Risk of pancreatic cancer associated with family history of cancer and other medical conditions by accounting for smoking among relatives

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1 Figure

Supplementary Material

List of abbreviations:

PC: Pancreatic cancer

BMI: Body mass index

FDR: First-degree relative

FH: Family history

FHC: Family history of cancer

FHPC: Family history of pancreatic cancer

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

FHCP: Family history of chronic pancreatitis

OR: Odds ratio

HR: Hazard ratio

CI: Confidence interval

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

Abstract

Background: Family history (FH) of pancreatic cancer (PC) has been associated with an increased risk of PC but little is known regarding the role of inherited/environmental factors or that of FH of other co-morbidities in PC risk. We aimed to address these issues using multiple methodological approaches.

Methods: Case-control study including 1,431 PC cases and 1,090 controls and a reconstructed-cohort study (N=16,747) made up of their first-degree relatives (FDR). Logistic regression was used to evaluate PC risk associated with FH of cancer, diabetes, allergies, asthma, cystic fibrosis and chronic pancreatitis by relative type and number of affected relatives, by smoking status and other potential effect modifiers, and by tumour stage and location. Familial aggregation of cancer was assessed within the cohort using Cox proportional-hazard regression.

Results: FH of PC was associated with an increased PC risk (OR=2.68; 95%CI: 2.27–4.06) when compared to 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 FHPC*smoking *p-value*=0.04). PC cumulative risk by age 75 was 2.2% among FDRs of cases and 0.7% in those of controls (HR=2.42; 95%CI: 2.16-2.71). PC risk was significantly associated with FH of 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: The concordant findings using both approaches strengthen the notion that FH of cancer, PC or diabetes confer a higher PC risk. Smoking notably increases PC risk associated with FH of PC. Further evaluation of these associations should be undertaken to guide PC prevention strategies.

KEY MESSAGE (characters: 363)

1. Complementary analytical approaches confirm that, regardless of non-genetic risk factors, risk of pancreatic cancer is by about two-and-a-half times higher among family members with more than two relatives affected with this disease, with this risk becoming stronger in current smokers.
2. Family history of any cancer and of selected cancer types (e.g. prostate, multiple primaries, or the smoking-related ones) also confers higher risk of pancreatic cancer.
3. Family history of diabetes mellitus is associated with a moderately increased risk of pancreatic cancer, mainly for advanced-stage tumours.
4. The incorporation of detailed information on family history of pancreatic cancer and other related-medical conditions into risk prediction models will help to identify subgroups of the population among whom routine screening and surveillance programs could be considered in an effective and optimal way.

Introduction

Pancreatic cancer (PC) remains the cancer with the lowest five-year survival rate (<7%).[1,2] PC risk/protective factors include a constellation of medical conditions, such as diabetes, chronic pancreatitis, obesity, allergies and asthma, some lifestyle-related factors (smoking and heavy alcohol intake), non-O blood group, and family history (FH) of PC.[3] Several of these medical conditions, as well as PC, may share inherited genetic factors but their relationships and interactions have largely not been explored.

As many as 10% of all PCs are aggregated in families.[4] Familial pancreatic cancer is defined as two or more first-degree relatives (FDRs) affected with PC that do not meet any known cancer syndrome criteria. It is the largest (80%) FHPC group and genetic susceptibility explains less than 15% of the PC familial clustering, owing to the genetic heterogeneity of this disease.[5]

Findings from several epidemiological studies, including a meta-analysis of nine studies,[6] support that FHPC confers an increased PC risk among FDRs.[7–15] However, there is variability on the reported risk estimates despite all attempts to assess PC risk associated with FHPC.

In addition to PC, familial aggregation of other cancers, such as colorectal and breast, has been shown to be associated with an increased PC risk.[8,10,12,14] Mutations in genes responsible for hereditary cancer syndromes (i.e., BRCA1/2) may partly explain these associations.[4]

There is a need to better characterize the associations aforementioned to deepen our understanding on the underlying mechanisms of pancreas carcinogenesis. The current state of knowledge is, indeed, limited owing to drawbacks of earlier studies assessing familial-associated PC risk. Their reported differences in risk estimates are likely attributable to the inappropriate assessment of lifetime risks of PC among relatives.[16,17] Concerns have also been raised regarding failure to adjust for smoking or other potential confounders.[6] Non-genetic risk factors shared in the family environment may, indeed, contribute to familial cancer aggregation. Furthermore, given that several of the non-cancer co-morbidities associated with PC also present a heritable component,[18]

it would be important to explore the contribution of the latter to the risk of PC. Their impact on the development of specific PC phenotypes is another under-investigated subject. Until now, only two studies have addressed the association between FH of diabetes (FHD) and PC risk.[19,20] While these studies showed that FHD implies a greater PC risk, they also encountered several types of bias, casting doubt upon the reliability of these previous findings.

Our aim was to comprehensively assess these issues within the largest and most informative study of PC conducted to-date, which enabled us to perform a case-control study and to apply other novel design approaches, such as reconstructed relative cohort assessments.

Methods

Study population:

The European Study into Digestive Illnesses and Genetics (PanGenEU) is a large multicentric case-control study that was initiated in 2009 in six European countries (Spain, Italy, Germany, United Kingdom, Sweden and Ireland) to identify relevant risk factors of PC including lifestyle and environmental factors, biomarkers of exposure to these factors, and genetic factors. All potential eligible PC cases were recruited to overcome selection bias attributable to the rapid progression of the disease. Diagnosis of all included cases was verified thereafter through review of medical records. Eligible controls were subjects free of PC and of any conditions related to known PC risk factors. The final analytic sample comprised 1,431 cases and 1,090 controls with information available on FH of cancer and FH of chronic pancreatitis, and 1,258 cases and 800 controls with information available on FH of the remaining diseases. Data from Italy was excluded beforehand because no data was available for Italian controls.
All subjects provided written informed consent and the study was approved by the Ethical Committees of the participating centers. More details are provided in Supplementary Methods.

Data collection of FH and other variables:

All participating centers applied the same recruitment protocols and questionnaires. 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. For FDRs with FHC additional information about the cancer sites and age at every cancer diagnosis was gathered (Supplementary Methods). Information on age at diagnosis was also collected for FDRs with diabetes (in categories: childhood/youth and adulthood). Cases and controls were also inquired about the vital status of every FDR, their current age (or age at death) and whether they had ever smoked.

FH variables of these diseases were derived, along with variables by relative type and number of affected relatives. Composite score variables that combined number and type of relatives affected with the disease were also obtained. For FHC and FHD we also considered occurrence of either early or late-onset disease in relatives.

Cases and controls also provided information about exposures to PC known and suspected risk factors (Supplementary Methods). In addition, clinical data of the tumors were collected for a subset of PC cases (n=504).

Statistical analysis:

Two approaches were carried out to explore the association between FH of the diseases and 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 PC risk associated with a positive FH (*versus* a negative FH) of cancer and other diseases. ORs were obtained for each FH variable. Potential confounding variables evaluated were: age (continuous), sex (female, male), country (Spain, Italy, Germany, United Kingdom, Sweden, and Ireland), smoking status (non-smokers and tertiles of pack-years for former and current smokers), BMI (normal weight - <25 kg/m^2, overweight - ≥25-30 kg/m^2, obesity - ≥30 kg/m^2), and self-reported diabetes status (no, yes ≤ 2 years, yes > 2 years since diagnosis of diabetes),

educational level (< 5, 5 to 10, 11 to 13, > 14 years of education), asthma (no, yes), chronic pancreatitis (no, yes), nasal and skin allergies (no, yes), as well as FHPC (no, yes, FH of other cancers). These variables were added to age, sex and country adjusted models (Model 1). Variables changing the OR in more than 10% (BMI, diabetes and FHPC) were retained (Model 2). We additionally controlled for the number of relatives to account for the effect of family size, a major issue in family-based studies,[16] in a separate model (Model 3).

Effect modification by country, smoking (never, former, current), diabetes (yes, no), BMI (normal, overweight and obesity), sex and age at cancer diagnosis (<50, ≥50 years), as well as FHPC and FHD, was evaluated by comparing models with and without an interaction term between these variables and FH by means of the likelihood ratio test (LHR) statistic.

Heterogeneity by country was evidenced and random effects for country were therefore considered in mixed models.[21] We also examined whether the associations varied by stage and location of the tumor, using the same control population for each strata.

2) *Reconstructed-cohort study.* For each case- and control-relative we calculated follow-up time as the time elapsed between birth (age=0) and the end of follow-up, defined by the reported age at cancer diagnosis, age at death or age at the interview date, whichever came first. Cumulative risks of cancer were calculated for both case-relatives and control-relatives cohorts using the Nelson-Aalen method and differences were evaluated with the log-rank test.[22] 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.[23] In addition, we accounted for heterogeneity by country by using a frailty for this variable in the model.[24] 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.

For both approaches we conducted sensitivity analyses including generalized estimating equation (GEE) regression[23] to ensure the robustness of our results (Supplementary Methods). We handled imputation of missing data (Supplementary Methods and Supplemental Table 1) with the random forest algorithm.[25] Assumptions of logistic regression analyses were met as indicated by the Hosmer-Lemeshow goodness-of-fit test.[26] The proportional hazards assumption was also met as indicated by the Schoenfield residuals plots of each covariate.[27]

Statistical software used for the data analysis was R 3.2.1.[28]

Results

Case-control approach

The study population characteristics are shown in Table 1. Cases were more frequently smokers and diabetics and had a smaller family size as compared to controls. The proportion of positive FHC, FHPC and of FHD was also higher among cases than in controls.

Risk estimates of PC associated with FHC and FH of other diseases are shown in Tables 2 and Table 3, 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 PC risk was more pronounced in parents and siblings, and in advanced-aged FDRs. PC risk also increased with increasing number of relatives with cancer (*p-trend*=0.003). Analyses by cancer site also revealed statistically significant associations with FHPC (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 $\geq$2 FDRs were affected with PC (Table 2).

FHD was associated with a 24% (95%CI: 1.01-1.52) higher PC risk, an effect that was mostly driven by adult-onset diabetes. The PC risk increased with the number of FDR affected with

diabetes (OR=1.51; 95%CI: 1.22-1.87). No significant associations with PC risk were encountered for the occurrence of other co-morbidities in the family, although prevalence of FHCF and FHCP was probably too low to derive precise estimates (Table 3). Overall, family size had a negligible impact on the risk estimates.

Risk of PC associated with FHPC was higher among ever-smokers (OR=3.16, 95%CI: 2.56-5.78, interaction *p-value*=0.04) (Supplemental Table 2) with current and former smokers with FHPC exhibiting an even higher PC risk with respect to never smokers without FHC (OR~5) (Supplemental Table 3, Supplemental Figure 1). Risk estimates remained the same in ever-smokers after additionally controlling for smoking intensity and duration (data not shown).

PC cases with >2 affected FDRs with PC were more likely to present early-stage tumours (Supplemental Table 4). Conversely, having a single FDR with PC was found to be associated with a significant increased risk of late-stage tumours (OR=2.36, 95%CI: 1.67-4.73). Further, risk of late-stage PC tended to be positive for those having a FHD, whereas the association turned inverse for early-stage tumours (OR=0.63, 95%CI: 0.17-0.99), with differences in risk estimates by stage being statistically significant (p=0.003).

We did not observe effect modification by location (Supplemental Table 4) or any other variable (data not shown). Risk estimates remained almost unchanged in sensitivity analyses (Supplemental Table 5).

Reconstructed-cohort approach

Two cohorts were reconstructed with a total of 9,055 case-relatives and 7,360 control-relatives contributing 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 Table 1. Case-relatives had been more frequently ever smokers than control-relatives. Aggregation of cancer events including PC was also higher in case-relatives.

The cumulative risk of cancer by 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). Corresponding risks for PC were 2.2% and 0.7%, respectively (HR=2.4, 95%CI: 2.16-2.71). HRs of similar magnitude were also observed for multiple primary cancers. Cancers of the breast & ovary, prostate and those regarded as smoking-related were also more likely to aggregate among case-relatives than control-relatives (HR=1.14, 1.66 and 1.24, respectively).

Interaction analyses by age, relative type and smoking were not statistically significant (Supplemental Table 6). There was a differing aggregational relationship between cancer and PC in case-relatives compared to control-relatives by diabetes status (*p-value* for interaction=0.03), which was not manifested in other cancer sites. Results were consistent across all sensitivity analyses conducted (Supplemental Table 7).

Discussion

In this study, we characterized PC risk associated with FH of cancer and PC-associated co-morbidities by applying, for the first time, two complementary strategies: a standard case-control study and a reconstructed-cohort approach to deal with potential bias due to differential relative´s lifetime risk between cases and controls. In addition, we considered the effect of smoking and other familial shared risk factors so as to better address the contribution of inherited versus environmental factors on the familial aggregation of the diseases. Our findings point to a 2.7-fold increased risk of PC associated with a positive FHPC. They also suggest a positive association between FHD and FH of certain cancer types with PC risk. The excess risks increased with the number of affected relatives, i.e., PC risk increased by nearly four times when ≥2 FDRs were affected with PC.

Existing evidence support that FHPC increases PC risk. Our risk estimates are close to those reported by a meta-analysis including 2,617 cases and 6,284 controls (OR=2.82; 95%CI:

1.99–3.66),[6] and other case-control studies,[14,15] but higher when compared with few other cohort-based studies.[11,12] Our finding that subjects with ≥2 FDRs with a PC diagnosis have a higher PC risk are consistent with other studies showing similar risk estimates,[11] but of lower magnitude with regard to that of Klein et al.[7] Also, PC risk was increased for late-onset cancer 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.[8,10,12]

Reasons for the varying risk estimates of PC associated with FHPC include issues inherent to study design. Criticism has been raised when using case-control studies to assess the association between FH and disease risk due to differences in the number of relatives among cases and controls leading to dissimilar age distributions and inadequate assessment of the relatives´ lifetime risk.[17,18] The reconstructed cohort strategy has been proposed as a better approach to evaluate FH as a risk factor of disease,[16] albeit both seem to be equally valid.[17] Comparable results were achieved in our study using both approaches, which reinforces the described associations.

Our findings suggest a positive association between FH of prostate, colorectal, breast & ovary, and smoking-related cancers with PC risk. Other studies have also reported that FH of some cancer types increase PC risk.[9,13,14] Likewise, relatives of PC cases seem to have a higher risk of developing other cancers.[29] Previous studies assessing these associations did not consider FH of other cancers, some of which seem to contribute to PC risk, as a separate risk category. In fact, risk of PC dropped in our study if the reference category included positive FH of other cancers (Table 1). The positive association between FH of prostate cancer and PC risk was reported earlier,[12] as well as that of the other cancer sites,[8] supporting that certain cancer types in the family increase susceptibility to develop PC. These potential associations between FHC and PC risk may signal underlying common genetic and/or environmental risk factors. Indeed, known mutations in several high-penetrance genes (e.g. BRCA2, PALB2, ATM, among others) as well as newly identified genetic variants have been all linked to familial PC and the aforementioned cancers.[5,28]

Exposure to smoking in the family environment seemed to not influence the association between FH and PC risk but whether sharing of other environmental exposures such as dietary habits or overweight/obesity would trigger PC remains an open question.

Unlike most previous studies,[6] we addressed the importance of environmental factors on the association between FHC with PC risk by adjusting risk estimates for smoking and other factors. We observed a higher excess risk of PC in smokers with FHPC, which was also reported in some,[6,10] but not all previous studies.[11] The lack of an interaction between FHPC and smoking in the cohort could be due to sample size issues, or the inaccurate reporting of the relatives´ smoking status. Loss to follow-up could be another issue despite the fact that we reached acceptable follow-up rates (89%).[31] Adjusting for diabetes had a modest impact on risk estimates and it did not modify the PC-risk effect in the case-control study.

Our results on the association between FHD and PC risk are in agreement with those of a case-control (OR=1.37; 95%CI: 1.10–1.71),[20] and a population-based study (SIR=2.98; 95%CI: 2.85-3.11).[19] While diabetes genetic susceptibility variants associated with PC risk have not been identified,[32] their existence is plausible due to the well-established link between diabetes and PC risk.[3]

Our study presents some limitations. While our estimates rely on self-reported disease occurrence in the family, this information seems to be reliable either regarding common malignancies, or pancreatic cancer,[33] as well as diabetes.[34] Irrespective of these facts, misclassification of the exposure cannot be discarded. Also, we cannot preclude the possibility of having included benign tumours or metastatic sites as primary cancers. Occurrence of multiple primary cancers as a consequence of previous cancer treatments or genetic and non-genetic factors triggering subsequent cancers is another consideration to be taken into account. Our sensitivity analyses and the procedures adopted, however, indicate that these circumstances should not have affected our results.

363 The study also has multiple strengths. This is the first large case–control study addressing
364 the association between FHC, FHPC and FH of non-cancer co-morbidities with PC risk. Another
365 outstanding feature is the two different approaches used to evaluate these associations. Our study
366 is also the first considering characteristics of the cases and controls and relatives thereof, ruling
367 out bias due to unmeasured confounding. In fact, characterizing these associations by accounting
368 for the contribution of environmental factors is of utmost importance to define PC prevention
369 actions. Equally important is to investigate clinical features of familial associated-PC in order to
370 foster the development of early detection strategies. For instance, our results point towards the
371 existence of different phenotypes in PC patients with FHD or FHPC.
372
373 In conclusion, we confirm using two independent analytical strategies that FHPC and FHC
374 are associated with an increased PC risk. Furthermore, we provide evidence that FHD is also
375 associated with a modest increase in PC risk. Together, our findings call for further research to
376 advance our understanding on how to reduce the PC burden in families at higher risk of PC.
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Table 2: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with family history (FH) of cancer overall, FH of pancreatic cancer (FHPC) and FH of other cancer types.

Table 3: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with family history (FH) of other medical conditions (diabetes, asthma, allergies, cystic fibrosis, and chronic pancreatitis).

Figure 1: Cumulative risk of cancer and cancer types including pancreatic cancer (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. Sex-specific cumulative risks are presented for prostate and ovarian&breast cancer.

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

Supplemental Table 3: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with familial history (FH) of several cancers according to the smoking status (never, former and current smokers) of the subject.

Supplemental Table 4: Association between pancreatic cancer (PC) risk and family history (FH) of cancer, FH of pancreatic cancer (FHPC) and FH of diabetes (FHD) by cases´ tumor stage and location.

Supplemental Table 5: Sensitivity analyses regarding PC risk associated with family history of cancer overall and by cancer sites. Case-control approach.

Supplemental Table 6: Hazard Ratios (HR) and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with familial aggregation of cancer overall and by cancer types. Cohort approach.

Supplemental Table 7: Sensitivity analyses regarding pancreatic cancer PC risk associated with family history (FH) of cancer overall and by cancer sites. Cohort approach.

Supplemental Figure 1: Odd ratios (OR) for the joint effect of FHC / FHPC and smoking on pancreatic cancer (PC) risk. Case-control approach. Multivariate-adjusted ORs with 95% confidence intervals (CI) for PC according to the combined effects of smoking status (never, former, current) and FHPC. Reference category deemed as never smokers without any FHC. ORs marked with asterisks (*) are statistically significant.

Table 1: Baseline characteristics of the 1,431 cases and 1,090 controls of the PanGenEU study, and that of their corresponding relatives.

Case-control approach	**Cases**	**Controls**	*p-value*[*]
Age, mean ± SD	65.4 ± 11.7	65.6 ± 13.1	0.74
Men, N (%)	809 (56.6)	569 (52.3)	0.03
Obese, BMI ≥ 30 kg/m^2, N (%)	292 (21.8)	218 (21.3)	0.96
Ever smokers, N (%)	858 (60.0)	555 (50.9)	<0.001
Number of cigarretes smoked, mean ± SD	25.3 ± 44.9	16.5 ± 30.3	<0.001
Diabetes, N (%)	362 (25.3)	140 (12.8)	<0.001
Asthma, N (%)	99 (7.2)	115 (10.8)	0.002
Atopic diseases, N (%)	265 (18.5)	293 (26.9)	0.001
Chronic pancreatitis, N (%)	9 (0.7)	1 (0.1)	0.05
Family size and characteristics [†]			
Number of relatives, mean (range)	6.1 (0-23)	6.5 (0-22)	0.01
Age of the father, mean ± SD	51.5 ± 14.9	51.8 ± 14.1	0.92
Father ever smoked, N (%)	928 (64.8)	726 (66.6)	0.91
Age of the mother, mean ± SD	59.1 ± 14.0)	58.6 ± 14.5	0.47
Mother ever smoked, N (%)	203 (14.2)	167 (15.3)	0.77
Number of siblings, mean (range)	4.1 (0-18)	4.4 (0-16)	0.01
Number of offspring, mean (range)	3.1 (0-11)	3.2 (0-14)	0.97
Cohort approach [¥]	**Case-relatives**	**Control-relatives**	*p-value*
Age, mean ± SD	57.0 ± 21.0	56.9 ± 21.2	0.90
Men, N (%)	4,671 (50.8)	3,794 (50.6)	0.88
Alive, N (%)	6,027 (65.9)	4,902 (66.2)	0.77
By relative type			0.05
Parents, N (%)	2,634 (28.5)	2,031 (27.0)	
Siblings, N (%)	3,855 (41.8)	3,285 (43.4)	
Offspring, N (%)	2,713 (29.4)	2,178 (29.0)	
Ever smokers, N (%)	5,494 (59.5)	3,820 (50.8)	<0.001
Diabetes, N (%) [#]	598 (8.1)	350 (7.6)	0.34
Asthma, N (%) [#]	387 (5.2)	220 (4.7)	0.26
Allergies, N (%) [#]	571 (7.8)	326 (7.1)	0.19
Cystic fibrosis, N (%) [#]	16 (0.2)	8 (0.2)	0.76
Chronic pancreatitis, N (%)	51 (0.6)	33 (0.5)	0.34
Cancer aggregation among relatives			
Cancer, N (%)	1,316 (15.7)	893 (13.2)	<0.001
Mean age at diagnosis ± SD	63.3 ± 28.7	63.5 ± 34.1	0.88
Mean follow-up in years ± SD	56.2 ± 20.8	56.2 (21.2)	0.96
Person-years	509,811	414,309	
PC, N (%)	107 (1.3)	35 (0.5)	<0.001
Mean age at diagnosis ± SD	67.0 ± 11.3	66.9 ± 14.1	0.96
Mean follow-up in years ± SD	57.0 ± 21.0	56.9 ± 21.2	0.99
Person-years	525,691	428,030	
Colorectal cancer, N (%)	214 (2.0)	151 (2.3)	0.43
Mean age at diagnosis ± SD	63.7 ± 11.7	65.8 ± 13.5	0.14

Mean follow-up in years ± SD	69.1 ± 12.1	69.6 (13.5)	0.70
Person-years	522,912	425,972	
Prostate cancer (men), N (%)	114 (1.2)	58 (0.8)	0.01
Mean age at diagnosis ± SD	69.6 ± 9.6	71.4 ± 9.2	0.30
Mean follow-up in years ± SD	74.6 ± 9.7	75.9 (9.4)	0.42
Person-years (men)	259,671	212,584	
Breast and ovarian cancer (women), N (%)	177 (1.9)	136 (1.8)	0.89
Mean age at diagnosis ± SD	57.36± 14.5	54.7 ± 14.6	0.11
Mean follow-up in years ± SD	65.6 ± 14.9	64.4 (15.0)	0.47
Person-years (women)	263,037	212,571	
Smoking-related cancers, N (%)	740 (8.0)	465 (6.2)	<0.001
Mean age at diagnosis ± SD	64.4 ± 12.9	65.0 ± 13.4	0.44
Mean follow-up in years ± SD	67.9 ± 12.9	68.3 (13.3)	0.67
Person-years	518,055	421,983	
Multiple primary cancers, N (%)	759 (8.2)	490 (6.5)	<0.001
Mean age at diagnosis ± SD	67.3 ± 34.3	68.0 ± 42.1	0.76
Mean follow-up in years ± SD	71.1 ± 13.6	71.1 (13.6)	0.50
Person-years	509,801	414,309	

*_p-values_* were based on Wilcoxon rank-sum test for continuous variables, and chi-squared test for categorical variables (two-sided).

†Family size count excluded the index case and control subject.
Age at the date of the interview. Age at death was considered for those FDRs who died before the interview.

Cases and controls from Ireland were excluded for analyses on FHD, FHAS, FHAL and FHCF; there were 1,258 cases and 800 controls available for these analyses.

The numbers do not sum up due to missing data.

531 **Table 2**: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with family
532 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	552 (38.6)	481 (44.1)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	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.)
FHC < 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)
FHC ≥ 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)	1.26 (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 in parents	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 in sibblings	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 in offspring	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 Score[1]					
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 (but FH other cancers)	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					
FHPC < *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)
FHPC ≥ *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 PC 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.

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536 **Table 3**: Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated with family
537 history (FH) of other medical conditions (diabetes, asthma, allergies, cystic fibrosis and chronic pancreatitis).

	Cases (%)	Controls (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (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 FHD	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 FHD	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 FHD	952 (75.7)	630 (78.8)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes in parents	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 FHD	1076 (85.5)	699 (87.4)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes in siblings	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 FHD	1219 (96.9)	779 (97.4)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes in offspring	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 Score[1]					
No FHD	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)¶					
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 PC cases and 800 controls.
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[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.

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