also collected for FDRs with positive FHD (in age categories: childhood, youth and adulthood). Cases and controls were also inquired about the vital status of every family member, their current age (or age at death) and whether they had ever smoked.

Main exposure variables derived from this data were: FH of any cancer (FHC), including FHPC and other cancers potentially related to PC via inherited genetic or environmental factors (prostate, breast/ovarian, colorectal, smoking-related and multiple primary cancers), diabetes (FHD), allergies (FHAL), asthma (FHAS), chronic pancreatitis (FHCP) and cystic fibrosis (FHCF), whereby a positive FH was assigned if any of their FDRs had ever been diagnosed with these diseases. FH variables of these diseases by subsets of family members were also derived. For FHC and FHD we also considered occurrence of either early or late-onset disease in the family if there was any young or old-aged FDR diagnosed with the disease, respectively. The number of FDRs with FH of a disease was calculated for each case and control to obtain variables by number of affected relatives. Composite variables, so-called score variables, that combined number and type of relatives affected with the disease were also obtained.

All participating centers adopted the same PanGenEU questionnaire. Ireland, however, collected data only for FHC and FHCP and could contribute with data only for these disease-specific analyses. We further excluded data from Italy due to incomplete recruitment of controls. Thus, the final analytic sample was comprised of 1,431 cases and 1,090 controls with information available on FHC and FHCP, and 1,258 cases and 800 controls with information available on FH of the remaining diseases.

Cases and controls also provided information regarding their own lifetime history of tobacco smoking, educational level, medical history (e.g. cancer, diabetes, asthma, allergies and chronic pancreatitis), and their height and weight at about two years prior to the cancer diagnosis. In addition, clinical and pathologic data of the tumors were collected for a subset of PC cases (n=504).

*Statistical analysis:*

A two-way approach was carried out to explore the association between FHC and FH of other diseases with PC risk (Supplementary Methods):

1. *Case-control study*

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) corresponding to risk of PC associated with a positive FH (versus a negative FH, deemed as reference category) of cancer and other diseases. Three separate regression models were performed including one accounting for the number of relatives24. Assumptions of logistic regression analyses were met as indicated by the Hosmer-Lemeshow goodness-of-fit test.31

ORs were obtained for each FH variable by subsets of family members, number of affected relatives and age at earliest diagnosis. Heterogeneity by country was evidenced and random effects for country were therefore considered in mixed models.32 We also examined whether the associations varied by stage and location of the tumor, using the same control population for each strata.

1. *Reconstructed cohort study*

The relatives of the cases and controls made up the reconstructed cohort. For each case- and control-relative we calculated follow-up time as the time elapsed between the date of birth (age=0) and the end of follow-up, defined by the reported age at the cancer diagnosis, age at death or age at the date of the interview, whichever came first. Cumulative risks of cancer were calculated for both cohorts using the Nelson-Aalen method and differences were evaluated with the log-rank test.33 Cox proportional hazard regression was used to obtain hazard ratios (HRs) and 95% CIs associated with cancer occurrence (overall and by cancer types) for the case-relatives (*versus* the control-relatives), stratified by sex, age (1-year intervals) and relative type, using for the latter a robust sandwich estimate of the covariance matrix.34 In addition, we accounted for heterogeneity by country by using a frailty for this variable in the regression model.35 Potential confounding and effect modification by other covariates (the relatives’ smoking status and occurrence of diseases, age, sex and the type of relative) was likewise assessed by evaluating changes in the HR estimate above 10% and testing interaction via the LHR, respectively. Potential confounding effects of smoking were considered in separate models. The proportional hazards assumption was evaluated by considering the interaction between every covariate and time and evaluating Schoenfield residuals.36 No evidence for violation of this assumption was observed.

For both the case-control and cohort study approaches we conducted number of sensitivity analyses to assure the robustness of our results (Supplementary Methods), such as analyses accounting for the influence of the relatives´ covariates on the associations by applying Generalized Estimating Equations (GEE).37

We handled imputation of missing data, which we assumed to be missing at random, with the random forest algorithm.38 Imputation was performed separately for the case-control and for the cohort studies´ datasets. More information is provided in Supplementary Methods and Supplemental Table 1.

Two-sided tests were used to compute statistical significance, which was deemed for p-values < 0.05. Statistical software used for the data analysis was R 3.2.1.39

**Results**

*Case-control approach*

The study population characteristics are shown in Supplemental Table 2. Cases were more frequently smokers and diabetics and had a slightly smaller family size as compared to controls. The proportion of positive FHC, including PC, and diabetes was also higher in cases than in controls.

Risk estimates of PC associated with FHC and FH of other diseases are shown Tables 1 and 2, respectively. A statistically significant positive association was observed in multivariate-adjusted models evaluating PC risk associated with a positive *versus* negative FHC (OR=1.30, 95%CI: 1.13-1.54). This increased cancer risk was more manifest when relatives were parents and siblings, and from relatives diagnosed with cancer at age older than 50 years. PC risk also increased with increasing number of relatives with cancer (*p-trend*=0.003). Analyses by cancer site also revealed statistically significant associations between FHC and PC risk (OR=2.68; 95%CI: 2.23-4.06), as well as for FH of breast&ovary, colorectal, prostate and smoking-related cancers (OR=1.45; 1.27; 1.70; 1.34, respectively).

The trend of the association across types of relatives and number of affected relatives was similar to that observed for FHC overall (data not shown). In particular, PC risk was nearly four-fold increased (OR=3.88; 95%CI: 2.97-9.72) when >2 FDRs were affected with PC (Table 1).

FHD in FDRs was associated with a 24% (95%CI: 1.01-1.52) higher PC risk, with this risk being mostly driven by diabetes diagnosed in the adulthood. We also observed a tendency towards a higher PC risk for increasing number of relatives affected with diabetes (OR=1.51; 95%CI: 1.22-1.87). No significant associations with PC risk were encountered for the occurrence of any other diseases in the family, probably due to its low prevalence (Table 2).

The effects of the subject´s characteristics on the multivariate-adjusted risk estimates were minor, except for smoking. Family size had also an overall negligible impact on the risk estimates. Risk estimates remained almost unchanged in sensitivity analyses (Supplemental Table 3).

Results of stratified analyses showed different estimates of association by smoking status (Table 3). Compared to a negative FHC, a notably higher PC risk was observed among ever-smokers with FHPC (OR=3.16, 95%CI: 2.56-5.78), with this risk being even higher among current-smokers (OR=5.59, 95%CI: 2.78-12.29) (Supplemental Table 4, Supplementary Figure 1), whereas PC risk turned out to be weaker in never-smokers (*p-value* for interaction=0.04). In contrast, the association between FHC and PC tended to be stronger in never-smokers; this pattern was consistent for FH of other cancer sites, although without evidence for a statistically significant interaction by smoking. Risk estimates remained the same in ever-smokers after additionally controlling for smoking intensity and duration (data not shown).

In analyses stratified by disease severity (Supplemental Table 5), we observed that FHPC with >2 affected FDRs were more likely early-stage tumors. However, the limited number of cases did not permit an explicit risk estimation. Conversely, having a single FDR with PC was found to be associated with a statistically significant increased risk of high-stage tumors (OR=2.36, 95%CI: 1.67-4.73). Further, risk of high-stage PC tended to be positive for those having a FHD, while the association turned inverse and statistically significant for early-stage tumors (OR=0.63, 95%CI: 0.17-0.99). We did not observe effect modification by any other variable.

*Reconstructed cohort approach*

A total of 9,055 case-relatives and 7,360 control-relatives contributed with 509,801 and 414,309 person-years to the cancer overall analyses (Supplemental Tables 6 and 7). Characteristics of case-relatives and control-relatives are shown in Supplemental Table 2. Case-relatives had been more frequently ever smokers than control-relatives. Aggregation of cancer events overall and of certain cancer types including PC was also higher in case-relatives compared to control-relatives.

The cumulative risk of cancer to age 75 was of 23.8% in case-relatives and 19.5% in control-relatives (HR=1.16, 95%CI: 1.05-1.29) (Figure 1). HRs of similar magnitude were also observed for FH of multiple primary cancers. Corresponding figures for PC were 2.2% and 0.7%, respectively (HR=2.4, 95%CI: 2.16-2.71). Cancers of the breast&ovary, prostate and those regarded as smoking-related were also more likely to aggregate among case-relatives (HR=1.14, 1.66 and 1.24, respectively), whereas familial aggregation of colorectal cancer failed to reach statistical significance.

Overall, the increased risks were more pronounced in relatives aged ≥ 50 years, in parents and siblings, and in ever-smokers, although interaction analyses by age, relative type and smoking did not result statistically significant (Supplemental Table 7). There was a differing aggregational relationship between cancer and PC in case-relatives compared to control-relatives by diabetes status (p for interaction=0.03), which was not manifest in other cancer sites. We did not observe any other statistically significant differences by subgroups in familial aggregation patterns of cancer, PC and other cancers among case-relatives and control-relatives. Results were consistent across all sensitivity analyses conducted (Supplemental Table 8).

**Discussion**

A positive FHPC was associated with a 2.7-fold increased risk of PC in this study, which is the first to consider a two-way evaluation of this association. Based on the consistency of our results in both assessments we report herein reliable risk estimates of PC following a previous PC diagnosis in FDRs. Our findings also suggest a positive association between FHD and FHC including FH of certain cancer types with PC risk. The excess risks were proportional to increasing number of affected relatives. For instance, PC risk increased by nearly four times when >2 FDRs were affected with PC.

A large body of evidence supports that FHPC increases PC risk. Our risk estimates are close to those reported by a meta-analysis of 2,617 cases and 6,284 controls (OR=2.82; 95%CI: 1.99–3.66),8 and other studies,11,15 but less similar if compared to the two cohort studies (including 3,951 PC cases) included in the meta-analysis (pooled RR=1.62; 95%CI: 1.28–1.97),13,17 the Cancer Prevention CPS-II cohort study based on 7,306 pancreatic cancer-related deaths,22 and the 1,183 cases and 1,205 controls nested within the PanScan cohort consortium.23 Our findings supporting that >2 FDRs with a PC diagnosis have a far higher PC risk (OR=3.8) are consistent with other studies showing similar risk estimates,22 but of lower magnitude with regard to others (OR=6.4).18 Also, PC risk was found to be increased for late-onset cancer (≥50 years of age) in FDRs. Fewer cases and controls were available for analyses evaluating PC risk associated with early-onset cancers in the family to confirm the stronger association reported in previous studies. 10,18,20,22

Reasons for this varying risk estimates of PC associated with FHPC include issues inherent to study design. Criticism has been leveled at case-control studies in assessing the association between FH and disease risk due to differences in the number of relatives among cases and controls and because the relatives´ lifetime risk cannot be adequately assessed owing to their dissimilar age distribution.24{FormattingCitation}225 In our study, risk estimates derived from the case-control design do not seem to be biased *per se* by family size. The reconstructed cohort has been therefore proposed as a better scenario to evaluate FH as a risk factor of disease.24 Despite controversies surrounding the appropriate study design, both seem to be valid for assessing risk associated with FH of diseases.25 The risk estimates we have obtained from either the case-control or the reconstructed cohort study are, indeed, of the same order of magnitude.

Two studies, one conducted within PanScan and the other one in a Swedish family registry have also reported that FH of some cancer types increase PC risk.19,23 Likewise, relatives of PC cases seem to have a higher risk of developing other cancers.40,41 We confirm a positive association between FHC and FH of prostate, colorectal, breast&ovary, and smoking-related cancers with PC risk, while we lacked sample size to provide risk estimates for other less frequent cancer types. Previous studies exploring these associations did not view FH of other cancers, of which some seem to contribute to PC risk, as a separate category. In fact, risk of PC considerably dropped for FH of some of these cancer sites if the reference category included positive FH of other cancers. These potential associations between FH of these cancers and PC risk may signal underlying genetic and/or common environmental risk factors leading to familial aggregation of these cancers together with PC. Familial aggregation of cancer was confirmed in our reconstructed cohort study, too. The positive association between FH of prostate cancer and PC risk was reported earlier (OR=1.45, 95%CI 1.12–1.89),23 as well as that of the other cancer sites,19 supporting that certain cancer types in the family increase susceptibility to develop PC. Known mutations in several high-penetrance genes (i.e. BRCA2, PALB2, p16/CDKN2A and others) as well as newly identified genetic variants have been all linked to familial PC and the cancers aforementioned.42,43

Unlike most studies,8 we addressed the importance of environmental factors on the association between FHC with PC risk by adjusting risk estimates for smoking or other factors. Indeed, smoking was in our study the variable influencing most the risk estimates. In exploring deeper the role of smoking in familial PC, we observed a considerably higher excess of PC risk in smokers with positive FHPC. A significantly higher PC risk among smokers with >2 FDR affected of PC was also reported in other studies,14,20 though not so by others.22 The lack of an interaction between FHPC and smoking in the cohort design, whereby the smoking status of relatives at an individual basis was accounted for, could be explained by several reasons including the fact that our study may have been underpowered to show differences between the groups, but also the multiple subgroup analyses undertaken. Also, reported data of the relatives´ smoking status might be inaccurate. Another issue is the potential loss to follow-up biasing effect on our risk estimates that may have arisen. Indeed, even though we reached acceptable follow-up rates (89%),44 relatives of the cases and controls who were excluded may have introduced bias.

Our results on the association between FHD and PC risk are in agreement with those reported within the PACIFIC study (OR=1.37; 95%CI: 1.10–1.71),28 as well as at the population level in Sweden (SIR=2.98; 95%CI: 2.85-3.11).27 To date, diabetes genetic susceptibility variants associated with PC risk have not been identified,45,46 but their existence is plausible due to the well-established link between diabetes and PC risk.

There are some limitations in our study to note. As in any other study addressing FH in relation to cancer risk, an issue of concern is the reliability of the information on disease occurrence in the family reported by the subjects. While the information on FH reported by cases and controls were not verified, self-reported FHC data seems to be reliable either regarding common malignancies ,47 or rarer cancers such as pancreatic cancer.48 Self-reported FHD can be regarded as reliable, too.49 Besides, the pattern of missing data for the FH variables was alike in cases and controls. Irrespective of these facts, misclassification of the exposure cannot be discarded. Also, we cannot preclude the possibility of having included benign tumors or metastatic sites as primary cancer. Occurrence of multiple primary cancers as a consequence of treatment or genetic and non-genetic factors triggering first and subsequent cancers is another consideration to be taken into account. Our sensitivity analyses and the procedures adopted support that these circumstances should not have affected our results.

There are also several strengths of this study worth noting. This is the first large case–control study addressing the association between FHC, FHPC and FH of pancreatic cancer-related diseases with PC risk. Another outstanding feature is the two different approaches used to evaluate and cross-check the associations. Our study is also the first exploring these associations considering characteristics of the cases and controls and relatives thereof, ruling out bias due to unmeasured confounding. Together, our findings call for research to advance our understanding about how to lessen PC risk in groups at higher risk of developing the disease, among which FHPC represents an important part of the disease spectrum. Importantly, FHD may have a role to play in this regard. Characterizing genetic susceptibility variants contributing to FPC and environmental factors triggering the disease is of utmost importance to define efficient prevention actions.50,51

In conclusion, we confirm that FHPC is associated with an increased PC risk among FDRs. Our results also suggest that FHC and FHD increases susceptibility to develop PC. Further research and evaluation of PC risk associated with FH of diseases should be undertaken to guide prevention strategies in families at higher risk of PC.

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**Tables:**

**Table 1:** Odds Ratios and 95% confidence intervals (CIs) of PC associated with family history (FH) of cancer overall, FH of pancreatic cancer (FHPC) and FH of other cancer types.

**Table 2:** Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer associated with family history (FH) of other medical conditions (diabetes, asthma, allergies, cystic fibrosis, and chronic pancreatitis).

**Table 3:** Odds Ratios and 95% confidence intervals (CIs) of PC associated with family history (FH) of several cancers according to the smoking status (never and ever-smokers) of the subject.

**Figures:**

**Figure 1:** Cumulative risk of cancer and cancer types including PC comparing case-relatives and control-relatives.

In all panels, black lines show the data based on case-relatives whereas the grey lines that of the control-relatives. P-values corresponding to log-rank tests comparing survival curves and cumulative risks to age 75 years are indicated in shaded boxes, along with Hazard Ratios (HR) and 95% confidence intervals (CIs) of PC associated with familial aggregation of cancer for case-relatives versus control-relatives.

**Supplemental Material:**

**Supplemental Annex**: PanGenEU centres and investigators.

**Supplemental Methods**: Additional information on study design and statistical analyses.

**Supplemental Table 1:** Missingness of main variables and results of imputation performance.

**Supplemental Table 2:** Baseline characteristics of the 1,431 cases and 1,090 controls of the PanGenEU study, and that of their corresponding relatives within the cohort study analytic sample.

**Supplemental Table 3**: Sensitivity analyses regarding PC risk associated with FH of cancer overall and by cancer sites. Case-control approach.

**Supplemental Table 4**: Odds Ratios and 95% confidence intervals (CIs) of PC associated with familial history (FH) of several cancers according to the smoking status (never, former and current smokers) of the subject.

**Supplemental Table 5:** Association between PC risk and Family History (FH) of Cancer, FH of pancreatic cancer (FHPC) and FH of Diabetes (FHD) with by cases´ tumor stage and location.

**Supplemental Table 6:** Counts regarding relatives included and excluded from the analytical samples in the cohort study.

**Supplemental Table 7:** Hazard Ratios (HR) and 95% confidence intervals (CIs) of PC associated with familial aggregation of cancer overall and by cancer types.

**Supplemental Table 8**: Sensitivity analyses regarding PC risk associated with FH of cancer overall and by cancer sites. Cohort approach.

**Supplementary Figure 1:** Odd ratios for the joint effect of FHC / FHPC and smoking on PC risk. Case-control approach.

**Table 1**: Odds Ratios and 95% confidence intervals (CIs) of PDAC associated with family history (FH) of cancer overall, FH of pancreatic cancer (FHPC) and FH of other cancer types.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cases (%)** | **Controls (%)** | **Model 1****OR (95 % CI)** | **Model 2****OR (95 % CI)** | **Model 3****OR (95 % CI)** |
| ***FH Cancer (FHC)*** |
| No (-) FHC | 552 (38.6) | 481 (44.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) FHC | 879 (61.4) | 609 (55.9) | 1.27 (1.10-1.49) | 1.29 (1.12-1.52) | 1.30 (1.13-1.54) |
| ***Age at earliest cancer diagnosis in relatives***  |
| No (-) FHC | 552 (38.6) | 481 (44.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| < 50 years | 126 (8.8) | 94 (8.6) | 1.20 (0.89-1.62) | 1.16 (0.84-1.58) | 1.16 (0.85-1.59) |
| ≥ 50 years | 753 (52.6) | 515 (47.2) | 1.27 (1.10-1.51) | 1.30 (1.13-1.55) | 1.32 (1.14-1.58) |
| ***Number of affected relatives with cancer***  |   |   |   |
| No (-) FHC | 552 (38.5) | 481 (44.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| 1 FDR | 536 (37.5) | 380 (34.9) | 1.24 (1.05-1.49) | 1.25 (1.06-1.51) | * 1. (1.07-1.52)
 |
| ≥ 2 FDRs | 343 (23.9) | 229 (21.0) | 1.32 (1.10-1.63) | 1.34 (1.12-1.68) | 1.37 (1.15-1.72) |
|  |  |  |  |  | *p-trend: 0.003* |
| ***FHC in Parents*** |   |   |   |   |
| No (-) FHC | 830 (58.0) | 667 (61.2) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 601 (42.0) | 423 (38.8) | 1.11 (0.94-1.31) | 1.14 (0.97-1.35) | 1.14 (0.98-1.35) |
| ***FHC in Siblings*** |   |   |   |   |
| No (-) FHC | 1020 (71.3) | 814 (74.7) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 411 (28.7) | 276 (25.3) | 1.28 (1.09-1.54) | 1.28 (1.09-1.55) | 1.32 (1.12-1.61) |
| ***FHC in Offspring*** |   |   |   |   |
| No (-) FHC | 1369 (95.7) | 1044 (95.8) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 62 (4.3) | 46 (4.2) | 1.02 (0.62-1.54) | 1.05 (0.64-1.59) | 1.06 (0.65-1.60) |
| ***FH Risk Score1*** |   |   |   |   |   |
| No (-) FHC | 552 (38.5) | 481 (44.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| 1-2 | 751 (52.5) | 528 (48.4) | 1.23 (1.06-1.46) | 1.25 (1.08-1.48) | 1.26 (1.08-1.50) |
| 3-4 | 91 (6.3) | 62 (5.7) | 1.30 (0.94-1.86) | 1.36 (0.99-1.96) | 1.39 (1.02-2.03) |
| 5-6 | 13 (0.9) | 6 (0.6) | 2.08 (1.08-5.70) | 2.41 (1.41-6.53) | 2.45 (1.46-6.66) |
|  |  |  |  |  | *p-trend: 0.002* |
| ***FH Pancreatic Cancer*** |  |  |  |  |  |
| No (-) FHPC | 1327 (92.7) | 1054 (96.7) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) FHPC | 104 (7.3) | 36 (3.3) | 2.39 (1.99-3.56) | 2.39 (1.99-3.58) | 2.40 (2.00-3.59) |
| ***FH Pancreatic Cancer*** |  |  |  |  |  |
| No (-) FHC | 552 (38.6) | 481 (44.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) FHPC | 104 (7.3) | 36 (3.3) | 2.63 (2.22-3.96) | 2.65 (2.24-4.01) | 2.68 (2.27-4.06) |
| Yes (+) FH other cancers | 775 (54.1) | 573 (52.6) | 1.18 (1.01-1.40) | 1.20 (1.03-1.43) | 1.21 (1.04-1.44) |
| ***Age at PC diagnosis in relatives*** |
| *< 50 years* | 7 (0.5) | 3 (0.3) | 1.85 (0.43-7.62) | 1.97 (0.54-8.23) | 2.03 (0.60-8.52) |
| ≥ *50 years* | 97 (6.8) | 33 (3.0) | 2.70 (2.27-4.12) | 2.71 (2.28-4.16) | 2.74 (2.31-4.21) |
| ***Number affected relatives with PC*** |
| 1 FDR | 76 (5.3) | 30 (2.7) | 2.37 (1.92-3.73) | 2.41 (1.96-3.81) | 2.43 (1.97-3.84) |
| ≥ 2 FDRs (FPC) | 28 (1.9) | 6 (0.6) | 3.86 (2.95-9.57) | 3.82 (2.90-9.55) | 3.88 (2.96-9.73) |
|  |  |  |  |  | *p-trend: 0.033* |
| ***Type of relative with PC*** |   |   |   |   |   |
| Yes (+) in Parents | 68 (5.7) | 21 (2.6) | 2.54 (2.02-4.22) | 2.65 (2.12-4.47) | 2.64 (2.12-4.47) |
| Yes (+) in Siblings | 59 (4.1) | 19 (1.7) | 2.77 (2.23-4.75) | 2.75 (2.20-4.75) | 2.83 (2.28-4.90) |
| Yes (+) in Offspring | 4 (0.3) | 1 (0.1) | 3.97(1.74-36.90) | 3.91 (1.70-35.81) | 3.95 (1.74-36.19) |
| ***FH of other cancer sites*** |
| Yes (+) FH colorectal  | 188 (13.1) | 130 (11.9) | 1.29 (1.03-1.68) | 1.27 (1.00-1.66) | 1.28 (1.01-1.68) |
| Yes (+) FH prostate | 102 (7.1) | 57 (5.2) | 1.53 (1.17-2.18) | 1.68 (1.32-2.41) | 1.71 (1.34-2.45) |
| Yes (+) FH breast & ovary | 169 (12.0) | 121 (11.2) | 1.27 (1.00-1.67) | 1.30 (1.03-1.72)  | 1.31 (1.03-1.73) |
| Yes (+) FH smoking-related  | 572 (40.0) | 376 (34.5) | 1.32 (1.13-1.58) | 1.33 (1.14-1.61) | 1.35 (1.15-1.63) |
| Yes (+) FH multiple primaries | 755 (52.8) | 497 (45.6) | 1.30 (1.13-1.54) | 1.33 (1.16-1.58) | 1.33 (1.16-1.58) |

|  |
| --- |
| Model 1: sex, age and country-adjusted Model 2: additionally adjusted for smoking in pack-years (non-smokers, and tertiles of pack-years for former and current smokers), BMI (normal weight, overweight, obesity), and self-reported diabetes status (no, yes ≤ 2 years, yes > 2 years since diagnosis of diabetes) Model 3: additionally adjusted for number of relatives (family size) Analytic sample size was based on 1,431 PDAC cases and 1,090 controls. Reference category is “negative FH of any cancer” for cancer overall and for every cancer site, unless stated otherwise. For site-specific analyses, we considered other cancers in a separate category; these results are not shown as they resemble those reported for FH of cancer overall.  P-value for trends across strata was evaluated by fitting linear models. 1 Composite score variable calculated by summing up points that were assigned proportionally to the number of affected FDRs in each type of relative: 2 points if there were more than 2 FDRs affected, 1 point if there was 1 FDR affected and 0 points if there was not any FDR affected. The score ranged from 0 to 6 points. |

**Table 2**: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer associated with family history (FH) of other medical conditions (diabetes, asthma, allergies, cystic fibrosis, and chronic pancreatitis).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cases (%) | Controls (%) | Model 1 OR (95% CI) | Model 2OR (95% CI) | Model 3OR (95% CI) |
| FH Diabetes (FHD)¶ ¥ |
| No (-) | 828 (65.8) | 557 (69.6) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 430 (34.2) | 243 (30.4) | 1.28 (1.05-1.56) | 1.25 (1.02-1.52) | 1.24 (1.01-1.52) |
| *Age at diabetes diagnosis in relatives* |
| No (-) | 828 (65.8) | 557 (69.6) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) in youth | 29 (2.3) | 29 (3.6) | 0.69 (0.16-1.18) | 0.70 (0.16-1.20) | 0.69 (0.16-1.19)  |
| Yes (+) in adulthood | 401 (31.9) | 214 (26.7) | 1.30 (1.10-1.59) | 1.27 (1.06-1.55)  | 1.26 (1.06-1.55) |
| *Number of affected relatives with diabetes* |
| No (-) | 828 (65.8) | 557 (69.6) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) in 1 FDR | 309 (24.5) | 174 (21.8) | 1.22 (1.01-1.52) | 1.18 (0.96-1.47) | 1.18 (0.96-1.47) |
| Yes (+) in ≥ 2 FDRs | 121 (9.7) | 69 (8.6) | 1.25 (0.93-1.71) | 1.24 (0.93-1.72) | 1.24 (0.92-1.71)  |
|  |  |  |  |  | *p-trend:0.082* |
| FHD in Parents |
| No (-) | 952 (75.7) | 630 (78.8) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+)  | 306 (24.3) | 170 (21.2) | 1.22 (0.99-1.52) | 1.17 (0.95-1.47) | 1.17 (0.94-1.47) |
| FHD in Siblings |
| No (-) | 1076 (85.5) | 699 (87.4) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 182 (14.5) | 101 (12.6) | 1.23 (0.96-1.60) | 1.20 (0.92-1.56) | 1.19 (0.91-1.57) |
| FHD in Offspring |
| No (-) | 1219 (96.9) | 779 (97.4) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 39 (3.1) | 21 (2.6) | 1.26 (0.71-2.17) | 1.29 (0.73-2.24) | 1.28 (0.72-2.23) |
| Diabetes Risk Score1 |
| No (-) | 828 (65.8) | 557 (69.6) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| 1-2 | 338 (26.8) | 196 (24.5) | 1.18 (0.96-1.45) | 1.14 (0.92-1.41) | 1.13 (0.92-1.40) |
| 3-4 | 87 (6.9) | 45 (5.6) | 1.37 (1.11-1.69) | 1.33 (1.08-1.65) | 1.31 (1.06-1.61) |
| 5-6 | 5 (0.4) | 2 (0.3) | 1.87 (1.52-2.31) | 1.55 (1.25-1.91) | 1.51 (1.22-1.87) |
|  |  |  |  |  | *p-trend:<0.001* |
| *FH Asthma (FHAS)* ¶ |
| No (-) | 954 (75.8) | 623 (77.9) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 304 (24.2) | 177 (22.1) | 1.11 (0.89-1.37) | 1.07 (0.84-1.33) | 1.06 (0.84-1.33) |
| FH Allergies (FHAL) ¶ |
| No (-) | 869 (69.1) | 569 (71.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 389 (30.9) | 231 (28.9) | 1.11 (0.91-1.35) | 1.06 (0.86-1.30) | 1.06 (0.95-1.30) |
| FH Cystic Fibrosis (FHCF) ¶ |
| No (-) | 1244 (98.9) | 793 (99.1) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 14 (1.1) | 7 (0.9) | 1.28 (0.36-3.23) | 1.41 (0.47-3.60) | 1.40 (0.47-3.58) |
| FH Chronic Pancreatitis (FHCP)π |
| No (-) | 1382 (96.6) | 1057 (97.0) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Yes (+) | 49 (3.4) | 33 (3.0) | 1.19 (0.73-1.90) | 1.04 (0.56-1.69) | 1.05 (0.57-1.71) |
| Model 1: sex-age and country-adjusted ORs.Model 2: additionally adjusted for smoking in pack-years (non-smokers-and tertiles of pack-years for former and current smokers), BMI (normal weight, overweight, obesity), family history of pancreatic cancer (no, yes, other cancer). Model 3: additionally adjusted for number of relatives (family size). P-value for trends across strata was evaluated by fitting linear models.¥ Multivariate-adjusted ORs included the same covariates except self-reported diabetes status. ¶ Analytic sample was based on 1,258 PDAC cases and 800 controls. π Analytic sample was based on 1,431 PDAC cases and 1,090 controls. 1 Composite score variable calculated by summing up points that were assigned proportionally to the number of affected FDRs in each type of relative: 2 points if there were more than 2 FDRs affected, 1 point if there was 1 FDR affected and 0 points if there was not any FDR affected. The score ranged from 0 to 6 points. |

**Table 3:** Odds Ratios and 95% confidence intervals (CIs) of PDAC associated with family history (FH) of several cancers according to the smoking status (never and ever-smokers) of the subject.

|  |  |  |
| --- | --- | --- |
| FH of Cancer | *Never smokers* | *Ever smokers* |
|  | **Cases (%)****N=573** | **Controls (%)****N=535** | **OR (95% CI)¥** | **Cases (%)****N=858** | **Controls (%)****N=555** | **OR (95% CI)¥** |
| No (-) FH Cancer | 204 (35.6) | 246 (46.0) | 1.00 (Ref.) | 348 (40.5) | 235 (42.3) | 1.00 (Ref.) |
| Yes (+) FH Cancer | 369 (64.4) | 289 (54.0) | 1.51 (1.25-1.95) | 510 (59.5) | 320 (57.7) | 1.10 (0.87-1.38) |
|  |  |  | *p for heterogeneity: 0.061* |
| Yes (+) FHPC (any relative) | 40 (7.0) | 21 (4.0) | 2.25 (1.67-4.04) | 64 (7.5) | 15 (2.7) | 3.16 (2.56-5.78) |
|  |  |  | *p for heterogeneity: 0.039* |
| Yes (+) FHPC in ≥ 2 FDRs  | 6 (1.0) | 3 (0.6) | 2.30 (0.84-9.90) | 22 (2.6) | 3 (0.5) | 5.41 (4.16-18.77) |
| Yes (+) FHPC in 1 FDR  | 34 (6.0) | 18 (3.4) | 2.25 (1.62-4.20) | 42 (4.9) | 12 (2.2) | 2.61 (1.93-5.16) |
|  |  |  | *p for heterogeneity:* 0.060 |
| Yes (+) FHC breast & ovarian  | 69 (12.0) | 51 (9.5) | 1.72 (1.30-2.65) | 100 (11.7) | 70 (12.6) | 1.00 (0.64-1.44) |
|  |  |  | *p for heterogeneity:* 0.060 |
| Yes (+) FHC colorectal  | 92 (16.1) | 59 (11.0) | 1.84 (1.44-2.74) | 96 (11.3) | 71 (12.8) | 0.91 (0.52-1.28) |
|  |  |  | *p for heterogeneity:* 0.035 |
| Yes (+) FHC prostate  | 41 (7.2) | 30 (5.6) | 1.68 (1.15-2.85) | 61 (7.1) | 27 (4.9) | 1.62 (1.13-2.67) |
|  |  |  | *p for heterogeneity:* 0.122 |
| Yes (+) FHC smoking-related  | 247 (43.1) | 178 (33.3) | 1.62 (1.33-2.14) | 325 (38.0) | 198 (35.7) | 1.10 (0.84-1.42) |
|  |  |  | *p for heterogeneity:* 0.076 |
| Yes (+) FHC multiple-primaries  | 307 (53.8) | 235 (43.9) | 1.62 (1.33-2.16) | 1.10 (0.84-1.42) |  |
|  |  |  | *p for heterogeneity:* 0.061 |

¥ Multivariate-adjusted OR for sex, age and country, BMI (normal weight, overweight, obesity), self-reported diabetes status (no, yes ≤ 2 years, yes > 2 years since diagnosis of diabetes) and number of relatives.

Ever smokers includes those who smoke at least one cigarette per week for six months or longer, including former smokers.

NA = not applicable

Reference category is “negative FH of any cancer” for cancer overall and for every cancer site. For site-specific analyses, we considered other cancers in a separate category; these results are not shown as they resemble those reported for FH of cancer overall.

Figure 1

