

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

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70 **Supplementary Material**

71

72 **List of abbreviations:**

73 PC: Pancreatic cancer

74 BMI: Body mass index

75 FDR: First-degree relative

76 FH: Family history

77 FHC: Family history of cancer

78 FHPC: Family history of pancreatic cancer

79 FPC: Familial pancreatic cancer

80 FHD: Family history of diabetes

81 FHAL: Family history of allergies

82 FHAS: Family history of asthma

83 FHCF: Family history of cystic fibrosis

84 FHCP: Family history of chronic pancreatitis

85 OR: Odds ratio

86 HR: Hazard ratio

87 CI: Confidence interval

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

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93 **Abstract**

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

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

105 **Results:** FH of PC was associated with an increased PC risk (OR=2.68; 95%CI: 2.27–4.06) when
106 compared to cancer-free FH, the risk being greater when ≥ 2 FDRs suffered PC (OR=3.88; 95%CI:
107 2.96-9.73) and among current-smokers (OR=3.16, 95%CI: 2.56-5.78, interaction FHPC*smoking
108 *p-value*=0.04). PC cumulative risk by age 75 was 2.2% among FDRs of cases and 0.7% in those
109 of controls (HR=2.42; 95%CI: 2.16-2.71). PC risk was significantly associated with FH of cancer
110 (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
111 diseases.

112 **Conclusion:** The concordant findings using both approaches strengthen the notion that FH of
113 cancer, PC or diabetes confer a higher PC risk. Smoking notably increases PC risk associated with
114 FH of PC. Further evaluation of these associations should be undertaken to guide PC prevention
115 strategies.

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118 **KEY MESSAGE** (characters: 363)

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

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132

133 **Introduction**

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

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

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

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

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

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

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

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167

168 **Methods**

169 *Study population:*

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

180 All subjects provided written informed consent and the study was approved by the Ethical
181 Committees of the participating centers. More details are provided in [Supplementary Methods](#).

182

183 *Data collection of FH and other variables:*

184 All participating centers applied the same recruitment protocols and questionnaires. Information on the
185 occurrence of diseases (cancer, diabetes, allergies, asthma, chronic pancreatitis and cystic
186 fibrosis) in FDRs of the cases and controls was collected through face-to-face interviews conducted
187 by trained monitors. For FDRs with FHC additional information about the cancer sites and age at
188 every cancer diagnosis was gathered ([Supplementary Methods](#)). Information on age at diagnosis
189 was also collected for FDRs with diabetes (in categories: childhood/youth and adulthood). Cases
190 and controls were also inquired about the vital status of every FDR, their current age (or age at
191 death) and whether they had ever smoked.

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

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

199

200 *Statistical analysis:*

201 Two approaches were carried out to explore the association between FH of the diseases and PC
202 risk ([Supplementary Methods](#)):

203 1) *Case-control study.* We used unconditional logistic regression to estimate odds ratios
204 (ORs) and 95% confidence intervals (CIs) corresponding to PC risk associated with a positive FH
205 (*versus* a negative FH) of cancer and other diseases. ORs were obtained for each FH variable.
206 Potential confounding variables evaluated were: age (continuous), sex (female, male), country (Spain, Italy,
207 Germany, United Kingdom, Sweden, and Ireland), smoking status (non-smokers and tertiles of pack-years
208 for former and current smokers), BMI (normal weight - <25 kg/m², overweight - ≥25-30 kg/m², obesity - ≥30
209 kg/m²), and self-reported diabetes status (no, yes ≤ 2 years, yes > 2 years since diagnosis of diabetes),

210 educational level (< 5, 5 to 10, 11 to 13, > 14 years of education), asthma (no, yes), chronic pancreatitis (no,
211 yes), nasal and skin allergies (no, yes), as well as FHPC (no, yes, FH of other cancers). These variables
212 were added to age, sex and country adjusted models (Model 1). Variables changing the OR in more than
213 10% (BMI, diabetes and FHPC) were retained (Model 2). We additionally controlled for the number of
214 relatives to account for the effect of family size, a major issue in family-based studies,¹⁶ in a separate model
215 (Model 3).

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

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

223 2) *Reconstructed-cohort study.* For each case- and control-relative we calculated follow-up
224 time as the time elapsed between birth (age=0) and the end of follow-up, defined by the reported
225 age at cancer diagnosis, age at death or age at the interview date, whichever came first. Cumulative
226 risks of cancer were calculated for both case-relatives and control-relatives cohorts using the
227 Nelson-Aalen method and differences were evaluated with the log-rank test.²² Cox proportional
228 hazard regression was used to obtain hazard ratios (HRs) and 95% CIs associated with cancer
229 occurrence (overall and by cancer types) for the case-relatives (*versus* the control-relatives),
230 stratified by sex, age (1-year intervals) and relative type, using for the latter a robust sandwich
231 estimate of the covariance matrix.²³ In addition, we accounted for heterogeneity by country by using
232 a frailty for this variable in the model.²⁴ Potential confounding and effect modification by other covariates
233 (the relatives' smoking status and occurrence of diseases, age, sex and the type of relative) was likewise
234 assessed by evaluating changes in the HR estimate above 10% and testing interaction via the LHR,
235 respectively.

236

237 For both approaches we conducted sensitivity analyses including generalized estimating equation
238 (GEE) regression²³ to ensure the robustness of our results (Supplementary Methods). We handled
239 imputation of missing data (Supplementary Methods and Supplemental Table 1) with the random
240 forest algorithm.²⁵ Assumptions of logistic regression analyses were met as indicated by the
241 Hosmer-Lemeshow goodness-of-fit test.²⁶ The proportional hazards assumption was also met as
242 indicated by the Schoenfeld residuals plots of each covariate.²⁷
243 Statistical software used for the data analysis was R 3.2.1.²⁸

244

245 **Results**

246 *Case-control approach*

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

250 Risk estimates of PC associated with FHC and FH of other diseases are shown in Tables
251 2 and Table 3, respectively. A statistically significant positive association was observed in
252 multivariate-adjusted models evaluating PC risk associated with a positive *versus* negative FHC
253 (OR=1.30, 95%CI: 1.13-1.54). This increased PC risk was more pronounced in parents and
254 siblings, and in advanced-aged FDRs. PC risk also increased with increasing number of relatives
255 with cancer (*p-trend*=0.003). Analyses by cancer site also revealed statistically significant
256 associations with FHPC (OR=2.68; 95%CI: 2.23-4.06), as well as for FH of breast & ovary,
257 colorectal, prostate and smoking-related cancers (OR=1.45; 1.27; 1.70; 1.34, respectively). The
258 trend of the association across types of relatives and number of affected relatives was similar to
259 that observed for FHC overall (data not shown). In particular, PC risk was nearly four-fold increased
260 (OR=3.88; 95%CI: 2.97-9.72) when ≥ 2 FDRs were affected with PC (Table 2).

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

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

267 Risk of PC associated with FHPC was higher among ever-smokers (OR=3.16, 95%CI:
268 2.56-5.78, interaction p -value=0.04) (Supplemental Table 2) with current and former smokers with
269 FHPC exhibiting an even higher PC risk with respect to never smokers without FHC (OR~5)
270 (Supplemental Table 3, Supplemental Figure 1). Risk estimates remained the same in ever-
271 smokers after additionally controlling for smoking intensity and duration (data not shown).

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

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

281

282 *Reconstructed-cohort approach*

283 Two cohorts were reconstructed with a total of 9,055 case-relatives and 7,360 control-relatives
284 contributing with 509,801 and 414,309 person-years to the cancer overall analyses (Supplemental
285 Tables 6 and 7). Characteristics of case-relatives and control-relatives are shown in Table 1. Case-
286 relatives had been more frequently ever smokers than control-relatives. Aggregation of cancer
287 events including PC was also higher in case-relatives.

288 The cumulative risk of cancer by age 75 was of 23.8% in case-relatives and 19.5% in
289 control-relatives (HR=1.16, 95%CI: 1.05-1.29) (Figure 1). Corresponding risks for PC were 2.2%
290 and 0.7%, respectively (HR=2.4, 95%CI: 2.16-2.71). HRs of similar magnitude were also observed
291 for multiple primary cancers. Cancers of the breast & ovary, prostate and those regarded as
292 smoking-related were also more likely to aggregate among case-relatives than control-relatives
293 (HR=1.14, 1.66 and 1.24, respectively).

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

299

300

301 Discussion

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

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

313 1.99–3.66),⁶ and other case-control studies,^{14,15} but higher when compared with few other cohort-
314 based studies.^{11,12} Our finding that subjects with ≥ 2 FDRs with a PC diagnosis have a higher PC
315 risk are consistent with other studies showing similar risk estimates,¹¹ but of lower magnitude with
316 regard to that of Klein et al.⁷ Also, PC risk was increased for late-onset cancer in FDRs. Fewer
317 cases and controls were available for analyses evaluating PC risk associated with early-onset
318 cancers in the family to confirm the stronger association reported in previous studies.^{8,10,12}

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

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

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

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

349 Our results on the association between FHD and PC risk are in agreement with those of a
350 case-control (OR=1.37; 95%CI: 1.10–1.71),²⁰ and a population-based study (SIR=2.98; 95%CI:
351 2.85-3.11).¹⁹ While diabetes genetic susceptibility variants associated with PC risk have not been
352 identified,³² their existence is plausible due to the well-established link between diabetes and PC
353 risk.³

354 Our study presents some limitations. While our estimates rely on self-reported disease
355 occurrence in the family, this information seems to be reliable either regarding common
356 malignancies, or pancreatic cancer,³³ as well as diabetes.³⁴ Irrespective of these facts,
357 misclassification of the exposure cannot be discarded. Also, we cannot preclude the possibility of
358 having included benign tumours or metastatic sites as primary cancers. Occurrence of multiple
359 primary cancers as a consequence of previous cancer treatments or genetic and non-genetic
360 factors triggering subsequent cancers is another consideration to be taken into account. Our
361 sensitivity analyses and the procedures adopted, however, indicate that these circumstances
362 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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474 **Table 2:** Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC) associated
475 with family history (FH) of cancer overall, FH of pancreatic cancer (FHPC) and FH of other cancer
476 types.

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

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482 **Figure 1:** Cumulative risk of cancer and cancer types including pancreatic cancer (PC) comparing
483 case-relatives and control-relatives. In all panels, black lines show the data based on case-relatives
484 whereas the grey lines that of the control-relatives. P-values corresponding to log-rank tests
485 comparing survival curves and cumulative risks to age 75 years are indicated in shaded boxes,
486 along with Hazard Ratios (HR) and 95% confidence intervals (CIs) of PC associated with familial
487 aggregation of cancer for case-relatives versus control-relatives. Sex-specific cumulative risks are
488 presented for prostate and ovarian&breast cancer.

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491 **Supplemental Material:**

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

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

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

495 **Supplemental Table 2.** Odds Ratios and 95% confidence intervals (CIs) of pancreatic cancer (PC)
496 associated with family history (FH) of several cancers according to the smoking status (never and
497 ever-smokers) of the subject.

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

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

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

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

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

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

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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 cigarettes 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 \pm SD	69.1 \pm 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 \pm SD	69.6 \pm 9.6	71.4 \pm 9.2	0.30
	Mean follow-up in years \pm SD	74.6 \pm 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 \pm SD	57.36 \pm 14.5	54.7 \pm 14.6	0.11
	Mean follow-up in years \pm SD	65.6 \pm 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 \pm SD	64.4 \pm 12.9	65.0 \pm 13.4	0.44
	Mean follow-up in years \pm SD	67.9 \pm 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 \pm SD	67.3 \pm 34.3	68.0 \pm 42.1	0.76
	Mean follow-up in years \pm SD	71.1 \pm 13.6	71.1 (13.6)	0.50
	Person-years	509,801	414,309	

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**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.

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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.

	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)
					<i>p-trend: 0.003</i>
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 siblings	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[†]					
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)
					<i>p-trend: 0.002</i>
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)
					<i>p-trend: 0.033</i>
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)
<i>FH of other cancer sites</i>					
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 \leq 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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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).

	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)
					<i>p-trend:0.082</i>
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 Score¹					
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)
					<i>p-trend:<0.001</i>
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.

π Analytic sample was based on 1,431 PC 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.