



**Pancreatic cancer risk in relation to lifetime smoking patterns, tobacco type, and dose-response relationships**

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| Keywords: | Pancreatic cancer risk, Smoking habit, Type of tobacco, Dose-response relationship, Case-control study  |
| Abstract: | <p>BACKGROUND: Despite smoking being a well-established risk factor for pancreatic cancer (PC), there is a need to further characterize the PC risk according to lifespan smoking patterns and other smoking features such as tobacco type. Our aim was to deeply investigate them within a large European case-control study.</p> <p>PATIENTS AND METHODS: Tobacco smoking habits and other relevant information was obtained from 2,009 cases and 1,532 controls recruited in the PanGenEU study using standardized tools. Multivariate logistic regression analysis was performed to evaluate PC risk by smoking characteristics and interactions with other PC risk factors. Fractional polynomials and restricted cubic splines were used to test for non-linearity of the dose-response relationships and to analyse their shape.</p> <p>RESULTS: Relative to never-smokers, current smokers (OR=1.72, 95%CI: 1.39-2.12), those inhaling into the throat (OR=1.48, 95%CI: 1.11-1.99), chest (OR=1.33, 95%CI: 1.12-1.58), or using non-filtered cigarettes (OR=1.69, 95%CI: 1.10-2.61), were all at an increased PC risk. PC risk was higher in current smokers of black tobacco (OR=2.08, 95%CI: 1.29-3.36). Childhood exposure to tobacco smoke from parental</p>  |

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|  | <p>smoking was also associated with increased PC risk (OR=1.24, 95%CI: 1.03-1.49). Dose-response relationships for smoking duration, intensity, cumulative dose, and smoking cessation were non-linear and showed different shapes by tobacco type. Effect modification were observed for family history of PC and diabetes status (p-value for interaction&lt;0.001). CONCLUSIONS: This study reveals differences in PC risk by tobacco type and other habit characteristics, as well as non-linear risk associations, emphasizing potential differences in the underlying mechanisms leading to PC.</p> |
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**Title:** Pancreatic cancer risk in relation to lifetime smoking patterns, tobacco type, and dose-response relationships

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## Abstract

BACKGROUND: Despite smoking being a well-established risk factor for pancreatic cancer (PC), there is a need to further characterize the PC risk according to lifespan smoking patterns and other smoking features such as tobacco type. Our aim was to deeply investigate them within a large European case-control study.

PATIENTS AND METHODS: Tobacco smoking habits and other relevant information was obtained from 2,009 cases and 1,532 controls recruited in the PanGenEU study using standardized tools. Multivariate logistic regression analysis was performed to evaluate PC risk by smoking characteristics and interactions with other PC risk factors. Fractional polynomials and restricted cubic splines were used to test for non-linearity of the dose-response relationships and to analyse their shape.

RESULTS: Relative to never-smokers, current smokers (OR=1.72, 95%CI: 1.39-2.12), those inhaling into the throat (OR=1.48, 95%CI: 1.11-1.99), chest (OR=1.33, 95%CI: 1.12-1.58), or using non-filtered cigarettes (OR=1.69, 95%CI: 1.10-2.61), were all at an increased PC risk. PC risk was higher in current smokers of black tobacco (OR=2.08, 95%CI: 1.29-3.36). Childhood exposure to tobacco smoke from parental smoking was also associated with increased PC risk (OR=1.24, 95%CI: 1.03-1.49). Dose-response relationships for smoking duration, intensity, cumulative dose, and smoking cessation were non-linear and showed different shapes by tobacco type. Effect modification were observed for family history of PC and diabetes status (p-value for interaction<0.001).

CONCLUSIONS: This study reveals differences in PC risk by tobacco type and other habit characteristics, as well as non-linear risk associations, emphasizing potential differences in the underlying mechanisms leading to PC.

**Key words:** Pancreatic cancer risk; Smoking habit; Type of tobacco; Dose-response relationship; Fractional polynomials; Restricted cubic splines; Case-control study.

**Key message:**

- This study sheds light on still unknown tobacco-related associations with pancreatic cancer risk. Differences in pancreatic cancer risk by tobacco type, as well as the non-linear risk associations by timing of the exposure, points to a complex multi-mechanism process underlying pancreatic carcinogenesis among smokers.

For Peer Review



## Introduction

Pancreatic cancer (PC) is one of the deadliest cancer types worldwide (5-year relative survival rate in the range 5-15%)[1], and within western countries[2]. It is estimated that 10-30% of all PC cases are caused by smoking[3]. However, a detailed characterization of tobacco smoking habits in relation to PC risk is still lacking. A meta-analysis including 10,490 cases and 526,813 controls, showed that being a current smoker, jointly with a longer smoking duration and a higher smoking intensity, was associated with an increase in PC risk[4]. However, the authors assumed a linear trend for PC risk associated with increasing smoking exposure, a fact disputed by *Zou et al.* in an updated analysis combining 9,044 cases and 32,039 controls showing a non-linear dose-response relationship (DRR) between several smoking features and PC risk[5]. A pooled analysis within the Pancreatic Cancer Case-Control Consortium (PanC4), including 6,507 cases and 12,890 controls, indicated that after a certain amount of smoking exposure PC risk levelled-off[6], shedding a different perspective on the DRR of smoking in relation to PC risk. In the aforementioned studies, an exploration of the shape of the association between smoking measures and PC risk was not further pursued.

Moreover, several aspects of tobacco smoking habits have not been considered until now. For instance, differences in PC risk by either black or blond tobacco use have not been explored despite the presumed differences in their chemical composition and damaging effects[7, 8]. In fact, several studies have shown that black tobacco is associated with higher risk of bladder[7], colorectal[9], oesophageal[10], and head-and-neck cancer[11, 12], than blond tobacco.

Therefore, we set out to investigate the association and DRR between tobacco smoking and PC risk in a large European population, considering every aspect of the smoking habit including use of black *versus* blond tobacco.

## Methods

### *Study design and participants*

Details of the study population are provided in supplementary methods and elsewhere[13, 14].

### *Variables*

Personal interviews were conducted by trained monitors using standardized protocols and questionnaires to obtain detailed information on lifetime smoking habits, among other PC risk factors. Information on smoking habits by tobacco type (only black, blond or both) was only collected in the Spanish centres. Further information is available in supplementary methods.

### *Statistical analysis*

Unconditional logistic regression analysis was performed to estimate odds ratios (OR) and 95% Confidence Intervals (95%CI). A comprehensive description of the model specifications is given in supplementary methods. The influence of confounding factors or effect modification on the association was assessed for several variables. Variables changing estimates by more than 10% or having a significant influence in the model (diabetes and family history of PC in some smoking-related variables) were considered as potential confounders. The le Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test indicated a high goodness of fit of the models[15]. Effect modification was assessed in interaction and stratified analyses. Additive interaction by time-related variables such as smoking duration was also evaluated by the relative excess risk due to interaction (RERI) and Delta-method CIs[16]. Imputation of missing values was performed using the Random Forest algorithm (R package missForest) (Supplementary methods and Supplementary Table 1). More information is provided in supplementary methods.

To assess the DRRs, PC risk estimates were calculated per 1-unit of increase in continuous smoking exposure variables considering linear and non-linear models if so indicated by fractional polynomials (FP) (R package mfp)[17]. In addition, restricted cubic splines (RCS) were used to confirm

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3 non-linear associations and for modelling the shape of the DRRs (R package splines)[18]. Non-linearity  
4 of the models was tested via the likelihood-ratio test comparing the model with and without RCS. Knots  
5 were set at the 10%, 50% and 90% percentile of the exposure distribution; comparable results were  
6 obtained with five knots[19]. Sensitivity analyses are described in supplementary methods. Specific  
7 analyses were devoted to RCS, which performance was assessed by additional smoothing, allowing  
8 more flexibility into the model[20].  
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12 The threshold for statistical significance in two-sided tests was set at  $p\text{-value} < 0.05$ . Data was  
13 analysed with R-project (version 3.4.1)[21].  
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## 18 19 20 21 22 23 24 25 26 **Results**

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28 PC cases (N=2,009) presented more frequently with a family history of PC and a diagnosis of  
29 diabetes or chronic pancreatitis than controls (N=1,532) (Supplementary Table 2).  
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33 The prevalence of smoking was higher in cases (27.4%) than in controls (17.6%), with a  
34 corresponding aOR of 1.72 (95%CI: 1.39-2.12) for current smokers compared to never-smokers (Table  
35 1 and Supplementary Table 3). Furthermore, a statistically significant increased trend ( $p\text{-value} < 0.001$ ) in  
36 PC risk was observed for longer smoking duration, higher smoking intensity and higher cumulative dose.  
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38 The use of non-filtered cigarettes increased risk of PC more prominently (aOR=1.69, 95%CI: 1.10-2.61),  
39 although use of filtered cigarettes was also associated with an increased PC risk (aOR=1.25, 95%CI:  
40 1.06-1.48). Marked increases in PC risk were also observed for inhalation into the throat (aOR=1.48,  
41 95%CI: 1.11-1.99) and chest (aOR=1.33, 95%CI: 1.12-1.58). Childhood exposure to ETS by smoking  
42 parents (vs. non-parental exposure) was associated with a 24% (95%CI: 1.03-1.49) increased PC risk.  
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44 Risk for former smokers decreased progressively with longer time since smoking cessation when  
45 compared to current smokers (aOR for 14-28 years after cessation=0.67, 95%CI: 0.51-0.88). No  
46 significant associations between PC risk and other smoking variables were observed (Supplementary  
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3 Table 4). Additional adjustment for diabetes and family history of PC led to minimal differences in risk  
4 estimates (Supplementary Table 4). Effect modification was apparent only for family history of PC and  
5 diabetes status (Supplementary Table 5), pointing towards a higher PC risk among current smokers with  
6 family history of the disease (aOR=2.24, 95%CI: 0.66-7.61) and former smokers with diabetes  
7 (aOR=1.44, 95%CI: 0.91-2.28) (p-value for interaction<0.001).  
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16 Table 1 also shows PC risk estimates by tobacco type in PanGenEU-Spain. Compared to never-  
17 smokers, PC risk was significantly increased for smokers of only black tobacco (aOR=1.55, 95%CI: 1.13-  
18 2.12) and of both tobacco types (aOR=1.58, 95%CI: 1.14-2.17). Among blond tobacco smokers, PC risk  
19 tended to be increased (aOR=1.23, 95%CI: 0.94-1.62), though without reaching statistical significance.  
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21 By smoking status, a significant increase in risk was observed for current smokers of only black tobacco  
22 (aOR=2.08, 95%CI 1.29 - 3.36). In combined effect analyses (Supplementary Table 6), smoking for ≥30  
23 years of both tobacco types was associated with a higher PC risk than smoking only black or blond  
24 tobacco (aOR=2.05, 95%CI: 1.25-3.36).  
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36 Adjusted FP models suggested non-linear associations and a statistically significantly higher PC  
37 risk per 1-unit increase in smoking duration, smoking intensity and cumulative dose, and decreasing PC  
38 risks for age at smoking initiation and time since smoking cessation (Supplementary Table 7). The RCS  
39 confirmed these non-linear associations. Compared to never-smokers, smoking for >25 years (Figure 1,  
40 A-B) and smoking >20 cigarettes/day (Figure 1, D-E) was associated with a statistically significant  
41 increase of PC risk. Similarly, a cumulative dose of >14 pack-years was associated with increased PC  
42 risk (Figure 1, C). Visual inspection for smoking intensity and cumulative dose was suggestive of  
43 plateauing of PC risk, at approximately 27 cigarettes/day or pack-years. Concerning time since smoking  
44 cessation (Figure 1, F-I), and relative to current smokers, risk appeared to decrease between 8 and 11  
45 years of cessation and after around 18 years of cessation regardless of cumulative dose. In between  
46 these periods, the significant effect disappeared. By tobacco type, corresponding periods of significant  
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3 decrease in PC risk were observed for black tobacco (after about 14 years since cessation) and for blond  
4 tobacco (between 2 and 8 years and after >20 years of cessation).  
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8 No relevant differences in the trend or magnitude of the estimates were found in sensitivity  
9 analyses (Supplementary Tables 8, 9, 10, and Supplementary Figure 1). In analyses adjusting for  
10 smoking intensity, risk estimates decreased in magnitude but showed a similar trend, even in black  
11 tobacco smokers despite being heavier smokers.(Supplementary Table 11). Importantly, adjustment for  
12 smoking duration led to non-significant risk estimates and change in the shape of the DRRs  
13 (Supplementary Table 12). Considering long-lasting smoking together with intense smoking increased  
14 PC risk, whereas for less intense smoking the association weakened (Supplementary Table 13).  
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## 28 Discussion

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30 The present study confirms that, in comparison to never-smokers, being a current smoker  
31 increases the risk of PC by 72%. In terms of attributable risk, around 16% (95%CI: 9.24-22.47) of all PC  
32 diagnoses could be avoided through tobacco preventive measures. A more detailed examination of  
33 smoking characteristics showed that the use of non-filtered cigarettes, deep inhalation into the throat or  
34 chest, and exposure to tobacco smoke in the parental household were all associated with increased PC  
35 risk. PC risk in black tobacco smokers was significantly higher compared to never-smokers, with blond  
36 tobacco smokers showing a less prominent risk pattern. Analysis of DRRs corroborated that a higher  
37 smoking intensity, longer smoking duration, and increased levels of cumulative dose were associated  
38 with an increased PC risk, whereas smoking cessation led to a gradual decline in PC risk, all in a non-  
39 linear manner.  
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54 Our results are concordant with earlier studies. Regarding the magnitude of PC risk associated  
55 with current versus never tobacco smoking, a meta-analysis and the PanC4 study showed similar  
56 estimates (RR=1.74, 95%CI: 1.61-1.87 and OR=2.20, 95%CI: 1.71-2.83, respectively)[4, 6]. Similarly,  
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3 our study confirmed the trends and timing of tobacco smoking[4, 6], the excess risk conferred by tobacco  
4 smoking[4], the non-linear tobacco-PC associations[5], and risk due to childhood ETS[22]. Compared  
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6 with studies restricting ETS exposure to never-smokers, we also did not observe significant risk estimates  
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8 (OR=1.24, 95%CI: 0.95-1.63)[23, 24]. In contrast to the positive association between current cigar/pipe  
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10 smokers and PC risk reported before[4, 25], we did not observe a significant associations, probably due  
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12 to low statistical power.  
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### 18 *Effect-modification factors*

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20 Former smoking diabetes patients tended to have a higher PC risk in this study. Lifestyle changes  
21 including smoking cessation among diabetics may explain this finding together with the fact that smoking  
22 and its cessation is associated with insulin resistance[26]. Indeed, this result is consistent with the  
23 findings of a study reporting that smoking cessation leading to weight gain increases diabetes risk[27].  
24 Previous studies suggested differences in smoking effects on PC risk by gender[5, 6], although they failed  
25 to demonstrate effect modification by this variable. Similarly, non-significant differences by gender were  
26 found in our study.  
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### 38 *Dose-response relationships*

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40 Non-linear relationships of the association between smoking variables and PC risk were  
41 supported by both FP and RCS approaches. For smoking duration, intensity, and cumulative dose, a  
42 plateauing in the DRR was apparent. This observed pattern was previously reported[5], and could be  
43 attributed to the saturation of the detoxification processes of tobacco carcinogens in the body[28], or to  
44 a presumably weaker inhalation of tobacco smoke but stronger DNA repair efficiency among heavy  
45 smokers[29,30], amongst other factors. Non-linear associations for smoking cessation were also  
46 suggested in previous studies[5].  
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### *Black versus blond tobacco-use*

Compared to never-smokers, black tobacco smokers showed a significantly higher PC risk. This potential harmful effect has also been observed in other cancers[7,9–12,31,32]. Smoking both black and blond tobacco for a long time ( $\geq 30$  years) tended to be related to higher PC risk, this also being shown in previous studies[7].

The difference between the two tobacco types could be explained by their smoke composition: black tobacco mostly contains early-stage carcinogens, such as N-nitrosamines and aromatic amines including 4-amino-biphenyl and 2-naphthylamine[33], whereas blond tobacco may mostly consist of late-stage carcinogens[31]. It is conceivable that black tobacco may predominantly cause DNA mutations whereas blond tobacco may preferentially act through epigenetic change, as has been shown for LINE-1[8]. As a consequence, an immediate and significantly higher increase in PC risk could be expected in black tobacco smokers, while blond tobacco might need a longer time to trigger PC development. This may also imply that following smoking cessation of blond tobacco PC risk can keep increasing for some time, slowing down after recovery of certain DNA methylation changes. In fact, methylation changes due to smoking seem to persist up to 22 years after smoking cessation[34]. For black tobacco, instead, the PC risk reduction effects might not take place or might require longer since smoking cessation. Our results support these hypotheses to some extent. Compared to never-smokers, not only did black tobacco smoking have a more detrimental effect on PC risk, but also the risk tended to increase soon after smoking initiation, whereas downward risks were observed after smoking cessation for  $>10$  years. A similar decreasing risk with long-term smoking cessation of black tobacco has been observed in bladder cancer [31,32]. Among blond tobacco smokers, the trend towards a reduction in PC risk became evident shortly after smoking cessation (Figure1). Thus, our study suggests that black tobacco consumption may play a role in several steps of the carcinogenic process with possibly both early and late-stage carcinogens being involved. For blond tobacco, our results point to a two-tier mechanism after smoking cessation driven by late-stage carcinogens, the first consisting of a sudden change in risk estimates with

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3 risk levels more akin to never-smokers likely due to desaturation of detoxification routes of tobacco-  
4 carcinogens[5,35], the second showing risks levelling-off once alteration of DNA methylation levels of key  
5 genes regain the state of normalcy.  
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11 Among the limitations of the study, stratifying by tobacco type and other variables might have  
12 underpowered the analyses to detect any differences. Also, we could not consider potential differences  
13 in the content of carcinogens because we lacked information on tobacco brands, likely to contain varying  
14 amounts of heavy metals[36] and other carcinogens[33]. Residual confounding can be therefore  
15 expected, also due to lack of, or imprecise, information on other relevant data such as ETS in adulthood.  
16 Moreover, differential misclassification of the exposure due to recall bias of smoking habits is possible..  
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25 Strengths of the study are the large number of PC cases representing a European-wide PC  
26 population and the degree of detail in the information collected about smoking habits even considering  
27 tobacco types. Also, as a novelty, the shapes of DRRs have been fully characterized using different  
28 modelling strategies to account for non-linear effects of smoking on PC risk.  
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35 In conclusion, findings of this study support and add to the previous evidence that smoking  
36 increases PC risk and demonstrates, for the first time, that both blond and black tobacco smoke are key  
37 in PC aetiology, though probably acting through different genetic mechanisms.  
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## Conflict of interest

The authors declare no conflict of interest.

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**Table 1:** Association between smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls).

|   | Cases (%)  | Controls (%) | p-value <sup>1</sup> | OR (95%CI)         | aOR (95%CI)              |
|---|------------|--------------|----------------------|--------------------|--------------------------|
| <b>Smoking status (cigarettes)</b>              |            |              | <b>&lt;0.001</b>     |                    | <b>p-trend &lt;0.001</b> |
| Never-smoker                                    | 759 (37.8) | 690 (45.0)   |                      | 1.00               | 1.00                     |
| Occasional                                      | 33 (1.6)   | 42 (2.7)     |                      | 0.72 (0.44 - 1.14) | 1.00 (0.61 - 1.67)       |
| Former  | 667 (33.2) | 530 (34.6)   |                      | 1.14 (0.98 - 1.33) | 1.14 (0.95 - 1.37)       |
| Current   | 550 (27.4) | 270 (17.6)   |                      | 1.85 (1.55 - 2.21) | 1.72 (1.39 - 2.12)       |
| <b>Cumulative dose in tertiles (pack-years)</b> |            |              | <b>&lt;0.001</b>     |                    | <b>p-trend &lt;0.001</b> |
| Never-smoker                                    | 759 (37.8) | 690 (45.0)   |                      | 1.00               | 1.00                     |
| < 14  | 279 (13.9) | 281 (18.3)   |                      | 0.90 (0.74 - 1.10) | 0.90 (0.72 - 1.13)       |
| 14 - 32   | 494 (24.6) | 275 (18.0)   |                      | 1.63 (1.36 - 1.96) | 1.57 (1.27 - 1.94)       |
| ≥ 32  | 477 (23.7) | 286 (18.7)   |                      | 1.52 (1.27 - 1.81) | 1.50 (1.21 - 1.84)       |

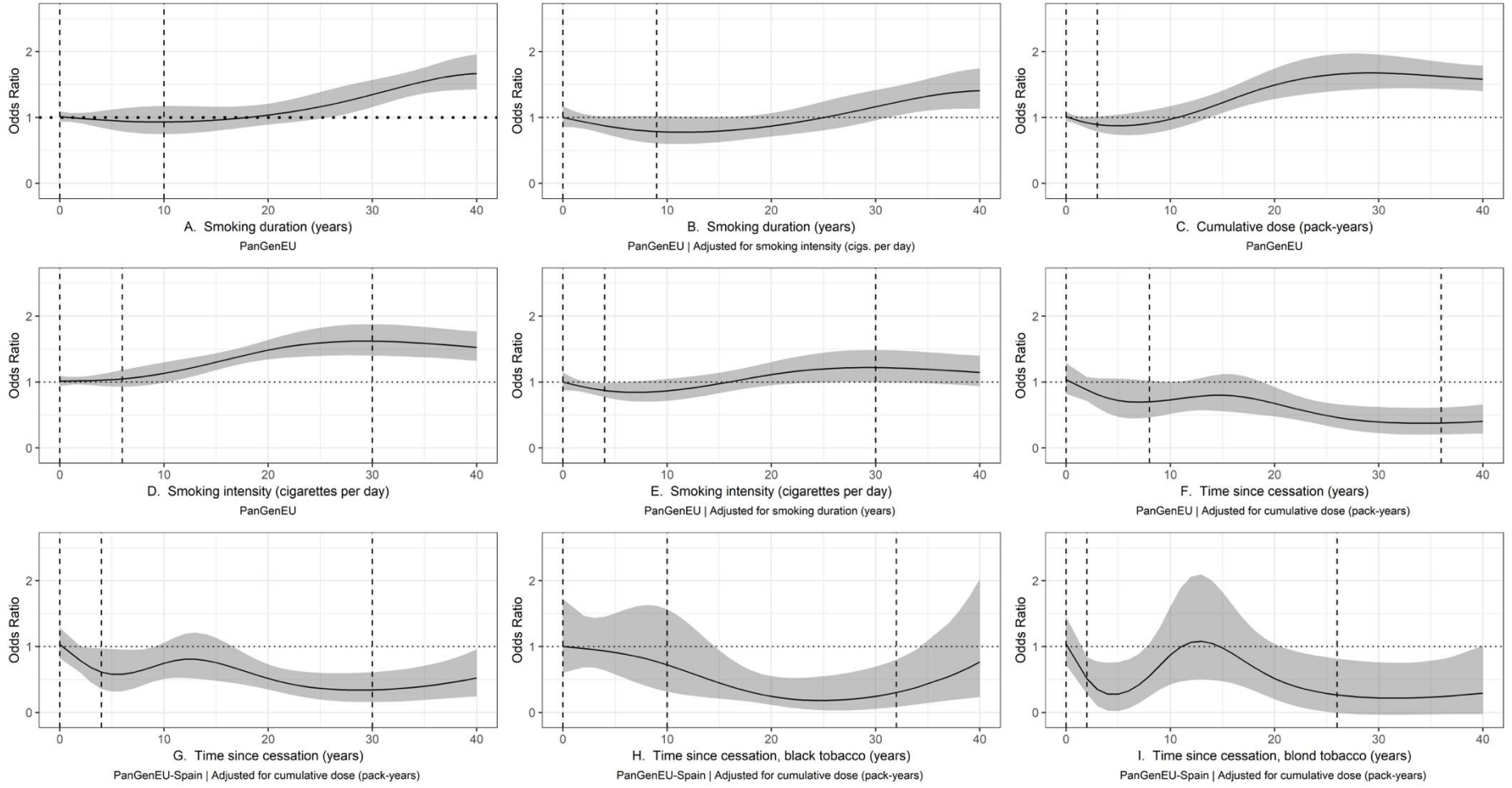
## Tables and figures

**Table 1:** Association between smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls).

**Figure 1 (A-I):** Dose-response relationships between several smoking variables and the risk of PC, depicted by restricted cubic splines with knots at 10%, 50% and 90%, represented as dashed, vertical lines. Adjusted for age, gender and country (for the PanGenEU study population), or region (for the PanGenEU-Spain study population). Restricted cubic splines are shown for the unimputed smoking variables, and additional adjustment variables were modelled as fractional polynomials to account for non-linear effects. The spline curve is shown as a black trend line and 95% confidence intervals are shadowed in grey. The dotted horizontal black line represents the reference odds ratio of 1. A: Smoking duration in years (PanGenEU); B: Smoking duration in years (PanGenEU), adjusted for smoking intensity (cigarettes per day); C: Cumulative dose in pack-years (PanGenEU); D: Smoking intensity in cigarettes per day (PanGenEU); E: Smoking intensity in cigarettes per day (PanGenEU), adjusted for smoking duration (years); F: Time since cessation in years (PanGenEU), adjusted for cumulative dose (pack-years); G: Time since cessation in years (PanGenEU-Spain), adjusted for cumulative dose (pack-years); I: Time since cessation in years for smokers of only black tobacco (PanGenEU-Spain), adjusted for cumulative dose (pack-years); J: Time since cessation in years for smokers of only blond tobacco (PanGenEU-Spain), adjusted for cumulative dose (pack-years). PC: pancreatic cancer; RCS: restricted cubic splines.

|    |  |             |            |  |                    |   |                    |                          |
|----|--|-------------|------------|--|--------------------|---|--------------------|--------------------------|
| 1  |  |             |            |  |                    |   |                    |                          |
| 2  |  |             |            |  |                    |   |                    |                          |
| 3  | <b>Inhalation</b>                                  |             |            |  | <b>&lt;0.001</b>   |   |                    | <b>p-trend &lt;0.001</b> |
| 4  | Never-smoker                                       | 759 (37.8)  | 690 (45.0) |  | 1.00               |   | 1.00               |                          |
| 5  | Mouth only   | 125 (6.2)   | 99 (6.5)   |  | 1.15 (0.86 - 1.53) |   | 1.10 (0.80 - 1.50) |                          |
| 6  | Throat   | 158 (7.9)   | 108 (7.1)  |  | 1.33 (1.02 - 1.74) |   | 1.48 (1.11 - 1.99) |                          |
| 7  | Chest  | 967 (48.1)  | 635 (41.4) |  | 1.38 (1.20 - 1.60) |   | 1.33 (1.12 - 1.58) |                          |
| 8  | <b>Filter-use</b>                                  |             |            |  | <b>&lt;0.001</b>   |   |                    | <b>p-trend &lt;0.001</b> |
| 9  | Never-smoker                                       | 759 (37.8)  | 690 (45.0) |  | 1.00               |   | 1.00               |                          |
| 10 | Filtered only                                      | 1042 (51.9) | 706 (46.1) |  | 1.34 (1.17 - 1.54) |   | 1.25 (1.06 - 1.48) |                          |
| 11 | Non-filtered only                                  | 65 (3.2)    | 49 (3.2)   |  | 1.20 (0.82 - 1.78) |   | 1.69 (1.10 - 2.61) |                          |
| 12 | Both   | 143 (7.1)   | 87 (5.7)   |  | 1.49 (1.12 - 1.99) |   | 1.65 (1.21 - 2.27) |                          |
| 13 | <b>ETS exposure during childhood</b>               |             |            |  | <b>&lt;0.001</b>   |   |                    | <b>p-trend = 0.610</b>   |
| 14 | Both parents were never-smokers                    | 420 (20.9)  | 391 (25.6) |  | 1.00               |   | 1.00               |                          |
| 15 | One of the parents smoked                          | 1378 (68.6) | 952 (62.1) |  | 1.35 (1.15 - 1.58) |   | 1.24 (1.03 - 1.49) |                          |
| 16 | Both parents smoked                                | 211 (10.5)  | 189 (12.3) |  | 1.04 (0.82 - 1.32) |   | 1.07 (0.81 - 1.42) |                          |
| 17 | <b>Time since cessation in tertiles (years)</b>    |             |            |  | <b>&lt;0.001</b>   |   |                    | <b>p-trend &lt;0.001</b> |
| 18 | <i>Current smoker</i>                              | 551 (27.4)  | 274 (17.9) |  | 1.00               |   | 1.00               |                          |
| 19 | < 14   | 320 (15.9)  | 191 (12.5) |  | 0.83 (0.66 - 1.05) |   | 0.81 (0.62 - 1.04) |                          |
| 20 | 14 - 28  | 229 (11.4)  | 185 (12.1) |  | 0.62 (0.48 - 0.78) |   | 0.67 (0.51 - 0.88) |                          |
| 21 | ≥ 28   | 150 (7.5)   | 192 (12.5) |  | 0.39 (0.30 - 0.50) |   | 0.49 (0.36 - 0.66) |                          |
| 22 | Never-smoker                                       | 759 (37.8)  | 690 (45.0) |  | -                  | - | -                  | -                        |
| 23 |  |             |            |  |                    |   |                    |                          |
| 24 | <b>By tobacco type in PanGen-Spain<sup>2</sup></b> |             |            |  |                    |   |                    |                          |
| 25 | <b>Tobacco type</b>                                |             |            |  | <b>0.012</b>       |   |                    |                          |
| 26 | Never-smoker                                       | 355 (40.5)  | 360 (47.2) |  | 1.00               |   | 1.00               |                          |
| 27 | Smoker of black tobacco only                       | 165 (18.8)  | 114 (15.0) |  | 1.47 (1.11 - 1.94) |   | 1.55 (1.13 - 2.12) |                          |
| 28 | Smoker of blond tobacco only                       | 204 (23.3)  | 182 (23.9) |  | 1.14 (0.89 - 1.46) |   | 1.23 (0.94 - 1.62) |                          |
| 29 | Smoker of both tobacco types                       | 152 (17.4)  | 106 (13.9) |  | 1.45 (1.09 - 1.94) |   | 1.58 (1.14 - 2.17) |                          |
| 30 | <b>Tobacco type by smoking status</b>              |             |            |  | <b>0.028</b>       |   |                    |                          |
| 31 | <i>Never-smoker</i>                                | 355 (40.5)  | 360 (47.2) |  | 1.00               |   | 1.00               |                          |
| 32 | <i>Occasional</i>                                  |             |            |  |                    |   |                    |                          |
| 33 | Black tobacco                                      | 1 (0.1)     | 4 (0.5)    |  | 0.28 (0.01 - 2.03) |   | 0.29 (0.03 - 2.64) |                          |
| 34 | Blond tobacco                                      | 11 (1.2)    | 11 (1.4)   |  | 1.01 (0.42 - 2.42) |   | 1.11 (0.47 - 2.62) |                          |
| 35 | Both   | 2 (0.2)     | 2 (0.4)    |  | 1.01 (0.11 - 9.78) |   | 1.16 (0.16 - 8.39) |                          |
| 36 | <i>Former</i>                                      |             |            |  |                    |   |                    |                          |
| 37 | Black tobacco                                      | 104 (11.9)  | 79 (10.4)  |  | 1.33 (0.96 - 1.85) |   | 1.39 (0.97 - 1.98) |                          |
| 38 | Blond tobacco                                      | 90 (10.3)   | 88 (11.5)  |  | 1.04 (0.75 - 1.44) |   | 1.11 (0.79 - 1.56) |                          |
| 39 | Both   | 76 (8.7)    | 58 (7.6)   |  | 1.33 (0.92 - 1.93) |   | 1.43 (0.96 - 2.12) |                          |
| 40 | <i>Current</i>                                     |             |            |  |                    |   |                    |                          |
| 41 | Black tobacco                                      | 60 (6.8)    | 31 (4.1)   |  | 1.96 (1.25 - 3.13) |   | 2.08 (1.29 - 3.36) |                          |
| 42 | Blond tobacco                                      | 103 (11.8)  | 83 (10.9)  |  | 1.26 (0.91 - 1.74) |   | 1.43 (1.00 - 2.03) |                          |
| 43 | Both   | 74 (8.5)    | 46 (6.0)   |  | 1.63 (1.10 - 2.44) |   | 1.80 (1.18 - 2.74) |                          |

ETS: environmental tobacco smoke. Risk estimates are shown for the imputed smoking variables. aOR: adjusted OR. Adjusted model for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden). Random effects model applied for country. <sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p-value < 0.05. <sup>2</sup> PanGenEU-Spain study population (876 cases and 762 controls). Adjusted model for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and region (East, Central and Northern Spain).





# Supplementary material

|  |    |
|--|----|
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| <b>Table 12.</b> Sensitivity analysis on the association between tobacco smoking and pancreatic cancer risk, in models additionally controlling for smoking duration and intensity, for the PC population (2,009 cases and 1,532 controls).....  | 28 |
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| <b>Figure 1 (A-G):</b> Dose-response relationships between several smoking variables and the risk of PC, depicted by restricted cubic splines with knots at 10%, 50% and 90%, represented as dashed, vertical lines. Not adjusted for age, gender and country (for the PanGenEU study population) or region (for the PanGenEU-Spain study population) or smoking intensity or duration. Splines are shown for the unimputed data. The spline curve with smoothing applied is shown as a black trend line, the original spline curve is shown as a reference in grey. The dashed horizontal black line represents the reference odds ratio of 1. .... | 33 |

## Supplementary methods

### *Study design and participants*

The PanGenEU (European Study on Digestive Illnesses and Genetics) is an ongoing multicentre case-control study recruiting participants from Germany, Ireland, Italy, Spain, Sweden and United Kingdom. Newly diagnosed pancreatic cancer (PC) patients >18 years old and controls matched by age, gender, and geographical area were included. A rapid ascertainment approach was applied: patients with a suspicion of PC were recruited and remained in the study if the diagnosis was verified by the treating physician. Controls were mostly hospital-based and eligible if principal diagnosis at admission was unrelated to known risk factors of PC. Population-based controls (Sweden and Ireland) were eligible if history of PC was absent. Participation rates were 86.3% for cases and 77.8% for controls. The study was approved by the IRB of all participant centres and all subjects gave written informed consent.

### *Variables*

The smoking status of the participants was categorized into never, former and current smokers based upon the information they provided. In particular, the smoking status of the participants was categorized into never-smokers if they smoked <100 cigarettes during their lifetime; occasional smokers if they smoked  $\geq 1$  cigarette/day for  $\geq 6$  months; former smokers if they quitted smoking for >1 year; and current smokers otherwise (>100 cigarettes during lifetime without permanent smoking cessation). Smoking exposure was further assessed by the age at smoking initiation (years), age when last smoked (years), cigarettes/cigar/pipe-use (yes, no), the amount of cigarettes/cigars/pipes smoked in units of time (days, months, years), depth of inhalation (mouth, throat, chest), filter-use (filtered cigarettes, non-filtered, both), and smoking status of the parents (never- or ever-smoker). From these characteristics, data on smoking duration (years), smoking intensity for cigarettes (per day) and cigars/pipes (per week), and time since cessation (years) was derived. Number of pack-years, representing cumulative dose, was

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3 calculated as (cigarettes per day/20)\*smoking duration in years. Smoking variables by use of tobacco  
4 type were generated likewise. Environmental tobacco smoke (ETS) exposure during childhood was  
5 categorized according to the smoking status of the parents (none, one, or both).  
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### 10 *Statistical analysis*

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13 Differences between cases and controls regarding smoking characteristics were evaluated by  $\chi^2$   
14 and Student's t-test (or Kruskal–Wallis test, where appropriate). Unconditional logistic regression analysis  
15 was performed to estimate odds ratios (OR) and 95% Confidence Intervals (95%CI). Never-smokers  
16 were chosen as the reference category, except for the variables “age when last smoked” and “time since  
17 smoking cessation”, where current smokers were taken as the reference. Tertiles were created for the  
18 continuous variables based on the distribution of controls. A p-value for trend was calculated by assuming  
19 ordinal variables in linear regression models. Age ( $\leq 54$ , 55-64, 65-74,  $\geq 75$  years), gender, and country-  
20 adjusted models (aOR) were considered. For the tobacco type-specific analyses within the Spanish  
21 PanGenEU study population, the same model was applied, but replacing country by region (East, Central  
22 and Northern Spain). The attributable risk (AR) of smoking in relation to PC was calculated by applying  
23 the same models. Since heterogeneity by country ( $p < 0.05$ ) was evident for all smoking variables, random  
24 effects for country were applied in mixed effects models. Due to absence of heterogeneity in the Spanish  
25 study population, logistic regression models without random effects were considered.  
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44 The influence of other factors on the association between tobacco smoking and PC risk was  
45 assessed for gender (female, male), age ( $< 65$  years,  $\geq 65$  years), obesity (body mass index  $> 30$ : yes,  
46 no), diabetes (no, yes less than 2 years, yes more than 2 years), asthma (yes, no), chronic pancreatitis  
47 (yes, no), alcohol status/consumption (never, former, current), presence of periodontitis (yes, no) and  
48 recession (yes, no), educational level as a proxy for socioeconomic status (low, medium, high), and family  
49 history of PC (yes, no).  
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3 To test for interaction, a likelihood ratio (LR) test was performed comparing models with and  
4 without an interaction term between the smoking variables and the covariates (e.g., age, gender, BMI  
5 and obesity, diabetes, asthma, alcohol, periodontitis, recession, educational level, and family history of  
6 PC). Effect modification was tested further via stratified analyses. To assess interaction by time-related  
7 variables we explored the combined effect of smoking duration and other smoking characteristics such  
8 as tobacco type on PC risk. Smoking duration was categorized into <20, 20-30, and  $\geq$ 30 years of smoking  
9 and stratified further by tobacco type considering never-smokers as the reference category.  
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### 20 *Imputation*

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22 Missing values were assumed to be at random. Predictor variables such as centre, country, and  
23 case-control status were kept in the imputation set. The performance of the imputation was assessed by  
24 calculating the out of bag mean square error (OOB), representing the mean of squared differences  
25 between each observed value and its prediction, based on random forest trees (n=100 was applied). The  
26 average OOB for all smoking variables was 5.27, with categorical variables presenting a markedly lower  
27 estimate (OOB=0.04), indicating a better imputation performance of the latter (Supplementary Table 1).  
28 Use of unimputed data of all continuous variables, for which the proportion of missing values was  
29 relatively low (6.7%), was therefore deemed more appropriate for dose-response analyses. The  
30 performance of the imputation was also assessed with concordance rates between the observed and  
31 imputed data, considering a test dataset consisting of only subjects with complete data and missing  
32 values introduced by following the missingness rates of the original data. The concordance of all  
33 categorical variables was 94.4% (Supplementary Table 1).  
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### 50 *Sensitivity analyses*

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53 Sensitivity analyses were performed comparing the risk estimates in magnitude and trend  
54 regarding the unimputed and imputed data, and the PanGenEU study population with and without Italy  
55 (since Italy provided cases only). As information bias could be induced by neglecting the quantity of  
56 smoking exposure, adjustment for cumulative dose (pack-years) was considered, thereby accounting for  
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3 both smoking duration and smoking intensity. Additional adjustments were made also for smoking  
4 intensity and duration separately, to assess both the individual and joined effects of smoking  
5 characteristics independent of smoking duration and/or intensity. These adjustment variables were  
6 considered on the continuous scale and modelled as FPs to account for non-linear effects.  
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**Supplementary Table 1.** Imputation performance on the PanGenEU study population (2,009 cases and 1,532 controls), shown by concordance tests and the OOB error.

|  | Number of<br>missings <sup>1</sup> | Proportion<br>missings | OOB error test set <sup>2</sup> | N concordant<br>values | N discordant<br>values | Total N imputations<br>(concordant +<br>discordant) | % concordance | OOB error imputed<br>data |
|--|------------------------------------|------------------------|---------------------------------|------------------------|------------------------|---|---------------|---------------------------|
| <b>Demographics</b>                            |                                    |                        |                                 |                        |                        |   |               |                           |
| Country  | 0                                  | 0.00                   | 0.00                            | 0                      | 0                      | 0   | NA            | 0.00                      |
| Center   | 0                                  | 0.00                   | 0.00                            | 0                      | 0                      | 0   | NA            | 0.00                      |
| Region   | 0                                  | 0.00                   | 0.00                            | 0                      | 0                      | 0   | NA            | 0.00                      |
| Study  | 0                                  | 0.00                   | 0.00                            | 0                      | 0                      | 0   | NA            | 0.00                      |
| Case-control status                            | 0                                  | 0.00                   | 0.00                            | 0                      | 0                      | 0   | NA            | 0.00                      |
| Age  | 12                                 | 0.34                   | 0.43                            | 0                      | 2                      | 2   | 0.00          | 0.41                      |
| Gender   | 4                                  | 0.11                   | 0.13                            | 4                      | 0                      | 4   | 100.00        | 0.12                      |
| Years of education (continuous)                | 751                                | 21.21                  | 9.58                            | 0                      | 152                    | 152   | 0.00          | 7.21                      |
| Educational level                              | 1252                               | 35.36                  | 0.50                            | 111                    | 109                    | 220   | 50.46         | 0.33                      |
| Socioeconomic status                           | 180                                | 5.08                   | 0.06                            | 49                     | 4                      | 53  | 92.45         | 0.02                      |
| Height (continuous)                            | 76                                 | 2.15                   | 19.35                           | 0                      | 11                     | 11  | 0.00          | 0.00                      |
| Height in tertiles                             | 76                                 | 2.15                   | 0.03                            | 13                     | 1                      | 14  | 92.86         | 0.01                      |
| Weight (continuous)                            | 120                                | 3.39                   | 31.39                           | 0                      | 30                     | 30  | 0.00          | 81.53                     |
| Weight in tertiles                             | 120                                | 3.39                   | 0.01                            | 36                     | 0                      | 36  | 100.00        | 0.01                      |
| BMI  | 170                                | 4.80                   | 0.11                            | 25                     | 6                      | 31  | 80.65         | 0.09                      |
| <b>Smoking variables</b>                       |                                    |                        |                                 |                        |                        |   |               |                           |
| Ever smoked 100 cigarettes                     | 12                                 | 0.34                   | 0.00                            | 2                      | 0                      | 2   | 100.00        | 0.00                      |
| Regular smoker                                 | 87                                 | 2.46                   | 0.01                            | 24                     | 0                      | 24  | 100.00        | 0.00                      |
| Tobacco type <sup>3</sup>                      | 1185                               | 33.47                  | 0.22                            | 161                    | 43                     | 204   | 78.92         | 0.14                      |
| Age at smoking initiation (continuous)         | 75                                 | 2.12                   | 5.93                            | 1                      | 16                     | 17  | 5.88          | 7.89                      |
| Age at smoking initiation in tertiles          | 75                                 | 2.12                   | 0.02                            | 20                     | 1                      | 21  | 95.24         | 0.00                      |
| Current smoker                                 | 69                                 | 1.95                   | 0.02                            | 20                     | 0                      | 20  | 100.00        | 0.01                      |
| Age last smoked (continuous)                   | 97                                 | 2.74                   | 18.20                           | 3                      | 17                     | 20  | 15.00         | 13.77                     |
| Age last smoked in tertiles                    | 98                                 | 2.77                   | 0.02                            | 17                     | 1                      | 18  | 94.44         | 0.01                      |
| Ever quit smoking >6 months                    | 223                                | 6.30                   | 0.00                            | 49                     | 0                      | 49  | 100.00        | 0.00                      |
| Time of ever quitting (continuous)             | 266                                | 7.51                   | 2.93                            | 17                     | 37                     | 54  | 31.48         | 5.42                      |
| Time of ever quitting in tertiles              | 266                                | 7.51                   | 0.04                            | 59                     | 2                      | 61  | 96.72         | 0.00                      |
| Inhalation                                     | 341                                | 9.63                   | 0.16                            | 60                     | 12                     | 72  | 83.33         | 0.15                      |
| Filter-use                                     | 393                                | 11.10                  | 0.10                            | 67                     | 10                     | 77  | 87.01         | 0.11                      |
| Smoking cigar                                  | 437                                | 12.34                  | 0.01                            | 97                     | 0                      | 97  | 100.00        | 0.00                      |
| Intensity of smoking cigars (continuous)       | 556                                | 15.70                  | 0.87                            | 38                     | 83                     | 121   | 31.41         | 12.73                     |
| Intensity of smoking cigars in tertiles        | 558                                | 15.76                  | 0.03                            | 133                    | 4                      | 137   | 97.08         | 0.01                      |
| Smoking pipe                                   | 439                                | 12.40                  | 0.00                            | 91                     | 0                      | 91  | 100.00        | 0.00                      |
| Intensity of smoking pipes (continuous)        | 586                                | 16.55                  | 0.28                            | 84                     | 38                     | 122   | 68.85         | 10.99                     |
| Intensity of smoking pipes in tertiles         | 586                                | 16.55                  | 0.02                            | 121                    | 1                      | 122   | 99.18         | 0.01                      |
| Tobacco type for pipe                          | 631                                | 17.82                  | 0.01                            | 112                    | 2                      | 114   | 98.25         | 0.03                      |
| Smoking status (cigarettes)                    | 113                                | 3.19                   | 0.00                            | 23                     | 0                      | 23  | 100.00        | 0.00                      |
| Smoking status (incl. occasional)              | 85                                 | 2.40                   | 0.01                            | 29                     | 0                      | 29  | 100.00        | 0.00                      |
| Smoking duration (continuous)                  | 332                                | 9.38                   | 25.03                           | 3                      | 61                     | 64  | 4.69          | 10.22                     |
| Smoking duration in tertiles                   | 333                                | 9.40                   | 0.01                            | 64                     | 3                      | 67  | 95.52         | 0.00                      |
| Smoking intensity (continuous)                 | 110                                | 3.11                   | 13.45                           | 1                      | 27                     | 28  | 3.57          | 23.37                     |
| Smoking intensity in tertiles                  | 110                                | 3.11                   | 0.02                            | 20                     | 0                      | 20  | 100.00        | 0.00                      |
| Cumulative dose (continuous)                   | 356                                | 10.05                  | 177.11                          | 16                     | 52                     | 68  | 23.53         | 82.15                     |
| Cumulative dose in tertiles                    | 356                                | 10.05                  | 0.01                            | 81                     | 1                      | 82  | 98.78         | 0.00                      |
| Time since cessation (continuous)              | 145                                | 4.10                   | 6.24                            | 7                      | 25                     | 32  | 21.88         | 6.31                      |
| Time since cessation in tertiles               | 145                                | 4.10                   | 0.01                            | 28                     | 1                      | 29  | 96.55         | 0.00                      |
| Quit smoking <10 or ≥ 10 years ago             | 144                                | 4.07                   | 0.00                            | 25                     | 0                      | 25  | 100.00        | 0.00                      |
| Childhood exposure to ETS                      | 537                                | 15.17                  | 0.02                            | 123                    | 5                      | 128   | 96.09         | 0.01                      |
| Combined use of cigarettes, cigars, pipes      | 444                                | 12.54                  | 0.49                            | 48                     | 49                     | 97  | 49.49         | 0.47                      |
| <b>Medical history</b>                         |                                    |                        |                                 |                        |                        |   |               |                           |
| Ever been diagnosed with asthma                | 329                                | 9.29                   | 0.09                            | 60                     | 5                      | 65  | 92.31         | 0.09                      |
| Ever been diagnosed with diabetes              | 54                                 | 1.53                   | 0.00                            | 11                     | 0                      | 11  | 100.00        | 0.00                      |
| Ever been diagnosed with diabetes (incl. time) | 92                                 | 2.60                   | 0.10                            | 18                     | 2                      | 20  | 90.00         | 0.07                      |
| Ever been diagnosed with chronic pancreatitis  | 128                                | 3.62                   | 0.01                            | 35                     | 0                      | 35  | 100.00        | 0.01                      |
| Ever been diagnosed with acid regurgitation    | 334                                | 9.43                   | 0.26                            | 64                     | 19                     | 83  | 77.11         | 0.23                      |

|  |      |       |         |     |     |     |        |       |
|--|------|-------|---------|-----|-----|-----|--------|-------|
| Alcohol status                         | 32   | 0.90  | 0.00    | 6   | 1   | 7   | 85.71  | 0.00  |
| Alcohol intake (continuous)            | 798  | 22.54 | 4078.85 | 1   | 164 | 165 | 0.61   | 13.51 |
| Alcohol intake in categories           | 802  | 22.65 | 0.05    | 146 | 12  | 158 | 92.41  | 0.02  |
| Ever been diagnosed with obesity       | 176  | 4.97  | 0.00    | 45  | 0   | 45  | 100.00 | 0.00  |
| Ever been diagnosed with periodontitis | 936  | 26.43 | 0.19    | 148 | 28  | 176 | 84.09  | 0.18  |
| Ever been diagnosed with recession     | 1319 | 37.25 | 0.33    | 155 | 62  | 217 | 71.43  | 0.28  |
| Smoking status mother                  | 364  | 10.28 | 0.03    | 74  | 2   | 76  | 97.37  | 0.00  |
| Smoking status father                  | 498  | 14.06 | 0.02    | 105 | 3   | 108 | 97.22  | 0.00  |
| Family history of PC                   | 124  | 3.50  | 0.05    | 26  | 1   | 27  | 96.30  | 0.05  |

OOB: out of bag; BMI: body mass index; ETS: environmental tobacco smoke; PC: pancreatic cancer.

<sup>1</sup> Total proportion of missings in the PanGenEU study population, for adjustment and stratification variables was 8.5% (9.7% for cases, 6.9% for controls); Total proportion of missings in the PanGenEU-Spain study population, for adjustment and stratification variables was 4.7% (4.8% for cases, 4.5% for controls).

<sup>2</sup> The test set contains only subjects without missing (N=841).

<sup>3</sup> Tobacco type was only collected for Spanish subjects.

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**Supplementary Table 3:** Association between selected smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls).

|   |                  | Unadjusted  |              |                      | Adjusted         |              |                      |
|---|------------------|-------------|--------------|----------------------|------------------|--------------|----------------------|
| <b>Supplementary Table 2: Baseline characteristics of the PanGenEU study population (2,009 cases and 1,532 controls).</b> |                  |             |              |                      |                  |              |                      |
|   |                  | PanGenEU    |              |                      | PanGenEU - Spain |              |                      |
|   |                  | Cases (%)   | Controls (%) | p-value <sup>2</sup> | Cases (%)        | Controls (%) | p-value <sup>2</sup> |
| <b>Country</b>  |                  |             |              | <0.001               |                  |              | --                   |
|   | Spain            | 876 (43.6)  | 762 (49.7)   |                      | 876 (100.0)      | 762 (100.0)  |                      |
|   | England          | 126 (6.3)   | 22 (1.4)     |                      | -                | -            |                      |
|   | Germany          | 130 (6.5)   | 111 (7.3)    |                      | -                | -            |                      |
|   | Ireland          | 173 (8.6)   | 290 (18.9)   |                      | -                | -            |                      |
|   | Italy            | 533 (26.5)  | 0 (0.0)      |                      | -                | -            |                      |
|   | Sweden           | 171 (8.5)   | 347 (22.7)   |                      | -                | -            |                      |
| <b>Gender</b>   |                  |             |              | 0.164                |                  |              | 0.455                |
|   | Female           | 871 (43.4)  | 701 (45.8)   |                      | 384 (43.8)       | 349 (45.8)   |                      |
|   | Male             | 1138 (56.6) | 831 (54.2)   |                      | 492 (56.2)       | 413 (54.2)   |                      |
| <b>Age</b>  |                  |             |              | <0.001               |                  |              | 0.086                |
|   | ≤54              | 413 (20.6)  | 262 (17.1)   |                      | 157 (17.9)       | 155 (20.3)   |                      |
|   | 55-64            | 497 (24.7)  | 321 (21.0)   |                      | 203 (23.2)       | 173 (22.7)   |                      |
|   | 65-74            | 699 (34.8)  | 495 (32.3)   |                      | 285 (32.5)       | 208 (27.3)   |                      |
|   | ≥75              | 400 (19.9)  | 454 (29.6)   |                      | 231 (26.4)       | 226 (29.7)   |                      |
| <b>BMI (kg/m<sup>2</sup>)</b>   |                  |             |              | 0.997                |                  |              | 0.900                |
|   | < 25             | 769 (38.3)  | 588 (38.4)   |                      | 303 (34.6)       | 271 (35.6)   |                      |
|   | 25-29.99         | 854 (42.5)  | 651 (42.5)   |                      | 397 (45.3)       | 343 (45.0)   |                      |
|   | ≥ 30             | 386 (19.2)  | 293 (19.1)   |                      | 176 (20.1)       | 148 (19.4)   |                      |
| <b>Alcohol status<sup>3</sup></b>   |                  |             |              | <0.001               |                  |              | 0.412                |
|   | Never-drinker    | 585 (29.1)  | 383 (25.0)   |                      | 273 (31.2)       | 254 (33.3)   |                      |
|   | Light drinker    | 805 (40.1)  | 756 (49.3)   |                      | 377 (43.0)       | 338 (44.4)   |                      |
|   | Moderate drinker | 564 (28.1)  | 360 (23.5)   |                      | 214 (24.4)       | 160 (21.0)   |                      |
|   | Heavy drinker    | 55 (2.7)    | 33 (2.2)     |                      | 12 (1.4)         | 10 (1.3)     |                      |
| <b>Family history of PC</b>   |                  |             |              | <0.001               |                  |              | <0.001               |
|   | No               | 1882 (93.7) | 1492 (97.4)  |                      | 815 (93.00)      | 739 (97.0)   |                      |
|   | Yes              | 127 (6.3)   | 40 (2.6)     |                      | 61 (7.0)         | 23 (3.0)     |                      |
| <b>Ever been diagnosed with asthma</b>  |                  |             |              | <0.001               |                  |              | 0.014                |
|   | No               | 1878 (93.5) | 1374 (89.7)  |                      | 817 (93.3)       | 684 (89.8)   |                      |
|   | Yes              | 131 (6.5)   | 158 (10.3)   |                      | 59 (6.7)         | 78 (10.2)    |                      |
| <b>Ever been diagnosed with diabetes</b>  |                  |             |              | <0.001               |                  |              | <0.001               |
|   | No               | 1515 (75.4) | 1349 (88.1)  |                      | 604 (68.9)       | 630 (82.7)   |                      |
|   | Yes, ≤ 2 years   | 214 (10.7)  | 27 (1.7)     |                      | 112 (12.8)       | 20 (2.6)     |                      |
|   | Yes, >2 years    | 280 (13.9)  | 156 (10.2)   |                      | 160 (18.3)       | 112 (14.7)   |                      |
| <b>Ever been diagnosed with chronic pancreatitis</b>  |                  |             |              | 0.004                |                  |              | 0.460                |
|   | No               | 1990 (99.1) | 1530 (99.9)  |                      | 871 (99.4)       | 760 (99.7)   |                      |
|   | Yes              | 19 (0.9)    | 2 (0.1)      |                      | 5 (0.6)          | 2 (0.3)      |                      |

PC: pancreatic cancer; BMI: body mass index.

Descriptives are shown for the imputed baseline characteristics. Descriptives of the unimputed baseline characteristics can be found in supplementary Table 8

<sup>1</sup>Chi-square test applied to evaluate differences between the groups. Significance was set at p-value<0.05.<sup>2</sup>Light drinker: 0-1 drink/day for men and women; Moderate drinker: men: 1-5drinks/day, women: 1-2.5 drinks/day; Heavy drinker: men: ≥5drinks/day, women: ≥2.5 drinks/day.



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|   | Cases (%)   | Controls (%) | p-value <sup>1</sup> | OR (95%CI)         | aOR (95%CI)        |
|---|-------------|--------------|----------------------|--------------------|--------------------|
| <b>Smoking status (cigarettes)</b>                        |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| Occasional  | 33 (1.6)    | 42 (2.7)     |                      | 0.72 (0.44 - 1.14) | 1.00 (0.61 - 1.67) |
| Former  | 667 (33.2)  | 530 (34.6)   |                      | 1.14 (0.98 - 1.33) | 1.14 (0.95 - 1.37) |
| Current   | 550 (27.4)  | 270 (17.6)   |                      | 1.85 (1.55 - 2.21) | 1.72 (1.39 - 2.12) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>Smoking intensity in tertiles (cigarettes per day)</b> |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| < 10  | 389 (19.4)  | 343 (22.5)   |                      | 1.03 (0.86 - 1.23) | 1.02 (0.83 - 1.25) |
| 10 - 20   | 533 (26.5)  | 287 (18.7)   |                      | 1.69 (1.42 - 2.02) | 1.64 (1.34 - 2.02) |
| ≥ 20  | 328 (16.3)  | 212 (13.8)   |                      | 1.41 (1.15 - 1.72) | 1.41 (1.12 - 1.78) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>Smoking duration in tertiles (years)</b>               |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| < 23  | 292 (14.5)  | 284 (18.5)   |                      | 0.93 (0.77 - 1.13) | 0.91 (0.72 - 1.14) |
| 23 - 35   | 477 (23.8)  | 281 (18.4)   |                      | 1.54 (1.29 - 1.85) | 1.52 (1.23 - 1.87) |
| ≥ 35  | 481 (23.9)  | 277 (18.1)   |                      | 1.58 (1.32 - 1.89) | 1.51 (1.23 - 1.86) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>Cumulative dose in tertiles (pack-years)</b>           |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| < 14  | 279 (13.9)  | 281 (18.3)   |                      | 0.90 (0.74 - 1.10) | 0.90 (0.72 - 1.13) |
| 14 - 32   | 494 (24.6)  | 275 (18.0)   |                      | 1.63 (1.36 - 1.96) | 1.57 (1.27 - 1.94) |
| ≥ 32  | 477 (23.7)  | 286 (18.7)   |                      | 1.52 (1.27 - 1.81) | 1.50 (1.21 - 1.84) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>Age at smoking initiation in tertiles (years)</b>      |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| < 15  | 423 (21.1)  | 278 (18.1)   |                      | 1.38 (1.15 - 1.66) | 1.36 (1.10 - 1.70) |
| 15 - 18   | 455 (22.6)  | 299 (19.6)   |                      | 1.38 (1.16 - 1.65) | 1.31 (1.06 - 1.61) |
| ≥ 18  | 372 (18.5)  | 265 (17.3)   |                      | 1.28 (1.06 - 1.54) | 1.29 (1.04 - 1.59) |
|   |             |              |                      |                    | p-trend = 0.010    |
| <b>Inhalation</b>   |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| Mouth only  | 125 (6.2)   | 99 (6.5)     |                      | 1.15 (0.86 - 1.53) | 1.10 (0.80 - 1.50) |
| Throat  | 158 (7.9)   | 108 (7.1)    |                      | 1.33 (1.02 - 1.74) | 1.48 (1.11 - 1.99) |
| Chest   | 967 (48.1)  | 635 (41.4)   |                      | 1.38 (1.20 - 1.60) | 1.33 (1.12 - 1.58) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>Filter-use</b>   |             |              | <0.001               |                    |                    |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | 1.00               | 1.00               |
| Filtered only   | 1042 (51.9) | 706 (46.1)   |                      | 1.34 (1.17 - 1.54) | 1.25 (1.06 - 1.48) |
| Non-filtered only   | 65 (3.2)    | 49 (3.2)     |                      | 1.20 (0.82 - 1.78) | 1.69 (1.10 - 2.61) |
| Both  | 143 (7.1)   | 87 (5.7)     |                      | 1.49 (1.12 - 1.99) | 1.65 (1.21 - 2.27) |
|   |             |              |                      |                    | p-trend <0.001     |
| <b>ETS exposure during childhood</b>                      |             |              | <0.001               |                    |                    |
| Both parents were never-smokers                           | 420 (20.9)  | 391 (25.6)   |                      | 1.00               | 1.00               |
| One of the parents smoked                                 | 1378 (68.6) | 952 (62.1)   |                      | 1.35 (1.15 - 1.58) | 1.24 (1.03 - 1.49) |
| Both parents smoked                                       | 211 (10.5)  | 189 (12.3)   |                      | 1.04 (0.82 - 1.32) | 1.07 (0.81 - 1.42) |
|   |             |              |                      |                    | p-trend = 0.610    |
| <b>Time since cessation in tertiles (years)</b>           |             |              | <0.001               |                    |                    |
| Current smoker  | 551 (27.4)  | 274 (17.9)   |                      | 1.00               | 1.00               |
| < 14  | 320 (15.9)  | 191 (12.5)   |                      | 0.83 (0.66 - 1.05) | 0.81 (0.62 - 1.04) |
| 14 - 28   | 229 (11.4)  | 185 (12.1)   |                      | 0.62 (0.48 - 0.78) | 0.67 (0.51 - 0.88) |
| ≥ 28  | 150 (7.5)   | 192 (12.5)   |                      | 0.39 (0.30 - 0.50) | 0.49 (0.36 - 0.66) |
| Never-smoker  | 759 (37.8)  | 690 (45.0)   |                      | -                  | -                  |
|   |             |              |                      |                    | p-trend <0.001     |

ETS: environmental tobacco smoke.

Risk estimates are shown for the imputed smoking variables. Risk estimates of the unimputed smoking variables can be found in supplementary Table 4 Adjusted model for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden). Random effects model applied for country.

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p-value<0.05.

**Supplementary Table 4.** Association between other smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls).

|  | Cases, % |       | Controls, % |       | p-value <sup>1</sup> | Unadjusted    |               | Model 1       |               | Model 2       |               |
|--|----------|-------|-------------|-------|----------------------|---------------|---------------|---------------|---------------|---------------|---------------|
|  |          |       |             |       |                      | OR            | (95%CI)       | OR            | (95%CI)       | OR            | (95%CI)       |
| <b>Ever smoked 100 cigarettes</b>        |          |       |             |       | <0.001               |               |               |               |               |               |               |
| No                                       | 764      | 38.00 | 691         | 45.10 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Yes                                      | 1245     | 62.00 | 841         | 54.90 |                      | 1.34          | (1.17 - 1.53) | 1.30          | (1.11 - 1.53) | 1.28          | (1.09 - 1.51) |
| <b>Regular smoker</b>                    |          |       |             |       | <0.001               |               |               |               |               |               |               |
| Never-smoker                             | 759      | 37.80 | 690         | 45.00 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Regular smoker                           | 1217     | 60.60 | 800         | 52.20 |                      | 1.38          | (1.21 - 1.58) | 1.33          | (1.13 - 1.57) | 1.31          | (1.11 - 1.55) |
| Occasional smoker                        | 33       | 1.64  | 42          | 2.74  |                      | 0.72          | (0.44 - 1.14) | 1.01          | (0.61 - 1.68) | 1.06          | (0.63 - 1.77) |
| <b>Tobacco type<sup>2</sup></b>          |          |       |             |       | 0.012                |               |               |               |               |               |               |
| Never-smoker                             | 355      | 40.50 | 360         | 47.20 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Smoker of black tobacco only             | 165      | 18.80 | 114         | 15.0  |                      | 1.47          | (1.11 - 1.94) | 1.55          | (1.13 - 2.12) | 1.46          | (1.06 - 2.02) |
| Smoker of blond tobacco only             | 204      | 23.30 | 182         | 23.90 |                      | 1.14          | (0.89 - 1.46) | 1.23          | (0.94 - 1.62) | 1.23          | (0.93 - 1.63) |
| Smoker of both tobacco types             | 152      | 17.40 | 106         | 13.90 |                      | 1.45          | (1.09 - 1.94) | 1.58          | (1.14 - 2.17) | 1.59          | (1.15 - 2.20) |
| <b>Current smoker</b>                    |          |       |             |       | <0.001               |               |               |               |               |               |               |
| Never-smoker                             | 759      | 37.80 | 690         | 45.00 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Current smoker                           | 391      | 19.50 | 231         | 15.10 |                      | 1.54          | (1.27 - 1.87) | 1.36          | (1.08 - 1.70) | 1.35          | (1.07 - 1.70) |
| Former smoker                            | 859      | 42.80 | 611         | 39.90 |                      | 1.28          | (1.10 - 1.48) | 1.30          | (1.10 - 1.55) | 1.28          | (1.07 - 1.53) |
| <b>Ever quit smoking &gt;6 months</b>    |          |       |             |       | <0.001               |               |               |               |               |               |               |
| Never-smoker                             | 759      | 37.80 | 690         | 45.00 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Yes                                      | 457      | 22.70 | 291         | 19.00 |                      | 1.43          | (1.19 - 1.71) | 1.35          | (1.10 - 1.68) | 1.36          | (1.10 - 1.69) |
| No                                       | 793      | 39.50 | 551         | 36.00 |                      | 1.31          | (1.13 - 1.52) | 1.30          | (1.09 - 1.55) | 1.27          | (1.06 - 1.52) |
| <b>Inhalation</b>                        |          |       |             |       | <0.001               |               |               |               |               |               |               |
| Never-smoker                             | 759      | 37.80 | 690         | 45.00 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Mouth only                               | 125      | 6.22  | 99          | 6.46  |                      | 1.15          | (0.86 - 1.53) | 1.10          | (0.80 - 1.50) | 1.01          | (0.73 - 1.40) |
| Throat                                   | 158      | 7.86  | 108         | 7.05  |                      | 1.33          | (1.02 - 1.74) | 1.48          | (1.11 - 1.99) | 1.43          | (1.06 - 1.93) |
| Chest                                    | 967      | 48.10 | 635         | 41.40 |                      | 1.38          | (1.20 - 1.60) | 1.33          | (1.12 - 1.58) | 1.33          | (1.11 - 1.59) |
|  |          |       |             |       |                      | p-trend<0.001 |               | p-trend<0.001 |               | p-trend<0.001 |               |
| <b>Filter-use</b>                        |          |       |             |       | <0.001               |               |               |               |               |               |               |
| Never-smoker                             | 759      | 37.80 | 690         | 45.00 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Filtered only                            | 1042     | 51.90 | 706         | 46.10 |                      | 1.34          | (1.17 - 1.54) | 1.25          | (1.06 - 1.48) | 1.23          | (1.04 - 1.47) |
| Non-filtered only                        | 65       | 3.24  | 49          | 3.20  |                      | 1.20          | (0.82 - 1.78) | 1.69          | (1.10 - 2.61) | 1.64          | (1.05 - 2.56) |
| Both                                     | 143      | 7.12  | 87          | 5.68  |                      | 1.49          | (1.12 - 1.99) | 1.65          | (1.21 - 2.27) | 1.68          | (1.21 - 2.31) |
|  |          |       |             |       |                      | p-trend<0.001 |               | p-trend<0.001 |               | p-trend<0.001 |               |
| <b>Smoking cigar</b>                     |          |       |             |       | 0.016                |               |               |               |               |               |               |
| No                                       | 1797     | 89.40 | 1408        | 91.90 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Yes                                      | 212      | 10.60 | 124         | 8.09  |                      | 1.34          | (1.06 - 1.69) | 1.00          | (0.76 - 1.32) | 0.98          | (0.74 - 1.30) |
| <b>Smoking pipe</b>                      |          |       |             |       | 0.001                |               |               |               |               |               |               |
| No                                       | 1742     | 86.70 | 1384        | 90.30 |                      | 1.00          |               | 1.00          |               | 1.00          |               |
| Yes                                      | 267      | 13.30 | 148         | 9.66  |                      | 1.43          | (1.16 - 1.78) | 1.13          | (0.86 - 1.49) | 1.11          | (0.84 - 1.47) |
| <b>Tobacco type for pipe<sup>3</sup></b> |          |       |             |       | <0.001               |               |               |               |               |               |               |
| No pipe smoker                           | 1742     | 86.70 | 1384        | 90.30 |                      | 1.00          |               | 1.00          |               | 1.00          |               |

|  |      |       |      |       |                 |               |                 |               |                 |               |
|--|------|-------|------|-------|-----------------|---------------|-----------------|---------------|-----------------|---------------|
| Black  | 14   | 0.70  | 16   | 1.04  | 0.70            | (0.33 - 1.44) | 0.78            | (0.37 - 1.66) | 0.65            | (0.29 - 1.43) |
| Blond  | 83   | 4.13  | 62   | 4.05  | 1.06            | (0.76 - 1.49) | 1.25            | (0.85 - 1.82) | 1.29            | (0.88 - 1.90) |
| Mixed  | 170  | 8.46  | 70   | 4.57  | 1.93            | (1.45 - 2.58) | 1.12            | (0.76 - 1.66) | 1.08            | (0.72 - 1.61) |
| <b>Smoking status (cigarettes)</b>                   |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| Former   | 699  | 34.80 | 568  | 37.10 | 1.12            | (0.96 - 1.30) | 1.14            | (0.95 - 1.36) | 1.11            | (0.93 - 1.34) |
| Current  | 551  | 27.40 | 274  | 17.90 | 1.83            | (1.53 - 2.18) | 1.69            | (1.37 - 2.09) | 1.69            | (1.37 - 2.10) |
|  |      |       |      |       | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| <b>Smoking status incl. occasional</b>               |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| Occasional   | 33   | 1.64  | 42   | 2.74  | 0.72            | (0.44 - 1.14) | 1.00            | (0.61 - 1.67) | 1.05            | (0.63 - 1.76) |
| Former   | 667  | 33.20 | 530  | 34.60 | 1.14            | (0.98 - 1.33) | 1.14            | (0.95 - 1.37) | 1.11            | (0.92 - 1.34) |
| Current  | 550  | 27.40 | 270  | 17.60 | 1.85            | (1.55 - 2.21) | 1.72            | (1.39 - 2.12) | 1.72            | (1.39 - 2.13) |
|  |      |       |      |       | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| <b>Quit smoking &lt;10 or ≥ 10 years ago</b>         |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Never-smoker and former smoker quit >10years         | 803  | 40.00 | 410  | 26.80 | 1.00            |               | 1.00            |               | 1.00            |               |
| Current smoker and former smoker quit ≤10years       | 1206 | 60.00 | 1122 | 73.20 | 0.55            | (0.48 - 0.63) | 0.64            | (0.54 - 0.76) | 0.64            | (0.54 - 0.76) |
| <b>Childhood exposure to ETS</b>                     |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Both parents were never-smokers                      | 420  | 20.90 | 391  | 25.50 | 1.00            |               | 1.00            |               | 1.00            |               |
| Only the father smoked                               | 1341 | 66.70 | 908  | 59.30 | 1.37            | (1.17 - 1.62) | 1.25            | (1.04 - 1.51) | 1.24            | (1.03 - 1.50) |
| Only the mother smoked                               | 37   | 1.84  | 44   | 2.87  | 0.78            | (0.49 - 1.24) | 1.02            | (0.62 - 1.70) | 0.96            | (0.57 - 1.62) |
| Both parents smoked                                  | 211  | 10.50 | 189  | 12.30 | 1.04            | (0.82 - 1.32) | 1.07            | (0.81 - 1.42) | 1.08            | (0.81 - 1.45) |
|  |      |       |      |       | p-trend = 0.977 |               | p-trend = 0.610 |               | p-trend = 0.586 |               |
| <b>Age at smoking initiation in tertiles (years)</b> |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| < 15   | 423  | 21.10 | 278  | 18.10 | 1.38            | (1.15 - 1.66) | 1.36            | (1.10 - 1.70) | 1.33            | (1.06 - 1.66) |
| 15 - 18  | 455  | 22.60 | 299  | 19.50 | 1.38            | (1.16 - 1.65) | 1.31            | (1.06 - 1.61) | 1.31            | (1.05 - 1.62) |
| ≥ 18   | 372  | 18.50 | 265  | 17.30 | 1.28            | (1.06 - 1.54) | 1.29            | (1.04 - 1.59) | 1.26            | (1.02 - 1.57) |
|  |      |       |      |       | p-trend<0.001   |               | p-trend = 0.010 |               | p-trend = 0.016 |               |
| <b>Age last smoked in tertiles (years)</b>           |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Current smoker                                       | 551  | 27.40 | 274  | 17.90 | 1.00            |               | 1.00            |               | 1.00            |               |
| < 38   | 192  | 9.56  | 198  | 12.90 | 0.48            | (0.38 - 0.62) | 0.56            | (0.43 - 0.74) | 0.58            | (0.44 - 0.77) |
| 38 - 50  | 255  | 12.70 | 193  | 12.60 | 0.66            | (0.52 - 0.83) | 0.71            | (0.55 - 0.93) | 0.69            | (0.52 - 0.90) |
| ≥ 50   | 252  | 12.50 | 177  | 11.60 | 0.71            | (0.56 - 0.90) | 0.76            | (0.58 - 1.01) | 0.72            | (0.54 - 0.96) |
| Never-smoker   | 759  | 37.80 | 690  | 45.00 | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| <b>Time of ever quitting in tertiles (years)</b>     |      |       |      |       | <0.001          |               |                 |               |                 |               |
| Current smoker who never quitted                     | 793  | 39.50 | 551  | 36.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| < 2  | 175  | 8.71  | 108  | 7.05  | 1.13            | (0.87 - 1.47) | 0.93            | (0.69 - 1.26) | 0.96            | (0.71 - 1.30) |
| 2 - 6  | 132  | 6.57  | 86   | 5.61  | 1.07            | (0.80 - 1.43) | 0.94            | (0.68 - 1.30) | 0.95            | (0.68 - 1.33) |
| ≥ 6  | 150  | 7.47  | 97   | 6.33  | 1.07            | (0.81 - 1.42) | 1.32            | (0.96 - 1.82) | 1.38            | (1.00 - 1.92) |
| Never-smoker   | 759  | 37.80 | 690  | 45.00 | p-trend = 0.020 |               | p-trend = 0.024 |               | p-trend = 0.015 |               |
| <b>Smoking duration in tertiles (years)</b>          |      |       |      |       | <0.001          |               |                 |               |                 |               |

|    |  |      |       |      |       |                 |               |                 |               |                 |               |
|----|--|------|-------|------|-------|-----------------|---------------|-----------------|---------------|-----------------|---------------|
| 1  |  |      |       |      |       |                 |               |                 |               |                 |               |
| 2  | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| 3  | < 23   | 292  | 14.50 | 284  | 18.50 | 0.93            | (0.77 - 1.13) | 0.91            | (0.72 - 1.14) | 0.93            | (0.73 - 1.17) |
| 4  | 23 - 35  | 477  | 23.70 | 281  | 18.30 | 1.54            | (1.29 - 1.85) | 1.52            | (1.23 - 1.87) | 1.48            | (1.20 - 1.84) |
| 5  | ≥ 35   | 481  | 23.90 | 277  | 18.10 | 1.58            | (1.32 - 1.89) | 1.51            | (1.23 - 1.86) | 1.47            | (1.19 - 1.82) |
| 6  |  |      |       |      |       | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| 7  | <b>Smoking intensity in tertiles (cigarettes per day)</b>        |      |       |      |       | <0.001          |               |                 |               |                 |               |
| 8  | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| 9  | < 10   | 389  | 19.40 | 343  | 22.40 | 1.03            | (0.86 - 1.23) | 1.02            | (0.83 - 1.25) | 0.92            | (0.73 - 1.16) |
| 10 | 10 - 20  | 533  | 26.50 | 287  | 18.70 | 1.69            | (1.42 - 2.02) | 1.64            | (1.34 - 2.02) | 1.55            | (1.25 - 1.93) |
| 11 | ≥ 20   | 328  | 16.30 | 212  | 13.80 | 1.41            | (1.15 - 1.72) | 1.41            | (1.12 - 1.78) | 1.44            | (1.16 - 1.78) |
| 12 |  |      |       |      |       | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| 13 | <b>Cumulative dose in tertiles (pack-years)</b>                  |      |       |      |       | <0.001          |               |                 |               |                 |               |
| 14 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| 15 | < 14   | 279  | 13.90 | 281  | 18.30 | 0.90            | (0.74 - 1.10) | 0.90            | (0.72 - 1.13) | 1.01            | (0.82 - 1.25) |
| 16 | 14 - 32  | 494  | 24.60 | 275  | 18.00 | 1.63            | (1.36 - 1.96) | 1.57            | (1.27 - 1.94) | 1.63            | (1.32 - 2.01) |
| 17 | ≥ 32   | 477  | 23.70 | 286  | 18.70 | 1.52            | (1.27 - 1.81) | 1.50            | (1.21 - 1.84) | 1.37            | (1.08 - 1.74) |
| 18 |  |      |       |      |       | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| 19 | <b>Time since cessation in tertiles (years)</b>                  |      |       |      |       | <0.001          |               |                 |               |                 |               |
| 20 | Current smoker   | 551  | 27.40 | 274  | 17.90 | 1.00            |               | 1.00            |               | 1.00            |               |
| 21 | < 14   | 320  | 15.90 | 191  | 12.50 | 0.83            | (0.66 - 1.05) | 0.81            | (0.62 - 1.04) | 0.78            | (0.60 - 1.01) |
| 22 | 14 - 28  | 229  | 11.40 | 185  | 12.10 | 0.62            | (0.48 - 0.78) | 0.67            | (0.51 - 0.88) | 0.65            | (0.49 - 0.87) |
| 23 | ≥ 28   | 150  | 7.47  | 192  | 12.50 | 0.39            | (0.30 - 0.50) | 0.49            | (0.36 - 0.66) | 0.49            | (0.36 - 0.67) |
| 24 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | p-trend<0.001   |               | p-trend<0.001   |               | p-trend<0.001   |               |
| 25 | <b>Intensity of smoking cigars in tertiles (cigars per week)</b> |      |       |      |       | <0.001          |               |                 |               |                 |               |
| 26 | Never-smoker   | 1661 | 82.70 | 1356 | 88.50 | 1.00            |               | 1.00            |               | 1.00            |               |
| 27 | < 1.0  | 145  | 7.22  | 68   | 4.44  | 1.74            | (1.30 - 2.35) | 0.95            | (0.67 - 1.34) | 0.96            | (0.67 - 1.37) |
| 28 | 1.0 - 6.2  | 86   | 4.28  | 48   | 3.13  | 1.46            | (1.02 - 2.11) | 0.91            | (0.59 - 1.39) | 0.91            | (0.59 - 1.41) |
| 29 | ≥ 6.2  | 117  | 5.82  | 60   | 3.92  | 1.59            | (1.16 - 2.20) | 1.20            | (0.84 - 1.73) | 1.16            | (0.80 - 1.69) |
| 30 |  |      |       |      |       | p-trend<0.001   |               | p-trend = 0.571 |               | p-trend = 0.678 |               |
| 31 | <b>Intensity of smoking pipes in tertiles (pipes per week)</b>   |      |       |      |       | <0.001          |               |                 |               |                 |               |
| 32 | Never-smoker   | 1697 | 84.50 | 1363 | 89.00 | 1.00            |               | 1.00            |               | 1.00            |               |
| 33 | < 5.0  | 96   | 4.78  | 58   | 3.79  | 1.33            | (0.95 - 1.86) | 1.13            | (0.78 - 1.64) | 1.12            | (0.76 - 1.65) |
| 34 | 5.0 - 14.4   | 173  | 8.61  | 53   | 3.46  | 2.62            | (1.92 - 3.62) | 1.32            | (0.89 - 1.97) | 1.29            | (0.85 - 1.94) |
| 35 | ≥ 14.4   | 43   | 2.14  | 58   | 3.79  | 0.60            | (0.40 - 0.89) | 1.20            | (0.78 - 1.85) | 1.19            | (0.76 - 1.85) |
| 36 |  |      |       |      |       | p-trend = 0.007 |               | p-trend = 0.141 |               | p-trend = 0.188 |               |

PC: pancreatic cancer; ETS: environmental tobacco smoke.

Results are shown for the categorical, imputed smoking variables. For the risk estimates of the continuous smoking variables, the unimputed data was used. The unimputed, continuous smoking variables and can be found in supplementary Table 5.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden). Random effects model applied for country;

Model 2: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female), country (Spain, England, Germany, Ireland, Italy, Sweden), family history of PC (yes/no) and diabetes (yes/no) Random effects model applied for country.

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p<0.05.

<sup>2</sup> Type of tobacco was only collected for Spain.

<sup>3</sup> Type of pipe was not collected for Ireland.

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3**Supplementary Table 5.** Association between smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls), stratified by gender, diabetes status and status for family history of pancreatic cancer.

|   | Model 1 |               | Gender           |               |                |               | Diabetes    |               |             |               | Family history of PC |               |             |                |
|---|---------|---------------|------------------|---------------|----------------|---------------|-------------|---------------|-------------|---------------|----------------------|---------------|-------------|----------------|
|   | OR      | (95%CI)       | Females (N=1572) |               | Males (N=1969) |               | No (N=2861) |               | Yes (N=680) |               | No (N=3374)          |               | Yes (N=167) |                |
|   |         |               | OR               | (95%CI)       | OR             | (95%CI)       | OR          | (95%CI)       | OR          | (95%CI)       | OR                   | (95%CI)       | OR          | (95%CI)        |
| <b>Ever smoked 100 cigarettes</b>       |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 9 No                                    | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 10 Yes                                  | 1.30    | (1.11 - 1.53) | 1.19             | (0.93 - 1.54) | 1.44           | (1.16 - 1.80) | 1.28        | (1.07 - 1.53) | 1.20        | (0.78 - 1.83) | 1.29                 | (1.09 - 1.52) | 1.64        | (0.68 - 3.98)  |
| 11 p-value for interaction <sup>1</sup> |         |               | 0.170            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Regular smoker</b>                   |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 13 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 14 Regular smoker                       | 1.33    | (1.13 - 1.57) | 1.23             | (0.95 - 1.58) | 1.48           | (1.18 - 1.85) | 1.31        | (1.09 - 1.57) | 1.25        | (0.81 - 1.91) | 1.32                 | (1.12 - 1.56) | 1.73        | (0.70 - 4.24)  |
| 15 Occasional smoker                    | 1.01    | (0.61 - 1.68) | 0.93             | (0.39 - 2.24) | 1.13           | (0.61 - 2.12) | 1.20        | (0.69 - 2.09) | 0.54        | (0.15 - 1.99) | 1.04                 | (0.62 - 1.75) | 0.11        | (0.00 - 30.94) |
| 16 p-value for interaction              |         |               | 0.398            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Tobacco type<sup>2</sup></b>         |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 17 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 18 Smoker of black tobacco only         | 1.55    | (1.13 - 2.12) | 0.99             | (0.46 - 2.10) | 1.73           | (1.20 - 2.51) | 1.62        | (1.13 - 2.34) | 1.12        | (0.57 - 2.19) | 1.62                 | (1.18 - 2.24) | 0.55        | (0.10 - 3.12)  |
| 19 Smoker of blond tobacco only         | 1.23    | (0.94 - 1.62) | 1.23             | (0.83 - 1.82) | 1.23           | (0.84 - 1.80) | 1.20        | (0.88 - 1.64) | 1.23        | (0.66 - 2.29) | 1.29                 | (0.98 - 1.70) | 1.32        | (0.24 - 7.40)  |
| 20 Smoker of both tobacco types         | 1.58    | (1.14 - 2.17) | 1.02             | (0.52 - 1.98) | 1.77           | (1.20 - 2.61) | 1.67        | (1.16 - 2.41) | 1.34        | (0.64 - 2.82) | 1.57                 | (1.13 - 2.18) | 1.35        | (0.19 - 9.81)  |
| 21 p-value for interaction              |         |               | 0.309            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Current smoker</b>                   |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 22 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 23 Current smoker                       | 1.36    | (1.08 - 1.70) | 1.39             | (0.96 - 2.00) | 1.42           | (1.06 - 1.91) | 1.52        | (1.18 - 1.95) | 0.62        | (0.34 - 1.13) | 1.35                 | (1.07 - 1.70) | 1.84        | (0.48 - 6.99)  |
| 24 Former smoker                        | 1.30    | (1.10 - 1.55) | 1.14             | (0.87 - 1.50) | 1.48           | (1.17 - 1.86) | 1.23        | (1.01 - 1.49) | 1.44        | (0.92 - 2.25) | 1.29                 | (1.08 - 1.54) | 1.58        | (0.62 - 4.06)  |
| 25 p-value for interaction              |         |               | 0.208            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Ever quit smoking &gt;6 months</b>   |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 27 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 28 Yes                                  | 1.35    | (1.10 - 1.68) | 1.22             | (0.87 - 1.73) | 1.51           | (1.14 - 1.99) | 1.29        | (1.02 - 1.64) | 1.78        | (0.98 - 3.25) | 1.37                 | (1.10 - 1.70) | 1.05        | (0.30 - 3.65)  |
| 29 No                                   | 1.30    | (1.09 - 1.55) | 1.21             | (0.91 - 1.60) | 1.44           | (1.14 - 1.82) | 1.31        | (1.08 - 1.60) | 1.03        | (0.66 - 1.61) | 1.28                 | (1.06 - 1.53) | 1.97        | (0.74 - 5.20)  |
| 30 p-value for interaction              |         |               | 0.385            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Inhalation</b>                       |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 31 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 32 Mouth only                           | 1.10    | (0.80 - 1.50) | 0.84             | (0.52 - 1.36) | 1.44           | (0.93 - 2.22) | 0.90        | (0.62 - 1.31) | 1.38        | (0.69 - 2.77) | 1.02                 | (0.74 - 1.41) | 5.83        | (0.66 - 51.52) |
| 33 Throat                               | 1.48    | (1.11 - 1.99) | 1.71             | (1.11 - 2.63) | 1.40           | (0.93 - 2.11) | 1.44        | (1.03 - 2.00) | 1.27        | (0.63 - 2.54) | 1.54                 | (1.14 - 2.07) | 0.64        | (0.13 - 3.19)  |
| 34 Chest                                | 1.33    | (1.12 - 1.58) | 1.20             | (0.90 - 1.60) | 1.47           | (1.17 - 1.85) | 1.36        | (1.12 - 1.65) | 1.13        | (0.71 - 1.79) | 1.32                 | (1.10 - 1.58) | 1.61        | (0.60 - 4.34)  |
| 35 p-value for interaction              |         |               | 0.173            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |
| <b>Filter-use</b>                       |         |               |                  |               |                |               |             |               |             |               |                      |               |             |                |
| 36 Never-smoker                         | 1.00    |               | 1.00             |               | 1.00           |               | 1.00        |               | 1.00        |               | 1.00                 |               | 1.00        |                |
| 37 Filtered only                        | 1.25    | (1.06 - 1.48) | 1.24             | (0.96 - 1.60) | 1.34           | (1.06 - 1.69) | 1.25        | (1.04 - 1.51) | 1.09        | (0.70 - 1.68) | 1.25                 | (1.05 - 1.48) | 1.38        | (0.56 - 3.42)  |
| 38 Non-filtered only                    | 1.69    | (1.10 - 2.61) | 0.76             | (0.24 - 2.41) | 2.01           | (1.24 - 3.25) | 1.81        | (1.11 - 2.94) | 0.97        | (0.37 - 2.55) | 1.54                 | (0.99 - 2.41) | ###         | (0.00 - Inf)   |
| 39 Both                                 | 1.65    | (1.21 - 2.27) | 1.01             | (0.37 - 2.78) | 1.87           | (1.32 - 2.66) | 1.50        | (1.05 - 2.14) | 2.26        | (1.05 - 4.86) | 1.66                 | (1.2 - 2.28)  | 2.74        | (0.29 - 25.66) |
| 40 p-value for interaction              |         |               | 0.222            |               |                |               | <0.001      |               |             |               | <0.001               |               |             |                |

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|    |  |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
|----|--|------|---------------|-------|---------------|------|---------------|--------|---------------|------|---------------|--------|---------------|------|----------------|
| 1  |  |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 2  |  |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 3  | <b>Smoking cigar</b>                                 |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 4  | No   | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 5  | Yes  | 1.00 | (0.76 - 1.32) | 0.58  | (0.17 - 1.92) | 1.03 | (0.78 - 1.36) | 1.02   | (0.74 - 1.40) | 0.73 | (0.41 - 1.29) | 0.99   | (0.75 - 1.31) | 0.69 | (0.18 - 2.63)  |
| 6  | p-value for interaction                              |      |               | 0.402 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 7  | <b>Smoking pipe</b>                                  |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 8  | No   | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 9  | Yes  | 1.13 | (0.86 - 1.49) | 2.37  | (0.70 - 8.00) | 1.04 | (0.79 - 1.39) | 1.09   | (0.80 - 1.48) | 1.07 | (0.55 - 2.07) | 1.17   | (0.88 - 1.55) | 0.49 | (0.12 - 2.01)  |
| 10 | p-value for interaction                              |      |               | 0.274 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 11 | <b>Tobacco type for pipe<sup>3</sup></b>             |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 12 | No pipe smoker                                       | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 13 | Black  | 0.78 | (0.37 - 1.66) | 0.70  | (0.07 - 6.81) | 0.78 | (0.36 - 1.66) | 0.75   | (0.29 - 1.95) | 0.46 | (0.12 - 1.84) | 0.81   | (0.37 - 1.77) | 0.35 | (0.02 - 6.83)  |
| 14 | Blond  | 1.25 | (0.85 - 1.82) | 4.84  | (0.91 - 25.8) | 1.21 | (0.82 - 1.79) | 1.23   | (0.81 - 1.88) | 1.29 | (0.50 - 3.33) | 1.27   | (0.86 - 1.87) | ###  | (0.00 - Inf)   |
| 15 | Mixed  | 1.12 | (0.76 - 1.66) | 1.03  | (0.71 - 1.50) | 0.96 | (0.63 - 1.45) | 1.03   | (0.66 - 1.61) | 1.29 | (0.46 - 3.63) | 1.16   | (0.77 - 1.75) | 0.20 | (0.03 - 1.26)  |
| 16 | p-value for interaction                              |      |               | 0.158 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 17 | <b>Smoking status (cigarettes)</b>                   |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 18 | Never-smoker   | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 19 | Former   | 1.14 | (0.95 - 1.36) | 0.86  | (0.64 - 1.16) | 1.37 | (1.08 - 1.73) | 1.04   | (0.85 - 1.27) | 1.44 | (0.91 - 2.28) | 1.12   | (0.93 - 1.35) | 1.38 | (0.52 - 3.70)  |
| 20 | Current  | 1.69 | (1.37 - 2.09) | 1.96  | (1.40 - 2.73) | 1.67 | (1.26 - 2.20) | 1.89   | (1.50 - 2.38) | 0.83 | (0.48 - 1.42) | 1.69   | (1.37 - 2.09) | 2.24 | (0.66 - 7.61)  |
| 21 | p-value for interaction                              |      |               | 0.006 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 22 | <b>Smoking status incl. occasional</b>               |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 23 | Never-smoker   | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 24 | Occasional   | 1.00 | (0.61 - 1.67) | 0.90  | (0.38 - 2.17) | 1.13 | (0.61 - 2.12) | 1.19   | (0.69 - 2.07) | 0.55 | (0.15 - 2.05) | 1.04   | (0.62 - 1.74) | 0.11 | (0.00 - 3.75)  |
| 25 | Former   | 1.14 | (0.95 - 1.37) | 0.85  | (0.63 - 1.16) | 1.37 | (1.08 - 1.75) | 1.03   | (0.84 - 1.26) | 1.52 | (0.95 - 2.43) | 1.12   | (0.93 - 1.35) | 1.49 | (0.55 - 4.05)  |
| 26 | Current  | 1.72 | (1.39 - 2.12) | 1.98  | (1.42 - 2.77) | 1.69 | (1.28 - 2.23) | 1.91   | (1.52 - 2.41) | 0.86 | (0.50 - 1.48) | 1.71   | (1.38 - 2.12) | 2.25 | (0.66 - 7.69)  |
| 27 | p-value for interaction                              |      |               | 0.016 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 28 | <b>Quit smoking &lt;10 or ≥ 10 years ago</b>         |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 29 | Never-smoker and former                              | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 30 | smoker quit >10years                                 |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 31 | Current smoker and former                            | 0.64 | (0.54 - 0.76) | 0.55  | (0.41 - 0.72) | 0.69 | (0.56 - 0.85) | 0.58   | (0.48 - 0.71) | 1.10 | (0.72 - 1.68) | 0.64   | (0.54 - 0.76) | 0.47 | (0.17 - 1.31)  |
| 32 | smoker quit ≤10years                                 |      |               | 0.193 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 33 | p-value for interaction                              |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 34 | <b>Childhood exposure to ETS</b>                     |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 35 | Both parents were never-                             | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 36 | smokers  |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 37 | Only the father smoked                               | 1.25 | (1.04 - 1.51) | 1.36  | (1.02 - 1.80) | 1.18 | (0.92 - 1.52) | 1.24   | (1.01 - 1.53) | 1.21 | (0.78 - 1.90) | 1.23   | (1.02 - 1.49) | 1.75 | (0.59 - 5.22)  |
| 38 | Only the mother smoked                               | 1.02 | (0.62 - 1.70) | 0.95  | (0.44 - 2.05) | 1.06 | (0.53 - 2.12) | 1.00   | (0.57 - 1.73) | 1.08 | (0.24 - 4.83) | 0.90   | (0.53 - 1.55) | 3.29 | (0.23 - 46.93) |
| 39 | Both parents smoked                                  | 1.07 | (0.81 - 1.42) | 1.23  | (0.80 - 1.91) | 0.96 | (0.66 - 1.39) | 1.11   | (0.82 - 1.51) | 1.04 | (0.41 - 2.66) | 1.11   | (0.83 - 1.48) | 0.28 | (0.05 - 1.49)  |
| 40 | p-value for interaction                              |      |               | 0.785 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |
| 41 | <b>Age at smoking initiation in tertiles (years)</b> |      |               |       |               |      |               |        |               |      |               |        |               |      |                |
| 42 | Never-smoker   | 1.00 |               | 1.00  |               | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |                |
| 43 | < 15   | 1.38 | (1.15 - 1.66) | 0.95  | (0.6 - 1.50)  | 1.56 | (1.20 - 2.04) | 1.38   | (1.08 - 1.76) | 0.95 | (0.55 - 1.65) | 1.41   | (1.12 - 1.76) | 0.52 | (0.15 - 1.83)  |
| 44 | 15 - 18  | 1.38 | (1.16 - 1.65) | 1.04  | (0.74 - 1.47) | 1.53 | (1.16 - 2.01) | 1.35   | (1.07 - 1.70) | 0.99 | (0.57 - 1.72) | 1.27   | (1.03 - 1.58) | 2.01 | (0.58 - 6.97)  |
| 45 | ≥ 18   | 1.28 | (1.06 - 1.54) | 1.47  | (1.08 - 2.02) | 1.24 | (0.92 - 1.67) | 1.20   | (0.95 - 1.53) | 1.70 | (0.97 - 2.97) | 1.26   | (1.01 - 1.56) | 3.48 | (0.91 - 13.28) |
| 46 | p-value for interaction                              |      |               | 0.049 |               |      |               | <0.001 |               |      |               | <0.001 |               |      |                |

|    |  |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
|----|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|------|------|------|------|------|------|
| 1  |  |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 2  |  |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 3  | <b>Age last smoked in tertiles (years)</b>                       |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 4  | Current smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 5  | < 38   | 0.48 (0.38 - 0.62) | 0.24 (0.14 - 0.41) | 0.79 (0.57 - 1.10) | 0.49 (0.36 - 0.66) | 2.06 (0.85 - 4.96) | 0.55 (0.42 - 0.73) | 0.64 (0.13 - 3.16)  |      |      |      |      |      |      |
| 6  | 38 - 50  | 0.66 (0.52 - 0.83) | 0.56 (0.34 - 0.91) | 0.81 (0.58 - 1.11) | 0.56 (0.41 - 0.76) | 1.63 (0.86 - 3.10) | 0.72 (0.54 - 0.94) | 0.66 (0.12 - 3.63)  |      |      |      |      |      |      |
| 7  | ≥ 50   | 0.71 (0.56 - 0.90) | 0.64 (0.38 - 1.06) | 0.87 (0.62 - 1.21) | 0.64 (0.46 - 0.87) | 1.72 (0.91 - 3.25) | 0.75 (0.56 - 0.99) | 0.57 (0.12 - 2.70)  |      |      |      |      |      |      |
| 8  | Never-smoker   | 0.55 (0.46 - 0.65) | 0.53 (0.38 - 0.74) | 0.60 (0.46 - 0.79) | 0.53 (0.42 - 0.67) | 1.21 (0.70 - 2.08) | 0.60 (0.48 - 0.74) | 0.44 (0.13 - 1.51)  |      |      |      |      |      |      |
| 9  | p-value for interaction  |                    | 0.001              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 10 | <b>Time of ever quitting in tertiles (years)</b>                 |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 11 | Current smoker who never   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 12 | quitted  | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 13 | < 2  | 1.13 (0.87 - 1.47) | 1.09 (0.65 - 1.84) | 0.85 (0.59 - 1.23) | 0.87 (0.63 - 1.21) | 2.89 (0.95 - 8.79) | 0.95 (0.70 - 1.29) | 0.50 (0.11 - 2.22)  |      |      |      |      |      |      |
| 14 | 2 - 6  | 1.07 (0.80 - 1.43) | 0.74 (0.42 - 1.30) | 1.08 (0.71 - 1.63) | 0.92 (0.64 - 1.32) | 1.21 (0.50 - 2.91) | 0.99 (0.71 - 1.38) | 0.32 (0.05 - 2.21)  |      |      |      |      |      |      |
| 15 | ≥ 6  | 1.07 (0.81 - 1.42) | 1.29 (0.73 - 2.27) | 1.30 (0.88 - 1.93) | 1.24 (0.87 - 1.79) | 1.68 (0.74 - 3.82) | 1.32 (0.96 - 1.84) | ### (0.00 - Inf)    |      |      |      |      |      |      |
| 16 | Never-smoker   | 0.76 (0.66 - 0.89) | 0.83 (0.63 - 1.10) | 0.70 (0.55 - 0.88) | 0.76 (0.63 - 0.93) | 0.96 (0.61 - 1.50) | 0.78 (0.65 - 0.94) | 0.52 (0.20 - 1.37)  |      |      |      |      |      |      |
| 17 | p-value for interaction  |                    | 0.412              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 18 | <b>Smoking duration in tertiles (years)</b>                      |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 19 | Never-smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 20 | < 23   | 0.93 (0.77 - 1.13) | 0.57 (0.39 - 0.84) | 1.20 (0.89 - 1.61) | 0.87 (0.67 - 1.12) | 1.27 (0.66 - 2.45) | 0.89 (0.70 - 1.13) | 1.91 (0.50 - 7.30)  |      |      |      |      |      |      |
| 21 | 23 - 35  | 1.54 (1.29 - 1.85) | 1.59 (1.13 - 2.23) | 1.57 (1.19 - 2.06) | 1.47 (1.17 - 1.86) | 1.43 (0.82 - 2.48) | 1.53 (1.23 - 1.90) | 1.24 (0.35 - 4.41)  |      |      |      |      |      |      |
| 22 | ≥ 35   | 1.58 (1.32 - 1.89) | 1.72 (1.19 - 2.47) | 1.58 (1.21 - 2.06) | 1.60 (1.26 - 2.02) | 1.02 (0.62 - 1.68) | 1.48 (1.20 - 1.84) | 1.79 (0.59 - 5.42)  |      |      |      |      |      |      |
| 23 | p-value for interaction  |                    | 0.007              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 24 | <b>Smoking intensity in tertiles (cigarettes per day)</b>        |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 25 | Never-smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 26 | < 10   | 1.03 (0.86 - 1.23) | 0.93 (0.68 - 1.27) | 1.15 (0.86 - 1.54) | 1.00 (0.79 - 1.26) | 1.01 (0.60 - 1.71) | 0.98 (0.79 - 1.21) | 2.93 (0.76 - 11.28) |      |      |      |      |      |      |
| 27 | 10 - 20  | 1.69 (1.42 - 2.02) | 1.85 (1.31 - 2.62) | 1.64 (1.25 - 2.14) | 1.64 (1.31 - 2.06) | 1.47 (0.84 - 2.57) | 1.65 (1.33 - 2.04) | 1.84 (0.57 - 5.94)  |      |      |      |      |      |      |
| 28 | ≥ 20   | 1.41 (1.15 - 1.72) | 1.06 (0.65 - 1.73) | 1.61 (1.21 - 2.13) | 1.40 (1.08 - 1.82) | 1.21 (0.68 - 2.13) | 1.44 (1.13 - 1.83) | 0.73 (0.21 - 2.57)  |      |      |      |      |      |      |
| 29 | p-value for interaction  |                    | 0.271              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 30 | <b>Cumulative dose in tertiles (pack-years)</b>                  |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 31 | Never-smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 32 | < 14   | 0.90 (0.74 - 1.10) | 0.82 (0.58 - 1.16) | 1.01 (0.74 - 1.37) | 0.91 (0.70 - 1.17) | 0.94 (0.51 - 1.73) | 0.88 (0.69 - 1.11) | 2.12 (0.56 - 8.03)  |      |      |      |      |      |      |
| 33 | 14 - 32  | 1.63 (1.36 - 1.96) | 1.50 (1.06 - 2.11) | 1.70 (1.29 - 2.23) | 1.52 (1.20 - 1.92) | 1.56 (0.89 - 2.73) | 1.57 (1.27 - 1.95) | 1.52 (0.45 - 5.15)  |      |      |      |      |      |      |
| 34 | ≥ 32   | 1.52 (1.27 - 1.81) | 1.53 (1.04 - 2.25) | 1.59 (1.22 - 2.07) | 1.51 (1.20 - 1.91) | 1.13 (0.68 - 1.89) | 1.48 (1.20 - 1.84) | 1.44 (0.45 - 4.57)  |      |      |      |      |      |      |
| 35 | p-value for interaction  |                    | 0.681              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 36 | <b>Time since cessation in tertiles (years)</b>                  |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 37 | Current smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 38 | < 14   | 0.83 (0.66 - 1.05) | 0.62 (0.40 - 0.97) | 0.93 (0.68 - 1.27) | 0.67 (0.50 - 0.89) | 1.94 (1.02 - 3.69) | 0.81 (0.62 - 1.05) | 0.43 (0.09 - 1.98)  |      |      |      |      |      |      |
| 39 | 14 - 28  | 0.62 (0.48 - 0.78) | 0.43 (0.26 - 0.71) | 0.82 (0.59 - 1.14) | 0.56 (0.41 - 0.76) | 1.64 (0.84 - 3.19) | 0.66 (0.50 - 0.87) | 0.79 (0.16 - 3.84)  |      |      |      |      |      |      |
| 40 | ≥ 28   | 0.39 (0.30 - 0.50) | 0.21 (0.11 - 0.39) | 0.66 (0.46 - 0.94) | 0.39 (0.28 - 0.55) | 1.55 (0.74 - 3.26) | 0.47 (0.34 - 0.64) | 0.74 (0.13 - 4.38)  |      |      |      |      |      |      |
| 41 | Never-smoker   | 0.55 (0.46 - 0.65) | 0.50 (0.36 - 0.70) | 0.59 (0.45 - 0.78) | 0.52 (0.41 - 0.66) | 1.21 (0.70 - 2.07) | 0.58 (0.47 - 0.72) | 0.45 (0.13 - 1.54)  |      |      |      |      |      |      |
| 42 | p-value for interaction  |                    | 0.005              |                    | <0.001             |                    | <0.001             |                     |      |      |      |      |      |      |
| 43 | <b>Intensity of smoking cigars in tertiles (cigars per week)</b> |                    |                    |                    |                    |                    |                    |                     |      |      |      |      |      |      |
| 44 | Never-smoker   | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00               | 1.00                | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 45 | < 1.0  | 1.74 (1.30 - 2.35) | 1 (0.48 - 1.76)    | 0.96 (0.63 - 1.46) | 0.94 (0.63 - 1.41) | 1.14 (0.49 - 2.66) | 0.96 (0.66 - 1.38) | 0 (0.09 - 2.39)     |      |      |      |      |      |      |
| 46 | 1.0 - 6.2  | 1.46 (1.02 - 2.11) | 0.57 (0.11 - 2.82) | 0.94 (0.60 - 1.47) | 1.21 (0.72 - 2.02) | 0.34 (0.15 - 0.76) | 0.87 (0.56 - 1.35) | ### (0.00 - Inf)    |      |      |      |      |      |      |

|    |  |      |               |       |                |      |               |        |               |      |               |        |               |      |               |
|----|--|------|---------------|-------|----------------|------|---------------|--------|---------------|------|---------------|--------|---------------|------|---------------|
| 1  |  |      |               |       |                |      |               |        |               |      |               |        |               |      |               |
| 2  | ≥ 6.2  | 1.59 | (1.16 - 2.20) | 0.36  | (0.06 - 2.10)  | 1.27 | (0.88 - 1.84) | 1.06   | (0.69 - 1.61) | 1.59 | (0.66 - 3.86) | 1.26   | (0.86 - 1.83) | 0.30 | (0.07 - 1.27) |
| 3  | p-value for interaction  |      |               | 0.552 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 4  | <b>Intensity of smoking pipes in tertiles (pipes per week)</b> |      |               |       |                |      |               |        |               |      |               |        |               |      |               |
| 5  | Never-smoker   | 1.00 |               | 1.00  |                | 1.00 |               | 1.00   |               | 1.00 |               | 1.00   |               | 1.00 |               |
| 6  | < 5.0  | 1.33 | (0.95 - 1.86) | 2.03  | (0.77 - 5.36)  | 1.01 | (0.67 - 1.52) | 1.22   | (0.79 - 1.89) | 0.75 | (0.35 - 1.62) | 1.14   | (0.78 - 1.66) | ###  | (0 - Inf)     |
| 7  | 5.0 – 14.4   | 2.62 | (1.92 - 3.62) | 1.11  | (0.19 - 6.60)  | 1.28 | (0.85 - 1.93) | 1.20   | (0.77 - 1.88) | 2.32 | (0.73 - 7.36) | 1.34   | (0.88 - 2.03) | 0.57 | (0.09 - 3.44) |
| 8  | ≥ 14.4   | 0.60 | (0.40 - 0.89) | 2.38  | (0.15 - 38.63) | 1.10 | (0.70 - 1.73) | 1.13   | (0.69 - 1.85) | 1.29 | (0.41 - 4.02) | 1.32   | (0.84 - 2.06) | 0.16 | (0.02 - 1.62) |
| 9  | p-value for interaction  |      |               | 0.562 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 10 | <b>Smoking duration (years)</b>                                | 1.01 | (1.01 - 1.01) | 1.27  | (1.12 - 1.44)  | 1.21 | (1.09 - 1.35) | 1.24   | (1.13 - 1.36) | 1.02 | (0.83 - 1.25) | 1.22   | (1.12 - 1.33) | 1.33 | (0.80 - 2.23) |
| 11 | p-value for interaction  |      |               | 0.426 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 12 | <b>Smoking intensity (cigs/day)</b>                            | 1.01 | (1.00 - 1.01) | 1.10  | (0.98 - 1.24)  | 1.17 | (1.06 - 1.30) | 1.15   | (1.05 - 1.25) | 1.01 | (0.83 - 1.24) | 1.15   | (1.06 - 1.25) | 0.82 | (0.54 - 1.26) |
| 13 | p-value for interaction  |      |               | 0.984 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 14 | <b>Cumulative dose (pack-years)</b>                            | 1.01 | (1.00 - 1.01) | 1.20  | (1.06 - 1.36)  | 1.20 | (1.08 - 1.34) | 1.22   | (1.11 - 1.34) | 0.97 | (0.80 - 1.18) | 1.19   | (1.10 - 1.30) | 0.88 | (0.55 - 1.39) |
| 15 | p-value for interaction  |      |               | 0.161 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 16 | <b>Time since cessation (years)</b>                            | 0.98 | (0.97 - 0.99) | 0.50  | (0.39 - 0.63)  | 0.87 | (0.76 - 1.00) | 0.69   | (0.60 - 0.78) | 1.10 | (0.83 - 1.44) | 0.74   | (0.66 - 0.84) | 0.99 | (0.52 - 1.90) |
| 17 | p-value for interaction  |      |               | 0.001 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 18 | <b>Age at smoking initiation (years)</b>                       | 1.01 | (1.00 - 1.02) | 1.09  | (0.97 - 1.23)  | 1.12 | (1.02 - 1.24) | 1.10   | (1.01 - 1.19) | 1.08 | (0.89 - 1.30) | 1.09   | (1.01 - 1.18) | 1.35 | (0.88 - 2.09) |
| 19 | p-value for interaction  |      |               | 0.410 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 20 | <b>Age last smoked (years)</b>                                 | 1.01 | (1.00 - 1.01) | 1.17  | (1.04 - 1.31)  | 1.13 | (1.02 - 1.25) | 1.09   | (1.00 - 1.19) | 1.25 | (1.02 - 1.52) | 1.13   | (1.04 - 1.22) | 1.33 | (0.84 - 2.11) |
| 21 | p-value for interaction  |      |               | 0.658 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 22 | <b>Time of ever quitting (years)</b>                           | 1.00 | (0.98 - 1.03) | 1.01  | (0.89 - 1.15)  | 1.01 | (0.91 - 1.12) | 0.99   | (0.91 - 1.09) | 1.12 | (0.88 - 1.44) | 1.02   | (0.94 - 1.10) | 0.97 | (0.50 - 1.86) |
| 23 | p-value for interaction  |      |               | 0.899 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 24 | <b>Intensity of smoking cigars (cigars per week)</b>           | 1.00 | (0.98 - 1.02) | 0.98  | (0.86 - 1.11)  | 1.04 | (0.94 - 1.15) | 0.98   | (0.90 - 1.07) | 1.17 | (0.86 - 1.60) | 1.04   | (0.95 - 1.12) | 0.72 | (0.49 - 1.07) |
| 25 | p-value for interaction  |      |               | 0.696 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |
| 26 | <b>Intensity of smoking pipes (pipes per week)</b>             | 1.00 | (0.98 - 1.01) | 1.19  | (0.78 - 1.81)  | 0.99 | (0.89 - 1.10) | 0.99   | (0.90 - 1.08) | 1.07 | (0.87 - 1.33) | 1.02   | (0.94 - 1.11) | 0.68 | (0.44 - 1.04) |
| 27 | p-value for interaction  |      |               | 0.108 |                |      |               | <0.001 |               |      |               | <0.001 |               |      |               |

PC: pancreatic cancer; ETS: environmental tobacco smoke.

Results are shown for the categorical, imputed smoking variables, and for the continuous, unimputed smoking variables.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden).

For the stratified analysis by gender, the model was only adjusted for age and country, for the stratified analysis by age, the model was only adjusted by gender and country.

Interaction by covariate (gender, diabetes, family history of PC).

Type of tobacco was only collected for Spain (N=1,638). Numbers for gender: N=733 females, N=905 males; diabetes: N=1,234 no, N=404 yes; and family history of PC: N=1,554 no, N=84 yes.

Type of pipe was not collected for Ireland.



**Supplementary Table 6:** Combined effects of smoking duration and tobacco type on pancreatic cancer risk in the PanGenEU-Spain study population (876 cases and 762 controls).

|   |              | Smoking duration of blond tobacco (years) |                   |                    |                   |                     |                   |                    |                   |
|---|--------------|---|-------------------|--------------------|-------------------|---------------------|-------------------|--------------------|-------------------|
|   |              | Never-smoker                              |                   | <20 years          |                   | 20-30 years         |                   | ≥ 30 years         |                   |
|   |              | aOR<br>(95%CI)                            | Case/<br>Controls | aOR<br>(95%CI)     | Case/<br>Controls | aOR<br>(95%CI)      | Case/<br>Controls | aOR<br>(95%CI)     | Case/<br>Controls |
| Smoking duration of black tobacco (years) | Never-smoker | 1.00                                      | 355/360           | 1.03 (0.65 - 1.64) | 42/47             | 1.27 (0.81 - 2.00)  | 51/45             | 1.33 (0.95 - 1.84) | 112/90            |
|   | <20 years    | 1.37 (0.71 - 2.64)                        | 25/17             | 0.84 (0.66 - 1.07) | 25/32             | 0.93 (0.52 - 1.67)  | 10/8              | 1.43 (0.54 - 3.76) | 6/5               |
|   | 20-30 years  | 1.68 (0.92 - 3.09)                        | 31/21             | 1.28 (0.38 - 4.28) | 7/2               | 3.91 (0.79 - 19.33) | 13/6              | 2.61 (0.96 - 7.09) | 1/1               |
|   | ≥ 30 years   | 1.58 (1.11 - 2.27)                        | 109/76            | 1.86 (0.84 - 4.13) | 18/11             | 1.83 (0.79 - 4.26)  | 15/10             | 2.05 (1.25 - 3.36) | 56/31             |

Risk estimates are shown for the imputed smoking variables.

Adjusted OR for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and region (East, Central and Northern Spain).

Relative excess risk due to interaction = RERI=0.206, 95%CI: -0.49 - 0.91.

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**Supplementary Table 7:** Non-linear association between continuous smoking variables and pancreatic cancer risk per 1-unit increase in the variables for the PanGenEU study population (2,009 cases and 1,532 controls).

|  | Restricted Cubic splines        | Fractional polynomials   | aOR (95% CI) per 1-unit increase |                    |                    |
|--|---------------------------------|--|----------------------------------|--------------------|--------------------|
|  |                                 |  | Model 1                          | Model 2            | Model 3            |
|  | LR test <sup>1</sup><br>p-value | Formula resulting from the fractional polynomials <sup>2</sup>   | aOR (95%CI)                      | aOR (95%CI)        | aOR (95%CI)        |
| Age at smoking initiation (years)                                | 0.031                           | $\left(\frac{\text{smoke first} + 1}{10}\right)^{-2}$  | 1.11 (1.04 - 1.20)               | 1.00 (0.89 - 1.11) | 0.96 (0.87 - 1.07) |
| Age last smoked (years)  | 0.008                           | $\left(\frac{\text{smoke last} + 1}{10}\right)^{0.5} + \left(\left(\frac{\text{smoke last} + 0.1}{10}\right)^{0.5} * \log\left(\frac{\text{smoke last} + 0.1}{10}\right)\right)$ | 1.07 (1.04 - 1.10)               | 1.05 (1.00 - 1.11) | 0.99 (0.93 - 1.06) |
| Smoking duration (years)   | 0.020                           | $\left(\frac{\text{duration} + 0.1}{10}\right)^3 + \left(\left(\frac{\text{duration} + 0.1}{10}\right)^3 * \log\left(\frac{\text{duration} + 0.1}{10}\right)\right)$             | 1.04 (1.02 - 1.05)               | 1.03 (1.02 - 1.05) | N.A.               |
| Smoking intensity (cigarettes per day)                           | 0.001                           | $\left(\frac{\text{intensity} + 0.2}{10}\right)^{0.5}$   | 1.29 (1.18 - 1.45)               | N.A.               | 1.04 (0.88 - 1.23) |
| Cumulative dose (pack-years)                                     | 0.000                           | $\left(\frac{\text{pack - years} + 0.1}{10}\right)^{0.5}$  | 1.24 (1.16 - 1.35)               | N.A.               | N.A.               |
| Time since cessation (years) <sup>3</sup>                        | 0.016                           | $\left(\frac{\text{cessation} + 1}{10}\right)^1 + \left(\frac{\text{cessation} + 1}{10}\right)^3$  | 0.81 (0.74 - 0.88)               | 0.80 (0.72 - 0.87) | 0.89 (0.71 - 1.05) |
| Time since cessation (years) for PanGenEU – Spain <sup>3,4</sup> | 0.073                           | $\left(\frac{\text{cessation} + 1}{10}\right)^1 + \left(\frac{\text{cessation} + 1}{10}\right)^3$  | 0.85 (0.74 - 0.96)               | 0.85 (0.73 - 0.96) | 0.88 (0.66 - 1.11) |

PC: pancreatic cancer; N.A.: not applicable.  
 Risk estimates are shown for the unimputed continuous smoking variables.  
 Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden);  
 Model 2: Model 1 plus additional adjustment for smoking intensity (cigarettes per day, continuous, non-linear);  
 Model 3: Model 1 plus additional adjustment for smoking duration (years, continuous, non-linear).

<sup>1</sup> Likelihood ratio test (LR test) comparing two models, adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female), and country (Spain, England, Germany, Ireland, Italy, Sweden), with and without restricted cubic splines applied (knots at 10, 50 and 90%).  
<sup>2</sup> Fractional polynomials adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female), and country (Spain, England, Germany, Ireland, Italy, Sweden).  
<sup>3</sup> Never-smokers were removed from time since cessation variables.  
<sup>4</sup> The PanGenEU-Spain study population consists of 876 cases and 762 controls. The model was adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and region (East, Central and Northern Spain).

**Supplementary Table 8.** Association between smoking variables and pancreatic cancer risk in the PanGenEU study population (2,009 cases and 1,532 controls) before imputation.

|                                       | Cases, % |       | Controls, % |       | p-value <sup>1</sup> | Unadjusted |               | Model 1 |               | Model 2 |               |
|---------------------------------------|----------|-------|-------------|-------|----------------------|------------|---------------|---------|---------------|---------|---------------|
|                                       |          |       |             |       |                      | OR         | (95%CI)       | OR      | (95%CI)       | OR      | (95%CI)       |
| <b>Ever smoked 100 cigarettes</b>     |          |       |             |       | <0.001               |            |               |         |               |         |               |
| No                                    | 764      | 38.00 | 691         | 45.10 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Yes                                   | 1234     | 61.40 | 840         | 54.80 |                      | 1.33       | (1.16 - 1.52) | 1.32    | (1.12 - 1.55) | 1.28    | (1.08 - 1.51) |
| Missing                               | 11       | 0.55  | 1           | 0.07  |                      |            |               |         |               |         |               |
| <b>Regular smoker</b>                 |          |       |             |       | <0.001               |            |               |         |               |         |               |
| Never-smoker                          | 759      | 37.80 | 690         | 45.00 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Regular smoker                        | 1144     | 56.90 | 792         | 51.70 |                      | 1.31       | (1.14 - 1.51) | 1.34    | (1.14 - 1.58) | 1.30    | (1.09 - 1.53) |
| Occasional smoker                     | 27       | 1.34  | 42          | 2.74  |                      | 0.59       | (0.35 - 0.96) | 0.81    | (0.47 - 1.39) | 0.83    | (0.48 - 1.45) |
| Missing                               | 79       | 3.93  | 8           | 0.52  |                      |            |               |         |               |         |               |
| <b>Tobacco type<sup>2</sup></b>       |          |       |             |       | 0.003                |            |               |         |               |         |               |
| Never-smoker                          | 355      | 40.50 | 360         | 47.20 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Smoker of black tobacco only          | 165      | 18.80 | 114         | 15.00 |                      | 1.47       | (1.11 - 1.94) | 1.56    | (1.14 - 2.14) | 1.46    | (1.05 - 2.02) |
| Smoker of blond tobacco only          | 191      | 21.80 | 179         | 23.50 |                      | 1.08       | (0.84 - 1.39) | 1.17    | (0.89 - 1.54) | 1.15    | (0.86 - 1.53) |
| Smoker of both tobacco types          | 152      | 17.40 | 106         | 13.90 |                      | 1.45       | (1.09 - 1.94) | 1.58    | (1.15 - 2.18) | 1.56    | (1.12 - 2.17) |
| Missing                               | 13       | 1.50  | 3           | 0.40  |                      |            |               |         |               |         |               |
| <b>Current smoker</b>                 |          |       |             |       | <0.001               |            |               |         |               |         |               |
| Never-smoker                          | 759      | 37.80 | 690         | 45.00 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Current smoker                        | 391      | 19.50 | 231         | 15.10 |                      | 1.54       | (1.27 - 1.87) | 1.38    | (1.10 - 1.74) | 1.34    | (1.06 - 1.69) |
| Former smoker                         | 819      | 40.80 | 582         | 38.00 |                      | 1.28       | (1.10 - 1.48) | 1.32    | (1.11 - 1.57) | 1.28    | (1.07 - 1.53) |
| Missing                               | 40       | 1.99  | 29          | 1.89  |                      |            |               |         |               |         |               |
| <b>Ever quit smoking &gt;6 months</b> |          |       |             |       | <0.001               |            |               |         |               |         |               |
| Never-smoker                          | 759      | 37.80 | 690         | 45.00 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Yes                                   | 322      | 16.00 | 203         | 13.30 |                      | 1.44       | (1.18 - 1.77) | 1.33    | (1.04 - 1.68) | 1.34    | (1.05 - 1.72) |
| No                                    | 793      | 39.50 | 551         | 36.00 |                      | 1.31       | (1.13 - 1.52) | 1.35    | (1.13 - 1.61) | 1.29    | (1.07 - 1.55) |
| Missing                               | 135      | 6.72  | 88          | 5.74  |                      |            |               |         |               |         |               |
| <b>Inhalation</b>                     |          |       |             |       | <0.001               |            |               |         |               |         |               |
| Never-smoker                          | 730      | 36.30 | 663         | 43.30 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Mouth only                            | 108      | 5.38  | 98          | 6.40  |                      | 1.00       | (0.75 - 1.34) | 1.08    | (0.79 - 1.49) | 0.98    | (0.70 - 1.37) |
| Throat                                | 155      | 7.72  | 107         | 6.98  |                      | 1.31       | (1.01 - 1.72) | 1.55    | (1.16 - 2.08) | 1.54    | (1.13 - 2.08) |
| Chest                                 | 765      | 38.10 | 574         | 37.50 |                      | 1.21       | (1.04 - 1.41) | 1.39    | (1.16 - 1.67) | 1.35    | (1.12 - 1.63) |
| Missing                               | 251      | 12.50 | 90          | 5.87  |                      |            |               |         |               |         |               |
| <b>Filter-use</b>                     |          |       |             |       | <0.001               |            |               |         |               |         |               |
| Never-smoker                          | 730      | 36.30 | 663         | 43.30 |                      | 1.00       |               | 1.00    |               | 1.00    |               |
| Filtered only                         | 786      | 39.10 | 639         | 41.70 |                      | 1.12       | (0.96 - 1.30) | 1.20    | (1.00 - 1.43) | 1.16    | (0.96 - 1.39) |
| Non-filtered only                     | 62       | 3.09  | 49          | 3.20  |                      | 1.15       | (0.78 - 1.70) | 1.70    | (1.09 - 2.64) | 1.62    | (1.03 - 2.56) |
| Both                                  | 137      | 6.82  | 82          | 5.35  |                      | 1.52       | (1.13 - 2.04) | 1.73    | (1.25 - 2.39) | 1.72    | (1.23 - 2.41) |
| Missing                               | 294      | 14.60 | 99          | 6.46  |                      |            |               |         |               |         |               |
| <b>Smoking cigar</b>                  |          |       |             |       | <0.001               |            |               |         |               |         |               |
|                                       |          |       |             |       |                      |            |               |         |               |         |               |

|    |  |      |       |      |       |        |               |      |               |      |               |
|----|--|------|-------|------|-------|--------|---------------|------|---------------|------|---------------|
| 1  |  |      |       |      |       |        |               |      |               |      |               |
| 2  | No   | 1519 | 75.60 | 1325 | 86.50 | 1.00   |               | 1.00 |               | 1.00 |               |
| 3  | Yes  | 138  | 6.87  | 122  | 7.96  | 0.99   | (0.76 - 1.27) | 0.96 | (0.73 - 1.27) | 0.89 | (0.66 - 1.19) |
| 4  | Missing  | 352  | 17.50 | 85   | 5.55  |        |               |      |               |      |               |
| 5  | <b>Smoking pipe</b>                                  |      |       |      |       | <0.001 |               |      |               |      |               |
| 6  | No   | 1520 | 75.70 | 1306 | 85.20 | 1.00   |               | 1.00 |               | 1.00 |               |
| 7  | Yes  | 132  | 6.57  | 144  | 9.40  | 0.79   | (0.61 - 1.01) | 1.11 | (0.84 - 1.47) | 1.08 | (0.81 - 1.46) |
| 8  | Missing  | 357  | 17.80 | 82   | 5.35  |        |               |      |               |      |               |
| 9  | <b>Tobacco type for pipe<sup>3</sup></b>             |      |       |      |       | <0.001 |               |      |               |      |               |
| 10 | No pipe smoker                                       | 1467 | 73.00 | 1259 | 82.20 | 1.00   |               | 1.00 |               | 1.00 |               |
| 11 | Black  | 12   | 0.60  | 9    | 0.59  | 1.14   | (0.48 - 2.83) | 1.40 | (0.55 - 3.55) | 1.11 | (0.39 - 3.19) |
| 12 | Blond  | 41   | 2.04  | 41   | 2.68  | 0.86   | (0.55 - 1.34) | 1.06 | (0.66 - 1.70) | 1.14 | (0.69 - 1.87) |
| 13 | Mixed  | 42   | 2.09  | 39   | 2.55  | 0.92   | (0.59 - 1.44) | 1.26 | (0.76 - 2.11) | 1.20 | (0.70 - 2.08) |
| 14 | Missing  | 447  | 22.20 | 184  | 12.00 |        |               |      |               |      |               |
| 15 | <b>Smoking status (cigarettes)</b>                   |      |       |      |       | <0.001 |               |      |               |      |               |
| 16 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00   |               | 1.00 |               | 1.00 |               |
| 17 | Former   | 630  | 31.40 | 528  | 34.50 | 1.08   | (0.93 - 1.27) | 1.14 | (0.95 - 1.36) | 1.10 | (0.91 - 1.33) |
| 18 | Current  | 548  | 27.30 | 273  | 17.80 | 1.82   | (1.53 - 2.18) | 1.72 | (1.40 - 2.12) | 1.67 | (1.35 - 2.08) |
| 19 | Missing  | 72   | 3.58  | 41   | 2.68  |        |               |      |               |      |               |
| 20 | <b>Smoking status incl. occasional</b>               |      |       |      |       | <0.001 |               |      |               |      |               |
| 21 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00   |               | 1.00 |               | 1.00 |               |
| 22 | Occasional   | 27   | 1.34  | 42   | 2.74  | 0.59   | (0.35 - 0.96) | 0.80 | (0.47 - 1.38) | 0.83 | (0.47 - 1.44) |
| 23 | Former   | 610  | 30.40 | 512  | 33.40 | 1.08   | (0.93 - 1.27) | 1.13 | (0.94 - 1.36) | 1.09 | (0.90 - 1.32) |
| 24 | Current  | 547  | 27.20 | 269  | 17.60 | 1.85   | (1.55 - 2.21) | 1.74 | (1.41 - 2.14) | 1.69 | (1.36 - 2.10) |
| 25 | Missing  | 66   | 3.29  | 19   | 1.24  |        |               |      |               |      |               |
| 26 | <b>Quit smoking &lt;10 or ≥ 10 years ago</b>         |      |       |      |       | <0.001 |               |      |               |      |               |
| 27 | Never-smoker and former smoker quit >10years         | 1169 | 58.20 | 1090 | 71.10 | 1.00   |               | 1.00 |               | 1.00 |               |
| 28 | Current smoker and former smoker quit ≤10years       | 740  | 36.80 | 398  | 26.00 | 1.73   | (1.50 - 2.01) | 1.57 | (1.32 - 1.86) | 1.53 | (1.28 - 1.83) |
| 29 | Missing  | 100  | 4.98  | 44   | 2.87  |        |               |      |               |      |               |
| 30 | <b>Childhood exposure to ETS</b>                     |      |       |      |       | <0.001 |               |      |               |      |               |
| 31 | Both parents were never-smokers                      | 413  | 20.60 | 389  | 25.40 | 1.00   |               | 1.00 |               | 1.00 |               |
| 32 | Only the father smoked                               | 995  | 49.50 | 762  | 49.70 | 1.23   | (1.04 - 1.45) | 1.12 | (0.92 - 1.35) | 1.11 | (0.91 - 1.36) |
| 33 | Only the mother smoked                               | 37   | 1.84  | 44   | 2.87  | 0.79   | (0.50 - 1.25) | 1.19 | (0.71 - 2.00) | 1.11 | (0.65 - 1.88) |
| 34 | Both parents smoked                                  | 194  | 9.66  | 170  | 11.10 | 1.07   | (0.84 - 1.38) | 1.34 | (0.99 - 1.82) | 1.34 | (0.98 - 1.83) |
| 35 | Missing  | 370  | 18.40 | 167  | 10.90 |        |               |      |               |      |               |
| 36 | <b>Age at smoking initiation in tertiles (years)</b> |      |       |      |       | <0.001 |               |      |               |      |               |
| 37 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00   |               | 1.00 |               | 1.00 |               |
| 38 | < 16   | 550  | 27.40 | 352  | 23.00 | 1.42   | (1.20 - 1.68) | 1.42 | (1.16 - 1.74) | 1.35 | (1.10 - 1.67) |
| 39 | 16 - 18  | 289  | 14.40 | 189  | 12.30 | 1.39   | (1.13 - 1.72) | 1.26 | (0.98 - 1.61) | 1.19 | (0.92 - 1.54) |
| 40 | ≥ 18   | 372  | 18.50 | 265  | 17.30 | 1.28   | (1.06 - 1.54) | 1.34 | (1.08 - 1.65) | 1.32 | (1.06 - 1.65) |
| 41 | Missing  | 39   | 1.94  | 36   | 2.35  |        |               |      |               |      |               |
| 42 | <b>Age last smoked in tertiles (years)</b>           |      |       |      |       | <0.001 |               |      |               |      |               |
| 43 | Never-smoker   | 776  | 38.60 | 700  | 45.70 | 1.00   |               | 1.00 |               | 1.00 |               |
| 44 | < 37   | 188  | 9.36  | 202  | 13.20 | 0.84   | (0.67 - 1.05) | 0.78 | (0.60 - 1.02) | 0.82 | (0.62 - 1.07) |
| 45 | 37 - 52  | 318  | 15.80 | 214  | 14.00 | 1.34   | (1.10 - 1.64) | 1.34 | (1.06 - 1.69) | 1.28 | (1.00 - 1.63) |

|    |  |      |       |      |       |                    |                    |                    |  |
|----|--|------|-------|------|-------|--------------------|--------------------|--------------------|--|
| 1  |  |      |       |      |       |                    |                    |                    |  |
| 2  | ≥ 52   | 346  | 17.20 | 197  | 12.90 | 1.58 (1.29 - 1.94) | 1.62 (1.29 - 2.03) | 1.55 (1.22 - 1.97) |  |
| 3  | Missing  | 381  | 19.00 | 219  | 14.30 | p-trend<0.001      | p-trend<0.001      | p-trend<0.001      |  |
| 4  | <b>Time of ever quitting in tertiles (years)</b>                 |      |       |      |       | 0.069              |                    |                    |  |
| 5  | Current smoker   | 1552 | 77.30 | 1241 | 81.00 | 1.00               | 1.00               | 1.00               |  |
| 6  | < 1.3  | 104  | 5.18  | 65   | 4.24  | 1.28 (0.93 - 1.77) | 0.96 (0.66 - 1.40) | 1.02 (0.69 - 1.51) |  |
| 7  | 1.3 - 3.9  | 83   | 4.13  | 62   | 4.05  | 1.07 (0.76 - 1.50) | 1.07 (0.74 - 1.55) | 1.07 (0.72 - 1.57) |  |
| 8  | ≥ 3.9  | 102  | 5.08  | 66   | 4.31  | 1.23 (0.90 - 1.71) | 1.25 (0.87 - 1.78) | 1.27 (0.88 - 1.84) |  |
| 9  | Missing  | 168  | 8.36  | 98   | 6.40  | p-trend = 0.117    | p-trend = 0.402    | p-trend = 0.320    |  |
| 10 | <b>Smoking duration in tertiles (years)</b>                      |      |       |      |       | <0.001             |                    |                    |  |
| 11 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00               | 1.00               | 1.00               |  |
| 12 | < 22   | 227  | 11.30 | 238  | 15.50 | 0.87 (0.70 - 1.07) | 0.92 (0.72 - 1.18) | 0.93 (0.72 - 1.21) |  |
| 13 | 22 - 37  | 390  | 19.40 | 255  | 16.60 | 1.39 (1.15 - 1.68) | 1.40 (1.12 - 1.75) | 1.36 (1.08 - 1.70) |  |
| 14 | ≥ 37   | 421  | 21.00 | 228  | 14.90 | 1.68 (1.39 - 2.03) | 1.69 (1.36 - 2.10) | 1.58 (1.26 - 1.99) |  |
| 15 | Missing  | 212  | 10.60 | 121  | 7.90  | p-trend<0.001      | p-trend<0.001      | p-trend<0.001      |  |
| 16 | <b>Smoking intensity in tertiles (cigarettes per day)</b>        |      |       |      |       | <0.001             |                    |                    |  |
| 17 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00               | 1.00               | 1.00               |  |
| 18 | < 10   | 353  | 17.60 | 308  | 20.10 | 1.04 (0.87 - 1.25) | 1.03 (0.83 - 1.27) | 1.01 (0.81 - 1.26) |  |
| 19 | 10 - 20  | 505  | 25.10 | 276  | 18.00 | 1.66 (1.39 - 1.99) | 1.66 (1.34 - 2.04) | 1.62 (1.31 - 2.02) |  |
| 20 | ≥ 20   | 328  | 16.30 | 212  | 13.80 | 1.41 (1.15 - 1.72) | 1.47 (1.17 - 1.86) | 1.38 (1.08 - 1.76) |  |
| 21 | Missing  | 64   | 3.19  | 46   | 3.00  | p-trend<0.001      | p-trend<0.001      | p-trend<0.001      |  |
| 22 | <b>Cumulative dose in tertiles (pack-years)</b>                  |      |       |      |       | <0.001             |                    |                    |  |
| 23 | Never-smoker   | 759  | 37.80 | 690  | 45.00 | 1.00               | 1.00               | 1.00               |  |
| 24 | < 13   | 234  | 11.60 | 235  | 15.30 | 0.91 (0.73 - 1.12) | 0.95 (0.74 - 1.22) | 0.96 (0.75 - 1.24) |  |
| 25 | 13 - 36  | 401  | 20.00 | 239  | 15.60 | 1.52 (1.26 - 1.85) | 1.57 (1.26 - 1.97) | 1.53 (1.22 - 1.93) |  |
| 26 | ≥ 36   | 392  | 19.50 | 235  | 15.30 | 1.52 (1.25 - 1.84) | 1.59 (1.28 - 1.99) | 1.47 (1.17 - 1.85) |  |
| 27 | Missing  | 223  | 11.10 | 133  | 8.68  | p-trend<0.001      | p-trend<0.001      | p-trend<0.001      |  |
| 28 | <b>Time since cessation in tertiles (years)</b>                  |      |       |      |       | <0.001             |                    |                    |  |
| 29 | Current smoker   | 507  | 25.24 | 226  | 14.75 | 1.00               | 1.00               | 1.00               |  |
| 30 | < 15   | 273  | 13.59 | 185  | 12.08 | 0.66 (0.52 - 0.84) | 0.68 (0.52 - 0.88) | 0.66 (0.50 - 0.87) |  |
| 31 | 15 - 30  | 203  | 10.10 | 180  | 11.75 | 0.50 (0.39 - 0.65) | 0.52 (0.39 - 0.69) | 0.51 (0.37 - 0.69) |  |
| 32 | ≥ 30   | 126  | 6.27  | 160  | 10.44 | 0.35 (0.26 - 0.47) | 0.40 (0.29 - 0.56) | 0.42 (0.30 - 0.60) |  |
| 33 | Missing  | 900  | 44.80 | 781  | 50.98 | p-trend<0.001      | p-trend<0.001      | p-trend<0.001      |  |
| 34 | <b>Intensity of smoking cigars in tertiles (cigars per week)</b> |      |       |      |       | <0.001             |                    |                    |  |
| 35 | Never-smoker   | 1471 | 73.20 | 1280 | 83.60 | 1.00               | 1.00               | 1.00               |  |
| 36 | < 2  | 26   | 1.29  | 38   | 2.48  | 0.60 (0.36 - 0.98) | 0.50 (0.28 - 0.88) | 0.48 (0.27 - 0.87) |  |
| 37 | 2 - 10   | 55   | 2.74  | 42   | 2.74  | 1.14 (0.76 - 1.72) | 1.23 (0.80 - 1.89) | 1.09 (0.69 - 1.72) |  |
| 38 | ≥ 10   | 40   | 1.99  | 31   | 2.02  | 1.12 (0.70 - 1.82) | 1.12 (0.67 - 1.86) | 1.03 (0.60 - 1.77) |  |
| 39 | Missing  | 417  | 20.80 | 141  | 9.20  | p-trend = 0.771    | p-trend = 0.811    | p-trend = 0.786    |  |
| 40 | <b>Intensity of smoking pipes in tertiles (pipes per week)</b>   |      |       |      |       | <0.001             |                    |                    |  |
| 41 | Never-smoker   | 1467 | 73.00 | 1260 | 82.20 | 1.00               | 1.00               | 1.00               |  |
| 42 | < 7  | 48   | 2.39  | 48   | 3.13  | 0.86 (0.57 - 1.29) | 1.07 (0.68 - 1.66) | 1.11 (0.69 - 1.78) |  |
| 43 | 7 - 20   | 23   | 1.14  | 36   | 2.35  | 0.55 (0.32 - 0.93) | 0.78 (0.44 - 1.38) | 0.70 (0.39 - 1.28) |  |
| 44 | ≥ 20   | 31   | 1.54  | 42   | 2.74  | 0.63 (0.39 - 1.01) | 1.23 (0.75 - 2.04) | 1.22 (0.72 - 2.07) |  |
| 45 | Missing  | 440  | 21.90 | 146  | 9.53  | p-trend = 0.005    | p-trend = 0.899    | p-trend = 0.991    |  |

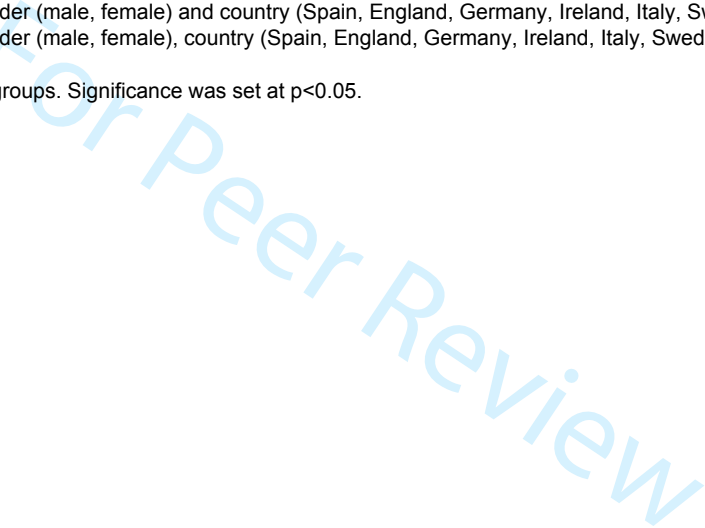
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|  | Mean  | SD    | Mean  | SD    | p-value <sup>1</sup> | OR   | (95%CI)       | OR   | (95%CI)       | OR   | (95%CI)       |
|--|-------|-------|-------|-------|----------------------|------|---------------|------|---------------|------|---------------|
| <b>Smoking duration (years)</b>                      | 19.00 | 19.40 | 15.20 | 18.50 | <0.001               | 1.01 | (1.01 - 1.01) | 1.01 | (1.01 - 1.01) | 1.01 | (1.00 - 1.01) |
| <b>Smoking intensity (cigarettes per day)</b>        | 12.70 | 15.60 | 10.50 | 15.30 | <0.001               | 1.01 | (1.00 - 1.01) | 1.01 | (1.00 - 1.01) | 1.01 | (1.00 - 1.01) |
| <b>Cumulative dose (pack-years)</b>                  | 21.50 | 32.10 | 16.50 | 29.60 | <0.001               | 1.01 | (1.00 - 1.01) | 1.01 | (1.00 - 1.01) | 1.00 | (1.00 - 1.01) |
| <b>Time since cessation (years)</b>                  | 10.70 | 14.00 | 16.20 | 16.00 | <0.001               | 0.98 | (0.97 - 0.98) | 0.98 | (0.97 - 0.99) | 0.98 | (0.97 - 0.99) |
| <b>Age at smoking initiation (years)</b>             | 11.00 | 9.70  | 9.92  | 10.30 | 0.001                | 1.01 | (1.00 - 1.02) | 1.01 | (1.00 - 1.02) | 1.01 | (1.00 - 1.02) |
| <b>Age last smoked (years)</b>                       | 25.10 | 26.20 | 21.20 | 24.90 | <0.001               | 1.01 | (1.00 - 1.01) | 1.01 | (1.00 - 1.01) | 1.00 | (1.00 - 1.01) |
| <b>Time of ever quitting (years)</b>                 | 0.68  | 2.64  | 0.63  | 3.82  | 0.597                | 1.01 | (0.98 - 1.03) | 1.00 | (0.98 - 1.03) | 1.00 | (0.98 - 1.03) |
| <b>Intensity of smoking cigars (cigars per week)</b> | 1.03  | 5.84  | 0.90  | 5.18  | 0.464                | 1.00 | (0.99 - 1.02) | 1.00 | (0.99 - 1.02) | 1.01 | (0.99 - 1.03) |
| <b>Intensity of smoking pipes (pipes per week)</b>   | 1.06  | 5.85  | 1.79  | 8.27  | 0.008                | 0.99 | (0.97 - 1.00) | 1.00 | (0.99 - 1.01) | 1.00 | (0.99 - 1.02) |

PC: pancreatic cancer; ETS: environmental tobacco smoke.  
Results are shown for the unimputed smoking variables.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden). Random effects model applied for country;  
Model 2: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female), country (Spain, England, Germany, Ireland, Italy, Sweden), family history of PC (yes/no) and diabetes (yes/no).  
Random effects model applied for country.

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p<0.05.  
<sup>2</sup> Type of tobacco was only collected for Spain.  
<sup>3</sup> Type of pipe was not collected for Ireland.



**Supplementary Table 9.** Sensitivity analysis on the association between tobacco smoking and pancreatic cancer risk, excluding Italy from the PanGenEU study population (1,476 cases and 1,532 controls).

|  |  |      |       |      | Model 1         |                    |                      |    |         |
|--|--|------|-------|------|-----------------|--------------------|----------------------|----|---------|
|  |  |      |       |      | Cases, %        | Controls, %        | p-value <sup>1</sup> | OR | (95%CI) |
| <b>Ever smoked 100 cigarettes</b>                    |  |      |       |      |                 |                    |                      |    |         |
|  | No   | 569  | 38.60 | 691  | 45.10           | <0.001             |                      |    |         |
|  | Yes  | 907  | 61.40 | 841  | 54.90           | 1.30 (1.11 - 1.53) |                      |    |         |
| <b>Regular smoker</b>                                |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | <0.001             |                      |    |         |
|  | Regular smoker                                 | 883  | 59.80 | 800  | 52.20           | 1.33 (1.13 - 1.57) |                      |    |         |
|  | Occasional smoker                              | 29   | 1.96  | 42   | 2.74            | 1.01 (0.61 - 1.68) |                      |    |         |
| <b>Current smoker</b>                                |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | <0.001             |                      |    |         |
|  | Current smoker                                 | 271  | 18.40 | 231  | 15.10           | 1.36 (1.08 - 1.70) |                      |    |         |
|  | Former smoker                                  | 641  | 43.40 | 611  | 39.90           | 1.30 (1.10 - 1.55) |                      |    |         |
| <b>Ever quit smoking &gt;6 months</b>                |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | 0.001              |                      |    |         |
|  | Yes  | 322  | 21.80 | 291  | 19.00           | 1.35 (1.10 - 1.68) |                      |    |         |
|  | No   | 590  | 40.00 | 551  | 36.00           | 1.30 (1.09 - 1.55) |                      |    |         |
| <b>Inhalation</b>                                    |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | 0.001              |                      |    |         |
|  | Mouth only                                     | 97   | 6.57  | 99   | 6.46            | 1.09 (0.80 - 1.50) |                      |    |         |
|  | Throat   | 132  | 8.94  | 108  | 7.05            | 1.48 (1.11 - 1.99) |                      |    |         |
|  | Chest  | 683  | 46.30 | 635  | 41.40           | 1.33 (1.12 - 1.58) |                      |    |         |
|  |  |      |       |      | p-trend<0.001   |                    |                      |    |         |
| <b>Filter-use</b>                                    |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | <0.001             |                      |    |         |
|  | Filtered only                                  | 721  | 48.80 | 706  | 46.10           | 1.25 (1.06 - 1.48) |                      |    |         |
|  | Non-filtered only                              | 56   | 3.79  | 49   | 3.20            | 1.69 (1.10 - 2.61) |                      |    |         |
|  | Both   | 135  | 9.15  | 87   | 5.68            | 1.65 (1.21 - 2.26) |                      |    |         |
|  |  |      |       |      | p-trend<0.001   |                    |                      |    |         |
| <b>Smoking cigar</b>                                 |  |      |       |      |                 |                    |                      |    |         |
|  | No   | 1340 | 90.80 | 1408 | 91.90           | 0.304              |                      |    |         |
|  | Yes  | 136  | 9.21  | 124  | 8.09            | 1.00 (0.76 - 1.32) |                      |    |         |
| <b>Smoking pipe</b>                                  |  |      |       |      |                 |                    |                      |    |         |
|  | No   | 1342 | 90.90 | 1384 | 90.30           | 0.628              |                      |    |         |
|  | Yes  | 134  | 9.08  | 148  | 9.66            | 1.13 (0.86 - 1.48) |                      |    |         |
| <b>Tobacco type for pipe<sup>3</sup></b>             |  |      |       |      |                 |                    |                      |    |         |
|  | No pipe smoker                                 | 1342 | 90.90 | 1384 | 90.30           | 0.790              |                      |    |         |
|  | Black  | 13   | 0.88  | 16   | 1.04            | 0.78 (0.37 - 1.66) |                      |    |         |
|  | Blond  | 63   | 4.27  | 62   | 4.05            | 1.25 (0.85 - 1.82) |                      |    |         |
|  | Mixed  | 58   | 3.93  | 70   | 4.57            | 1.12 (0.75 - 1.66) |                      |    |         |
| <b>Smoking status (cigarettes)</b>                   |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | <0.001             |                      |    |         |
|  | Former   | 519  | 35.20 | 568  | 37.10           | 1.14 (0.95 - 1.36) |                      |    |         |
|  | Current  | 393  | 26.60 | 274  | 17.90           | 1.69 (1.37 - 2.09) |                      |    |         |
|  |  |      |       |      | p-trend<0.001   |                    |                      |    |         |
| <b>Smoking status incl. occasional</b>               |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | <0.001             |                      |    |         |
|  | Occasional                                     | 29   | 1.96  | 42   | 2.74            | 1.01 (0.61 - 1.67) |                      |    |         |
|  | Former   | 491  | 33.30 | 530  | 34.60           | 1.14 (0.95 - 1.37) |                      |    |         |
|  | Current  | 392  | 26.60 | 270  | 17.60           | 1.72 (1.39 - 2.12) |                      |    |         |
|  |  |      |       |      | p-trend<0.001   |                    |                      |    |         |
| <b>Quit smoking &lt;10 or ≥ 10 years ago</b>         |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker and former smoker quit >10years   | 567  | 38.40 | 410  | 26.80           | <0.001             |                      |    |         |
|  | Current smoker and former smoker quit ≤10years | 909  | 61.60 | 1122 | 73.20           | 0.64 (0.54 - 0.76) |                      |    |         |
| <b>Childhood exposure to ETS</b>                     |  |      |       |      |                 |                    |                      |    |         |
|  | Both parents were never-smokers                | 295  | 20.00 | 391  | 25.50           | <0.001             |                      |    |         |
|  | Only the father smoked                         | 981  | 66.50 | 908  | 59.30           | 1.25 (1.04 - 1.51) |                      |    |         |
|  | Only the mother smoked                         | 31   | 2.10  | 44   | 2.87            | 1.03 (0.62 - 1.71) |                      |    |         |
|  | Both parents smoked                            | 169  | 11.40 | 189  | 12.30           | 1.07 (0.81 - 1.42) |                      |    |         |
|  |  |      |       |      | p-trend = 0.610 |                    |                      |    |         |
| <b>Age at smoking initiation in tertiles (years)</b> |  |      |       |      |                 |                    |                      |    |         |
|  | Never-smoker                                   | 564  | 38.20 | 690  | 45.00           | 0.001              |                      |    |         |
|  | < 15   | 327  | 22.20 | 278  | 18.10           | 1.36 (1.10 - 1.70) |                      |    |         |
|  | 15 - 18  | 317  | 21.50 | 299  | 19.50           | 1.31 (1.06 - 1.61) |                      |    |         |
|  | ≥ 18   | 268  | 18.20 | 265  | 17.30           | 1.29 (1.04 - 1.59) |                      |    |         |

|    |  |       |       |       |       |                      |                    |                 |
|----|--|-------|-------|-------|-------|----------------------|--------------------|-----------------|
| 1  |  |       |       |       |       |                      |                    |                 |
| 2  |  |       |       |       |       |                      |                    |                 |
| 3  | <b>Age last smoked in tertiles (years)</b>                       |       |       |       |       | <0.001               |                    | p-trend = 0.024 |
| 4  | Current smoker   | 393   | 26.60 | 274   | 17.90 |                      | 1.00               |                 |
| 5  | < 38   | 147   | 9.96  | 198   | 12.90 |                      | 0.56 (0.43 - 0.74) |                 |
| 6  | 38 - 50  | 173   | 11.70 | 193   | 12.60 |                      | 0.71 (0.55 - 0.94) |                 |
| 7  | ≥ 50   | 199   | 13.50 | 177   | 11.60 |                      | 0.76 (0.58 - 1.01) |                 |
| 8  | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      |                    | p-trend<0.001   |
| 9  | <b>Time of ever quitting in tertiles (years)</b>                 |       |       |       |       | 0.004                |                    |                 |
| 10 | Current smoker who never quit                                    | 590   | 40.00 | 551   | 36.00 |                      | 1.00               |                 |
| 11 | < 2  | 118   | 7.99  | 108   | 7.05  |                      | 0.93 (0.69 - 1.26) |                 |
| 12 | 2 - 6  | 93    | 6.30  | 86    | 5.61  |                      | 0.94 (0.68 - 1.30) |                 |
| 13 | ≥ 6  | 111   | 7.52  | 97    | 6.33  |                      | 1.32 (0.96 - 1.82) |                 |
| 14 | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      |                    | p-trend = 0.024 |
| 15 | <b>Smoking duration in tertiles (years)</b>                      |       |       |       |       | <0.001               |                    |                 |
| 16 | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      | 1.00               |                 |
| 17 | < 23   | 202   | 13.70 | 284   | 18.50 |                      | 0.91 (0.72 - 1.14) |                 |
| 18 | 23 - 35  | 335   | 22.70 | 281   | 18.30 |                      | 1.52 (1.23 - 1.87) |                 |
| 19 | ≥ 35   | 375   | 25.40 | 277   | 18.10 |                      | 1.51 (1.23 - 1.85) |                 |
| 20 |  |       |       |       |       |                      |                    | p-trend<0.001   |
| 21 | <b>Smoking intensity in tertiles (cigarettes per day)</b>        |       |       |       |       | <0.001               |                    |                 |
| 22 | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      | 1.00               |                 |
| 23 | < 10   | 263   | 17.80 | 343   | 22.40 |                      | 1.02 (0.83 - 1.25) |                 |
| 24 | 10 - 20  | 369   | 25.00 | 287   | 18.70 |                      | 1.64 (1.34 - 2.02) |                 |
| 25 | ≥ 20   | 280   | 19.00 | 212   | 13.80 |                      | 1.41 (1.12 - 1.78) |                 |
| 26 |  |       |       |       |       |                      |                    | p-trend<0.001   |
| 27 | <b>Cumulative dose in tertiles (pack-years)</b>                  |       |       |       |       | <0.001               |                    |                 |
| 28 | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      | 1.00               |                 |
| 29 | < 14   | 189   | 12.80 | 281   | 18.30 |                      | 0.90 (0.72 - 1.13) |                 |
| 30 | 14 - 32  | 337   | 22.80 | 275   | 18.00 |                      | 1.57 (1.27 - 1.94) |                 |
| 31 | ≥ 32   | 386   | 26.20 | 286   | 18.70 |                      | 1.50 (1.21 - 1.84) |                 |
| 32 |  |       |       |       |       |                      |                    | p-trend<0.001   |
| 33 | <b>Time since cessation in tertiles (years)</b>                  |       |       |       |       | <0.001               |                    |                 |
| 34 | Current smoker   | 393   | 26.60 | 274   | 17.90 |                      | 1.00               |                 |
| 35 | < 14   | 231   | 15.70 | 191   | 12.50 |                      | 0.81 (0.62 - 1.04) |                 |
| 36 | 14 - 28  | 167   | 11.30 | 185   | 12.10 |                      | 0.67 (0.51 - 0.88) |                 |
| 37 | ≥ 28   | 121   | 8.20  | 192   | 12.50 |                      | 0.49 (0.36 - 0.66) |                 |
| 38 | Never-smoker   | 564   | 38.20 | 690   | 45.00 |                      |                    | p-trend<0.001   |
| 39 | <b>Intensity of smoking cigars in tertiles (cigars per week)</b> |       |       |       |       | 0.011                |                    |                 |
| 40 | Never-smoker   | 1280  | 86.70 | 1356  | 88.50 |                      | 1.00               |                 |
| 41 | < 1.0  | 69    | 4.67  | 68    | 4.44  |                      | 0.94 (0.66 - 1.34) |                 |
| 42 | 1.0 - 6.2  | 44    | 2.98  | 48    | 3.13  |                      | 0.90 (0.59 - 1.39) |                 |
| 43 | ≥ 6.2  | 83    | 5.62  | 60    | 3.92  |                      | 1.20 (0.84 - 1.73) |                 |
| 44 |  |       |       |       |       |                      |                    | p-trend = 0.571 |
| 45 | <b>Intensity of smoking pipes in tertiles (pipes per week)</b>   |       |       |       |       | 0.384                |                    |                 |
| 46 | Never-smoker   | 1306  | 88.50 | 1363  | 89.00 |                      | 1.00               |                 |
| 47 | < 5.0  | 67    | 4.54  | 58    | 3.79  |                      | 1.13 (0.78 - 1.64) |                 |
| 48 | 5.0 - 14.4   | 61    | 4.13  | 53    | 3.46  |                      | 1.32 (0.88 - 1.97) |                 |
| 49 | ≥ 14.4   | 42    | 2.85  | 58    | 3.79  |                      | 1.20 (0.78 - 1.85) |                 |
| 50 |  |       |       |       |       |                      |                    | p-trend = 0.141 |
| 51 |  | Mean  | SD    | Mean  | SD    | p-value <sup>1</sup> | OR                 | (95%CI)         |
| 52 | <b>Smoking duration (years)</b>                                  | 19.40 | 19.70 | 15.20 | 18.50 | <0.001               | 1.22               | (1.12 - 1.33)   |
| 53 | <b>Smoking intensity (cigarettes per day)</b>                    | 13.50 | 16.70 | 10.50 | 15.30 | <0.001               | 1.15               | (1.06 - 1.25)   |
| 54 | <b>Cumulative dose (pack-years)</b>                              | 23.60 | 35.10 | 16.50 | 29.60 | <0.001               | 1.19               | (1.09 - 1.30)   |
| 55 | <b>Time since cessation (years)</b>                              | 11.00 | 14.30 | 16.20 | 16.00 | <0.001               | 0.75               | (0.66 - 0.84)   |
| 56 | <b>Age at smoking initiation (years)</b>                         | 10.90 | 9.79  | 9.92  | 10.30 | 0.008                | 1.10               | (1.02 - 1.19)   |
| 57 | <b>Age last smoked (years)</b>                                   | 25.70 | 26.60 | 21.20 | 24.90 | <0.001               | 1.18               | (1.08 - 1.28)   |
| 58 | <b>Time of ever quitting (years)</b>                             | 0.67  | 2.54  | 0.63  | 3.82  | 0.684                | 1.01               | (0.94 - 1.09)   |
| 59 | <b>Intensity of smoking cigars (cigars per week)</b>             | 1.21  | 6.42  | 0.90  | 5.18  | 0.165                | 1.03               | (0.95 - 1.12)   |
| 60 | <b>Intensity of smoking pipes (pipes per week)</b>               | 1.23  | 6.39  | 1.79  | 8.27  | 0.049                | 1.01               | (0.93 - 1.10)   |

PC: pancreatic cancer; ETS: environmental tobacco smoke.

Results are shown for the categorical, imputed smoking variables, and for the continuous, unimputed smoking variables.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden). Linear associations were assumed for continuous variables. See non-linear associations in Supplementary Table 7.

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p<0.05.

<sup>2</sup> Type of tobacco was only collected for Spain.

<sup>3</sup> Type of pipe was not collected for Ireland.



**Supplementary Table 10:** Baseline characteristics of the PanGenEU study population (2,009 cases and 1,532 controls) before imputation.

|  | PanGenEU    |              |                      | PanGenEU - Spain |              |                      |
|--|-------------|--------------|----------------------|------------------|--------------|----------------------|
|  | Cases (%)   | Controls (%) | p-value <sup>1</sup> | Cases (%)        | Controls (%) | p-value <sup>1</sup> |
| <b>Country</b>                                       |             |              | <0.001               |                  |              | <0.001               |
| Spain  | 876 (43.6)  | 762 (49.7)   |                      | 876 (100.0)      | 762 (100.0)  |                      |
| England  | 126 (6.3)   | 22 (1.4)     |                      | -                | -            |                      |
| Germany  | 130 (6.5)   | 111 (7.3)    |                      | -                | -            |                      |
| Ireland  | 173 (8.6)   | 290 (18.9)   |                      | -                | -            |                      |
| Italy  | 533 (26.5)  | 0 (0.0)      |                      | -                | -            |                      |
| Sweden   | 171 (8.5)   | 347 (22.7)   |                      | -                | -            |                      |
| <b>Gender</b>  |             |              | 0.313                |                  |              | 0.455                |
| Female   | 870 (43.3)  | 701 (45.8)   |                      | 384 (43.8)       | 349 (45.8)   |                      |
| Male   | 1137 (56.6) | 829 (54.1)   |                      | 492 (56.2)       | 413 (54.2)   |                      |
| Missing  | 2 (0.1)     | 2 (0.1)      |                      | -                | -            |                      |
| <b>Age</b>   |             |              | <0.001               |                  |              | 0.086                |
| ≤54  | 408 (20.3)  | 261 (17.0)   |                      | 157 (17.9)       | 155 (20.3)   |                      |
| 55-64  | 496 (24.7)  | 320 (20.9)   |                      | 203 (23.2)       | 173 (22.7)   |                      |
| 65-74  | 698 (34.7)  | 494 (32.3)   |                      | 285 (32.5)       | 208 (27.3)   |                      |
| ≥75  | 398 (19.8)  | 454 (29.6)   |                      | 231 (26.4)       | 226 (29.7)   |                      |
| Missing  | 9 (0.5)     | 3 (0.2)      |                      | -                | -            |                      |
| <b>BMI (kg/m<sup>2</sup>)</b>                        |             |              | 0.994                |                  |              | 0.841                |
| < 25   | 757 (37.7)  | 572 (37.3)   |                      | 299 (34.1)       | 262 (34.4)   |                      |
| 25-29.99   | 773 (38.5)  | 592 (38.7)   |                      | 346 (39.5)       | 295 (38.7)   |                      |
| ≥ 30   | 384 (19.1)  | 293 (19.1)   |                      | 175 (20.0)       | 148 (19.4)   |                      |
| Missing  | 95 (4.7)    | 75 (4.9)     |                      | 56 (6.4)         | 57 (7.5)     |                      |
| <b>Alcohol status<sup>2</sup></b>                    |             |              | <0.001               |                  |              | 0.009                |
| Never-drinker  | 565 (28.1)  | 372 (24.3)   |                      | 253 (28.9)       | 243 (31.9)   |                      |
| Light drinker  | 601 (29.9)  | 457 (29.8)   |                      | 331 (37.8)       | 277 (36.4)   |                      |
| Moderate drinker                                     | 413 (20.6)  | 247 (16.1)   |                      | 197 (22.5)       | 129 (16.9)   |                      |
| Heavy drinker  | 52 (2.6)    | 32 (2.1)     |                      | 12 (1.4)         | 10 (1.3)     |                      |
| Missing  | 378 (18.8)  | 424 (27.7)   |                      | 83 (9.4)         | 103 (13.5)   |                      |
| <b>Family history of PC</b>                          |             |              | <0.001               |                  |              | 0.001                |
| No   | 1771 (88.2) | 1479 (96.5)  |                      | 797 (91.0)       | 729 (95.7)   |                      |
| Yes  | 127 (6.3)   | 40 (2.6)     |                      | 61 (7.0)         | 23 (3.0)     |                      |
| Missing  | 111 (5.5)   | 13 (0.9)     |                      | 18 (2.0)         | 10 (1.3)     |                      |
| <b>Ever been diagnosed with asthma</b>               |             |              | <0.001               |                  |              | 0.021                |
| No   | 1580 (78.6) | 1343 (87.7)  |                      | 790 (90.2)       | 668 (87.7)   |                      |
| Yes  | 131 (6.6)   | 158 (10.3)   |                      | 59 (6.7)         | 78 (10.2)    |                      |
| Missing  | 298 (14.8)  | 31 (2.0)     |                      | 27 (3.1)         | 16 (2.1)     |                      |
| <b>Ever been diagnosed with diabetes</b>             |             |              | <0.001               |                  |              | <0.001               |
| No   | 1474 (73.4) | 1333 (87.00) |                      | 592 (67.6)       | 620 (81.4)   |                      |
| Yes, ≤ 2 years                                       | 200 (9.9)   | 27 (1.76)    |                      | 109 (12.4)       | 20 (2.6)     |                      |
| Yes, >2 years  | 263 (13.1)  | 152 (9.92)   |                      | 156 (17.8)       | 109 (14.3)   |                      |
| Missing  | 72 (3.6)    | 20 (1.31)    |                      | 19 (2.2)         | 13 (1.7)     |                      |
| <b>Ever been diagnosed with chronic pancreatitis</b> |             |              | <0.001               |                  |              | 0.296                |
| No   | 1885 (93.8) | 1507 (98.4)  |                      | 842 (96.1)       | 743 (97.5)   |                      |
| Yes  | 19 (1.0)    | 2 (0.1)      |                      | 5 (0.6)          | 2 (0.3)      |                      |
| Missing  | 105 (5.2)   | 23 (1.5)     |                      | 29 (3.3)         | 17 (2.2)     |                      |

BMI: body mass index; PC: pancreatic cancer.

Descriptives are shown for the unimputed baseline characteristics.

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p<0.05.

<sup>2</sup> Light drinker: 0-1 drink/day for men and women; Moderate drinker: men: 1-5drinks/day, women: 1-2.5 drinks/day; Heavy drinker: men: ≥5drinks/day, women: ≥2.5 drinks/day.

**Supplementary Table 11.** Association between smoking variables and pancreatic cancer risk in the PanGenEU-Spain study population (876 cases and 762 controls) per tobacco type.

|   | Model 1                       |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
|---|-------------------------------|-------|------------------|-------|-------------------------------|-------------|------------------|-------|------------------------------------|-------|------------------|-------------|------------|-------|-----|-------|------|-------------|
|   | Smoking black tobacco (N=279) |       |                  |       | Smoking blond tobacco (N=386) |             |                  |       | Smoking both tobacco types (N=258) |       |                  |             |            |       |     |       |      |             |
|   | Cases (N=165)                 |       | Controls (N=114) |       | Cases (N=204)                 |             | Controls (N=182) |       | Cases (N=152)                      |       | Controls (N=106) |             | OR (95%CI) |       |     |       |      |             |
|   | N                             | %     | N                | %     | OR                            | (95%CI)     | N                | %     | N                                  | %     | OR               | (95%CI)     | N          | %     | N   | %     | OR   | (95%CI)     |
| <b>Smoking status incl. occasional (cigarettes)</b>       |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 1.00                          |             | 355              | 63.50 | 360                                | 66.40 | 1.00             |             | 355        | 70.00 | 360 | 77.30 | 1.00 |             |
| Occasional  | 1                             | 0.19  | 4                | 0.84  | 0.29                          | (0.03-2.62) | 11               | 1.97  | 11                                 | 2.03  | 1.18             | (0.49-2.81) | 2          | 0.39  | 2   | 0.43  | 1.11 | (0.15-8.08) |
| Former  | 104                           | 20.00 | 79               | 16.70 | 1.39                          | (0.95-2.02) | 90               | 16.10 | 88                                 | 16.20 | 1.18             | (0.83-1.67) | 76         | 15.00 | 58  | 12.40 | 1.48 | (0.98-2.24) |
| Current   | 60                            | 11.50 | 31               | 6.54  | 2.05                          | (1.25-3.35) | 103              | 18.40 | 83                                 | 15.30 | 1.55             | (1.07-2.24) | 74         | 14.60 | 46  | 9.87  | 1.95 | (1.26-3.02) |
| <b>Smoking intensity in tertiles (cigarettes per day)</b> |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 1.00                          |             | 355              | 63.50 | 360                                | 66.40 | 1.00             |             | 355        | 70.00 | 360 | 77.30 | 1.00 |             |
| < 14  | 34                            | 6.54  | 37               | 7.81  | 0.99                          | (0.59-1.66) | 82               | 14.70 | 81                                 | 14.90 | 1.17             | (0.82-1.68) | 18         | 3.55  | 17  | 3.65  | 1.23 | (0.61-2.47) |
| 14-25   | 75                            | 14.40 | 44               | 9.28  | 1.83                          | (1.18-2.85) | 85               | 15.20 | 72                                 | 13.30 | 1.46             | (1.00-2.14) | 31         | 6.11  | 17  | 3.65  | 2.10 | (1.11-3.97) |
| ≥ 25  | 56                            | 10.80 | 33               | 6.96  | 1.82                          | (1.11-2.98) | 37               | 6.62  | 29                                 | 5.35  | 1.49             | (0.88-2.54) | 103        | 20.30 | 72  | 15.50 | 1.68 | (1.15-2.47) |
| <b>Smoking duration in tertiles (years)</b>               |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 1.00                          |             | 355              | 63.50 | 360                                | 66.40 | 1.00             |             | 355        | 70.00 | 360 | 77.30 | 1.00 |             |
| < 26  | 40                            | 7.69  | 30               | 6.33  | 1.41                          | (0.83-2.39) | 64               | 11.40 | 75                                 | 13.80 | 1.07             | (0.71-1.59) | 32         | 6.31  | 30  | 6.44  | 1.27 | (0.73-2.21) |
| 26-39   | 54                            | 10.40 | 35               | 7.38  | 1.68                          | (1.03-2.72) | 91               | 16.30 | 69                                 | 12.70 | 1.55             | (1.07-2.24) | 48         | 9.47  | 38  | 8.15  | 1.53 | (0.94-2.49) |
| ≥ 39  | 71                            | 13.70 | 49               | 10.30 | 1.53                          | (0.98-2.37) | 49               | 8.77  | 38                                 | 7.01  | 1.38             | (0.86-2.20) | 72         | 14.20 | 38  | 8.15  | 2.11 | (1.33-3.36) |
| <b>Cumulative dose in tertiles (pack-years)</b>           |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 1.00                          |             | 355              | 63.50 | 360                                | 66.40 | 1.00             |             | 355        | 70.00 | 360 | 77.30 | 1.00 |             |
| < 18  | 35                            | 6.73  | 32               | 6.75  | 1.20                          | (0.70-2.03) | 86               | 15.40 | 88                                 | 16.20 | 1.18             | (0.83-1.68) | 17         | 3.35  | 18  | 3.86  | 1.15 | (0.56-2.34) |
| 18-47   | 68                            | 13.10 | 44               | 9.28  | 1.66                          | (1.06-2.59) | 81               | 14.50 | 59                                 | 10.90 | 1.69             | (1.14-2.53) | 45         | 8.88  | 24  | 5.15  | 2.15 | (1.25-3.70) |
| ≥ 47  | 62                            | 11.90 | 38               | 8.02  | 1.73                          | (1.08-2.77) | 37               | 6.62  | 35                                 | 6.46  | 1.17             | (0.71-1.94) | 90         | 17.80 | 64  | 13.70 | 1.61 | (1.08-2.40) |
| <b>Age at smoking initiation in tertiles</b>              |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 1.00                          |             | 355              | 63.50 | 360                                | 66.40 | 1.00             |             | 355        | 70.00 | 360 | 77.30 | 1.00 |             |
| < 15  | 75                            | 14.40 | 56               | 11.80 | 1.46                          | (0.95-2.23) | 53               | 9.48  | 56                                 | 10.30 | 1.21             | (0.78-1.87) | 65         | 12.80 | 50  | 10.70 | 1.55 | (1.00-2.42) |
| 15 - 18   | 51                            | 9.81  | 30               | 6.33  | 1.81                          | (1.09-2.99) | 61               | 10.90 | 58                                 | 10.70 | 1.28             | (0.85-1.93) | 55         | 10.80 | 36  | 7.73  | 1.80 | (1.11-2.90) |
| ≥ 18  | 39                            | 7.50  | 28               | 5.91  | 1.42                          | (0.83-2.42) | 90               | 16.10 | 68                                 | 12.50 | 1.43             | (1.00-2.06) | 32         | 6.31  | 20  | 4.29  | 1.71 | (0.94-3.12) |
| <b>Age last smoked in tertiles (years)</b>                |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |
| Current smoker  | 60                            | 11.50 | 32               | 6.75  | 1.00                          |             | 104              | 18.60 | 85                                 | 15.70 | 1.00             |             | 74         | 14.60 | 46  | 9.87  | 1.00 |             |
| < 40  | 32                            | 6.15  | 21               | 4.43  | 0.82                          | (0.41-1.66) | 30               | 5.37  | 36                                 | 6.64  | 0.72             | (0.41-1.27) | 20         | 3.94  | 23  | 4.94  | 0.55 | (0.27-1.11) |
| 40 - 53   | 32                            | 6.15  | 29               | 6.12  | 0.59                          | (0.30-1.15) | 32               | 5.72  | 27                                 | 4.98  | 0.89             | (0.48-1.63) | 26         | 5.13  | 22  | 4.72  | 0.71 | (0.36-1.40) |
| ≥ 53  | 41                            | 7.88  | 32               | 6.75  | 0.67                          | (0.35-1.29) | 38               | 6.80  | 34                                 | 6.27  | 0.76             | (0.42-1.36) | 32         | 6.31  | 15  | 3.22  | 1.14 | (0.54-2.38) |
| Never-smoker  | 355                           | 68.30 | 360              | 75.90 | 0.50                          | (0.31-0.82) | 355              | 63.50 | 360                                | 66.40 | 0.66             | (0.46-0.95) | 355        | 70.00 | 360 | 77.30 | 0.52 | (0.34-0.81) |
| <b>Inhalation</b>   |                               |       |                  |       |                               |             |                  |       |                                    |       |                  |             |            |       |     |       |      |             |

|   |     |       |     |       |      |             |     |       |     |       |      |             |     |       |     |       |      |              |
|---|-----|-------|-----|-------|------|-------------|-----|-------|-----|-------|------|-------------|-----|-------|-----|-------|------|--------------|
| Never-smoker                                    | 355 | 68.30 | 360 | 75.90 | 1.00 |             | 355 | 63.50 | 360 | 66.40 | 1.00 |             | 355 | 70.00 | 360 | 77.30 | 1.00 |              |
| Mouth only                                      | 21  | 4.04  | 16  | 3.38  | 1.31 | (0.65-2.65) | 33  | 5.90  | 35  | 6.46  | 1.03 | (0.62-1.70) | 13  | 2.56  | 7   | 1.50  | 2.05 | (0.80-5.29)  |
| Throat  | 19  | 3.65  | 18  | 3.80  | 1.10 | (0.55-2.16) | 36  | 6.44  | 25  | 4.61  | 1.49 | (0.86-2.59) | 19  | 3.75  | 13  | 2.79  | 1.65 | (0.78-3.46)  |
| Chest   | 125 | 24.00 | 80  | 16.90 | 1.71 | (1.18-2.46) | 135 | 24.20 | 122 | 22.50 | 1.40 | (1.02-1.94) | 120 | 23.70 | 86  | 18.50 | 1.64 | (1.14-2.35)  |
| <b>Filter-use</b>                               |     |       |     |       |      |             |     |       |     |       |      |             |     |       |     |       |      |              |
| Never-smoker                                    | 355 | 68.30 | 360 | 75.90 | 1.00 |             | 355 | 63.50 | 360 | 66.40 | 1.00 |             | 355 | 70.00 | 360 | 77.30 | 1.00 |              |
| Filtered only                                   | 118 | 22.70 | 87  | 18.40 | 1.45 | (1.01-2.07) | 194 | 34.70 | 171 | 31.50 | 1.34 | (1.01-1.78) | 97  | 19.10 | 74  | 15.90 | 1.55 | (1.06-2.27)  |
| Non-filtered only                               | 7   | 1.35  | 6   | 1.27  | 1.23 | (0.40-3.79) | 1   | 0.18  | 4   | 0.74  | 0.31 | (0.03-2.79) | 3   | 0.59  | 1   | 0.21  | 3.10 | (0.32-30.32) |
| Both  | 40  | 7.69  | 21  | 4.43  | 2.08 | (1.16-3.75) | 9   | 1.61  | 7   | 1.29  | 1.68 | (0.61-4.67) | 52  | 10.30 | 31  | 6.65  | 1.91 | (1.14-3.18)  |
| <b>Childhood exposure to ETS</b>                |     |       |     |       |      |             |     |       |     |       |      |             |     |       |     |       |      |              |
| Both parents were never-smokers                 | 104 | 20.00 | 111 | 23.40 | 1.00 |             | 110 | 19.70 | 124 | 22.90 | 1.00 |             | 100 | 19.70 | 108 | 23.20 | 1.00 |              |
| One of the parents smoked                       | 405 | 77.90 | 350 | 73.80 | 1.24 | (0.92-1.69) | 426 | 76.20 | 392 | 72.30 | 1.23 | (0.92-1.65) | 393 | 77.50 | 344 | 73.80 | 1.24 | (0.91-1.68)  |
| Both parents smoked                             | 11  | 2.12  | 13  | 2.74  | 1.00 | (0.42-2.40) | 23  | 4.11  | 26  | 4.80  | 1.20 | (0.63-2.28) | 14  | 2.76  | 14  | 3.00  | 1.23 | (0.55-2.75)  |
| <b>Time since cessation in tertiles (years)</b> |     |       |     |       |      |             |     |       |     |       |      |             |     |       |     |       |      |              |
| Current smoker                                  | 60  | 11.50 | 32  | 6.75  | 1.00 |             | 104 | 18.60 | 85  | 15.70 | 1.00 |             | 74  | 14.60 | 46  | 9.87  | 1.00 |              |
| < 10  | 37  | 7.12  | 20  | 4.22  | 0.98 | (0.49-1.96) | 46  | 8.23  | 45  | 8.30  | 0.80 | (0.48-1.34) | 30  | 5.92  | 17  | 3.65  | 1.05 | (0.52-2.12)  |
| 10 - 22   | 35  | 6.73  | 25  | 5.27  | 0.75 | (0.38-1.47) | 33  | 5.90  | 30  | 5.54  | 0.82 | (0.45-1.48) | 26  | 5.13  | 22  | 4.72  | 0.68 | (0.34-1.35)  |
| ≥ 22  | 33  | 6.35  | 37  | 7.81  | 0.47 | (0.24-0.90) | 21  | 3.76  | 22  | 4.06  | 0.67 | (0.34-1.35) | 22  | 4.34  | 21  | 4.51  | 0.59 | (0.29-1.20)  |
| Never-smoker                                    | 355 | 68.30 | 360 | 75.90 | 0.50 | (0.31-0.82) | 355 | 63.50 | 360 | 66.40 | 0.65 | (0.45-0.94) | 355 | 70.00 | 360 | 77.30 | 0.51 | (0.33-0.80)  |

PC: pancreatic cancer; ETS: environmental tobacco smoke.

Results are shown for the imputed smoking variables.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and region (East, Central and Northern Spain).

<sup>1</sup> Chi-square test applied to evaluate differences between the groups per tobacco type. Significance was set at p<0.05.

**Supplementary Table 12.** Sensitivity analysis on the association between tobacco smoking and pancreatic cancer risk, in models additionally controlling for smoking duration and intensity, for the PC population (2,009 cases and 1,532 controls).

|  | Model 1 |               | Model 1a |             | Model 1b |             | Model 1c |             | Model 1d |             |
|--|---------|---------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|
|  | OR      | (95%CI)       | OR       | (95%CI)     | OR       | (95%CI)     | OR       | (95%CI)     | OR       | (95%CI)     |
| <b>Ever smoked 100 cigarettes</b>        |         |               |          |             |          |             |          |             |          |             |
| No                                       | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Yes                                      | 1.30    | (1.11-1.53)   | 0.96     | (0.72-1.27) | 0.87     | (0.69-1.11) | 0.74     | (0.54-1.00) | 0.92     | (0.71-1.18) |
| <b>Regular smoker</b>                    |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Regular smoker                           | 1.33    | (1.13-1.57)   | 1.02     | (0.76-1.35) | 0.91     | (0.71-1.16) | 0.78     | (0.57-1.07) | 0.96     | (0.74-1.24) |
| Occasional smoker                        | 1.01    | (0.61-1.68)   | 0.86     | (0.51-1.45) | 0.74     | (0.44-1.25) | 0.68     | (0.40-1.16) | 0.83     | (0.50-1.40) |
| <b>Tobacco type<sup>2</sup></b>          |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Smoker of black tobacco only             | 1.55    | (1.13 - 2.12) | 1.00     | (0.72-1.39) | 0.93     | (0.69-1.25) | 0.78     | (0.54-1.12) | 0.95     | (0.70-1.29) |
| Smoker of blond tobacco only             | 1.23    | (0.94 - 1.62) | 0.97     | (0.73-1.30) | 0.89     | (0.69-1.14) | 0.75     | (0.55-1.03) | 0.93     | (0.72-1.20) |
| Smoker of both tobacco types             | 1.58    | (1.14 - 2.17) | 0.85     | (0.56-1.31) | 0.88     | (0.62-1.23) | 0.68     | (0.43-1.07) | 0.79     | (0.54-1.17) |
| <b>Current smoker</b>                    |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Current smoker                           | 1.36    | (1.08-1.70)   | 1.02     | (0.73-1.41) | 0.79     | (0.57-1.11) | 0.69     | (0.47-1.01) | 0.91     | (0.66-1.26) |
| Former smoker                            | 1.30    | (1.10-1.55)   | 0.99     | (0.74-1.31) | 0.90     | (0.71-1.14) | 0.77     | (0.56-1.05) | 0.95     | (0.74-1.22) |
| <b>Ever quit smoking &gt;6 months</b>    |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Yes                                      | 1.35    | (1.10-1.68)   | 1.03     | (0.76-1.40) | 0.91     | (0.69-1.20) | 0.78     | (0.56-1.10) | 0.98     | (0.74-1.30) |
| No                                       | 1.30    | (1.09-1.55)   | 0.97     | (0.72-1.30) | 0.89     | (0.69-1.14) | 0.76     | (0.55-1.04) | 0.92     | (0.71-1.20) |
| <b>Inhalation</b>                        |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Mouth only                               | 1.10    | (0.80-1.50)   | 0.89     | (0.62-1.28) | 0.77     | (0.54-1.10) | 0.69     | (0.47-1.02) | 0.86     | (0.61-1.22) |
| Throat                                   | 1.48    | (1.11-1.99)   | 1.15     | (0.80-1.66) | 1.02     | (0.72-1.43) | 0.89     | (0.60-1.31) | 1.09     | (0.78-1.54) |
| Chest                                    | 1.33    | (1.12-1.58)   | 1.00     | (0.73-1.35) | 0.90     | (0.70-1.16) | 0.77     | (0.55-1.07) | 0.93     | (0.71-1.23) |
| <b>Filter-use</b>                        |         |               |          |             |          |             |          |             |          |             |
| Never-smoker                             | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Filtered only                            | 1.25    | (1.06-1.48)   | 0.97     | (0.73-1.29) | 0.84     | (0.66-1.08) | 0.74     | (0.54-1.01) | 0.91     | (0.71-1.17) |
| Non-filtered only                        | 1.69    | (1.10-2.61)   | 1.33     | (0.82-2.15) | 1.24     | (0.79-1.96) | 1.09     | (0.66-1.79) | 1.29     | (0.81-2.04) |
| Both                                     | 1.65    | (1.21-2.27)   | 1.22     | (0.80-1.84) | 1.10     | (0.76-1.58) | 0.93     | (0.60-1.44) | 1.12     | (0.76-1.65) |
| <b>Smoking cigar</b>                     |         |               |          |             |          |             |          |             |          |             |
| No                                       | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Yes                                      | 1.00    | (0.76-1.32)   | 0.92     | (0.7-1.21)  | 0.92     | (0.70-1.22) | 0.91     | (0.69-1.21) | 0.92     | (0.69-1.21) |
| <b>Smoking pipe</b>                      |         |               |          |             |          |             |          |             |          |             |
| No                                       | 1.00    | 1.00          | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Yes                                      | 1.13    | (0.86-1.49)   | 1.06     | (0.81-1.40) | 1.08     | (0.82-1.42) | 1.07     | (0.81-1.41) | 1.08     | (0.82-1.42) |
| <b>Tobacco type for pipe<sup>3</sup></b> |         |               |          |             |          |             |          |             |          |             |
| No pipe smoker                           | 1.00    |               | 1.00     |             | 1.00     |             | 1.00     |             | 1.00     |             |
| Black                                    | 0.78    | (0.37-1.66)   | 0.77     | (0.36-1.65) | 0.77     | (0.36-1.64) | 0.77     | (0.36-1.64) | 0.77     | (0.36-1.65) |

|   |      |             |      |             |      |             |      |             |      |             |
|---|------|-------------|------|-------------|------|-------------|------|-------------|------|-------------|
| Blond   | 1.25 | (0.85-1.82) | 1.18 | (0.81-1.73) | 1.16 | (0.79-1.70) | 1.16 | (0.79-1.69) | 1.18 | (0.80-1.72) |
| Mixed   | 1.12 | (0.76-1.66) | 1.03 | (0.69-1.53) | 1.09 | (0.73-1.62) | 1.08 | (0.72-1.60) | 1.06 | (0.72-1.58) |
| <b>Smoking status (cigarettes)</b>                        |      |             |      |             |      |             |      |             |      |             |
| Never-smoker  | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| Former  | 1.14 | (0.95-1.36) | 0.89 | (0.67-1.19) | 0.89 | (0.70-1.13) | 0.76 | (0.55-1.03) | 0.91 | (0.71-1.17) |
| Current   | 1.69 | (1.37-2.09) | 1.30 | (0.95-1.79) | 1.19 | (0.85-1.66) | 1.01 | (0.69-1.49) | 1.25 | (0.92-1.72) |
| <b>Smoking status incl. occasional</b>                    |      |             |      |             |      |             |      |             |      |             |
| Never-smoker  | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| Occasional  | 1.00 | (0.61-1.67) | 0.87 | (0.51-1.47) | 0.79 | (0.47-1.35) | 0.72 | (0.42-1.25) | 0.87 | (0.52-1.46) |
| Former  | 1.14 | (0.95-1.37) | 0.90 | (0.67-1.21) | 0.90 | (0.71-1.15) | 0.77 | (0.56-1.05) | 0.92 | (0.71-1.19) |
| Current   | 1.72 | (1.39-2.12) | 1.33 | (0.97-1.84) | 1.22 | (0.87-1.70) | 1.05 | (0.71-1.54) | 1.28 | (0.93-1.77) |
| <b>Quit smoking &lt;10 or ≥ 10 years ago</b>              |      |             |      |             |      |             |      |             |      |             |
| Never-smoker and former smoker quit >10years              | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| Current smoker and former smoker quit ≤10years            | 0.64 | (0.54-0.76) | 0.70 | (0.57-0.85) | 0.75 | (0.58-0.97) | 0.75 | (0.58-0.97) | 0.73 | (0.59-0.91) |
| <b>Childhood exposure to ETS</b>                          |      |             |      |             |      |             |      |             |      |             |
| Both parents were never-smokers                           | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| Only the father smoked                                    | 1.25 | (1.04-1.51) | 1.20 | (1.00-1.45) | 1.20 | (0.99-1.44) | 1.19 | (0.99-1.44) | 1.20 | (0.99-1.44) |
| Only the mother smoked                                    | 1.02 | (0.62-1.70) | 0.97 | (0.58-1.62) | 0.96 | (0.58-1.60) | 0.96 | (0.57-1.60) | 0.96 | (0.58-1.61) |
| Both parents smoked                                       | 1.07 | (0.81-1.42) | 1.01 | (0.76-1.34) | 1.01 | (0.76-1.34) | 1.00 | (0.75-1.33) | 1.01 | (0.76-1.34) |
| <b>Age at smoking initiation in tertiles (years)</b>      |      |             |      |             |      |             |      |             |      |             |
| Never-smoker  | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| < 15  | 1.36 | (1.10-1.70) | 1.00 | (0.71-1.40) | 0.88 | (0.65-1.19) | 0.73 | (0.50-1.07) | 0.90 | (0.65-1.25) |
| 15 - 18   | 1.31 | (1.06-1.61) | 0.99 | (0.72-1.35) | 0.89 | (0.68-1.17) | 0.75 | (0.54-1.06) | 0.93 | (0.70-1.24) |
| ≥ 18  | 1.29 | (1.04-1.59) | 1.00 | (0.74-1.35) | 0.91 | (0.69-1.18) | 0.78 | (0.56-1.08) | 0.96 | (0.73-1.26) |
| <b>Age last smoked in tertiles (years)</b>                |      |             |      |             |      |             |      |             |      |             |
| Current smoker  | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| < 38  | 0.56 | (0.43-0.74) | 0.58 | (0.44-0.76) | 0.75 | (0.50-1.13) | 0.73 | (0.48-1.10) | 0.64 | (0.47-0.86) |
| 38 - 50   | 0.71 | (0.55-0.93) | 0.72 | (0.55-0.95) | 0.78 | (0.57-1.07) | 0.77 | (0.56-1.05) | 0.75 | (0.57-0.99) |
| ≥ 50  | 0.76 | (0.58-1.01) | 0.77 | (0.58-1.01) | 0.73 | (0.55-0.97) | 0.74 | (0.56-0.98) | 0.77 | (0.58-1.01) |
| Never-smoker  | -    | -           | -    | -           | -    | -           | -    | -           | -    | -           |
| <b>Time of ever quitting in tertiles (years)</b>          |      |             |      |             |      |             |      |             |      |             |
| Current smoker who never quit                             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| < 2   | 0.93 | (0.69-1.26) | 0.94 | (0.69-1.27) | 0.92 | (0.68-1.24) | 0.92 | (0.68-1.25) | 0.93 | (0.69-1.26) |
| 2 - 6   | 0.94 | (0.68-1.30) | 0.97 | (0.69-1.35) | 0.88 | (0.63-1.22) | 0.90 | (0.64-1.25) | 0.95 | (0.68-1.32) |
| ≥ 6   | 1.32 | (0.96-1.82) | 1.36 | (0.98-1.87) | 1.35 | (0.97-1.86) | 1.37 | (0.99-1.89) | 1.37 | (0.99-1.88) |
| Never-smoker  | -    | -           | -    | -           | -    | -           | -    | -           | -    | -           |
| <b>Smoking duration in tertiles (years)</b>               |      |             |      |             |      |             |      |             |      |             |
| Never-smoker  | 1.00 |             | 1.00 |             | -    | -           | -    | -           | 1.00 |             |
| < 23  | 0.91 | (0.72-1.14) | 0.75 | (0.55-1.03) | -    | -           | -    | -           | 0.82 | (0.63-1.07) |
| 23 - 35   | 1.52 | (1.23-1.87) | 1.24 | (0.91-1.69) | -    | -           | -    | -           | 1.28 | (0.94-1.74) |
| ≥ 35  | 1.51 | (1.23-1.86) | 1.20 | (0.86-1.67) | -    | -           | -    | -           | 1.19 | (0.82-1.74) |
| <b>Smoking intensity in tertiles (cigarettes per day)</b> |      |             |      |             |      |             |      |             |      |             |
| Never-smoker  | 1.00 |             | -    | -           | 1.00 |             | -    | -           | 1.00 |             |

|    |  |      |             |      |             |      |             |      |             |      |             |
|----|--|------|-------------|------|-------------|------|-------------|------|-------------|------|-------------|
| 1  |  |      |             |      |             |      |             |      |             |      |             |
| 2  | < 10   | 1.02 | (0.83-1.25) | -    | -           | 0.76 | (0.58-0.98) | -    | -           | 0.83 | (0.63-1.08) |
| 3  | 10 - 20  | 1.64 | (1.34-2.02) | -    | -           | 1.15 | (0.87-1.52) | -    | -           | 1.13 | (0.78-1.64) |
| 4  | ≥ 20   | 1.41 | (1.12-1.78) | -    | -           | 0.96 | (0.70-1.31) | -    | -           | 0.78 | (0.46-1.34) |
| 5  | <b>Cumulative dose in tertiles (pack-years)</b>                  |      |             |      |             |      |             |      |             |      |             |
| 6  | Never-smoker   | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | -    | -           |
| 7  | < 14   | 0.90 | (0.72-1.13) | 0.90 | (0.66-1.22) | 0.78 | (0.60-1.01) | 0.70 | (0.48-1.01) | -    | -           |
| 8  | 14 - 32  | 1.57 | (1.27-1.94) | 1.56 | (1.08-2.26) | 1.19 | (0.88-1.62) | 1.00 | (0.60-1.66) | -    | -           |
| 9  | ≥ 32   | 1.50 | (1.21-1.84) | 1.49 | (0.90-2.45) | 1.05 | (0.72-1.52) | 0.80 | (0.39-1.64) | -    | -           |
| 10 | <b>Time since cessation in tertiles (years)</b>                  |      |             |      |             |      |             |      |             |      |             |
| 11 | Current smoker   | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| 12 | < 14   | 0.81 | (0.63-1.04) | 0.81 | (0.62-1.05) | 0.80 | (0.62-1.04) | 0.82 | (0.63-1.06) | 0.81 | (0.63-1.04) |
| 13 | 14 - 28  | 0.68 | (0.51-0.89) | 0.68 | (0.50-0.94) | 0.68 | (0.49-0.92) | 0.70 | (0.53-0.93) | 0.68 | (0.51-0.89) |
| 14 | ≥ 28   | 0.51 | (0.38-0.69) | 0.54 | (0.36-0.82) | 0.54 | (0.36-0.81) | 0.55 | (0.39-0.76) | 0.51 | (0.38-0.69) |
| 15 | Never-smoker   | -    |             | -    |             | -    |             | -    |             | -    |             |
| 16 | <b>Intensity of smoking cigars in tertiles (cigars per week)</b> |      |             |      |             |      |             |      |             |      |             |
| 17 | Never-smoker   | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| 18 | < 1.0  | 0.95 | (0.67-1.34) | 0.94 | (0.66-1.34) | 0.92 | (0.65-1.31) | 0.92 | (0.65-1.31) | 0.94 | (0.66-1.34) |
| 19 | 1.0 - 6.2  | 0.91 | (0.59-1.39) | 0.81 | (0.52-1.25) | 0.83 | (0.54-1.28) | 0.82 | (0.53-1.27) | 0.81 | (0.52-1.25) |
| 20 | ≥ 6.2  | 1.20 | (0.84-1.73) | 1.11 | (0.77-1.60) | 1.13 | (0.78-1.62) | 1.12 | (0.77-1.61) | 1.11 | (0.77-1.60) |
| 21 | <b>Intensity of smoking pipes in tertiles (pipes per week)</b>   |      |             |      |             |      |             |      |             |      |             |
| 22 | Never-smoker   | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             | 1.00 |             |
| 23 | < 5.0  | 1.13 | (0.78-1.64) | 1.14 | (0.78-1.66) | 1.15 | (0.79-1.68) | 1.15 | (0.79-1.68) | 1.15 | (0.79-1.68) |
| 24 | 5.0 – 14.4   | 1.32 | (0.89-1.97) | 1.21 | (0.81-1.82) | 1.24 | (0.83-1.86) | 1.23 | (0.82-1.85) | 1.22 | (0.82-1.83) |
| 25 | ≥ 14.4   | 1.20 | (0.78-1.85) | 1.13 | (0.73-1.75) | 1.15 | (0.75-1.79) | 1.15 | (0.74-1.78) | 1.15 | (0.74-1.78) |
| 26 | <b>Smoking duration (years)</b>                                  | 1.01 | (1.01-1.01) | 1.17 | (1.04-1.33) | -    | -           | -    | -           | 1.10 | (0.93-1.29) |
| 27 | <b>Smoking intensity (cigarettes per day)</b>                    | 1.01 | (1.00-1.01) | -    | -           | 1.02 | (0.93-1.12) | -    | -           | 0.82 | (0.69-0.98) |
| 28 | <b>Cumulative dose (pack-years)</b>                              | 1.01 | (1.00-1.01) | 1.08 | (0.93-1.26) | 1.05 | (0.94-1.17) | 1.06 | (0.9-1.24)  | -    | -           |
| 29 | <b>Time since cessation (years)</b>                              | 0.98 | (0.97-0.99) | 0.76 | (0.67-0.85) | 0.86 | (0.71-1.05) | 0.86 | (0.71-1.04) | 0.78 | (0.68-0.89) |
| 30 | <b>Age at smoking initiation (years)</b>                         | 1.01 | (1.00-1.02) | 0.98 | (0.88-1.08) | 0.95 | (0.86-1.04) | 0.92 | (0.83-1.03) | 0.97 | (0.89-1.07) |
| 31 | <b>Age last smoked (years)</b>                                   | 1.01 | (1.00-1.01) | 1.05 | (0.95-1.15) | 1.01 | (0.92-1.11) | 1.00 | (0.90-1.11) | 1.02 | (0.93-1.13) |
| 32 | <b>Time of ever quitting (years)</b>                             | 1.00 | (0.98-1.03) | 0.99 | (0.92-1.08) | 0.99 | (0.91-1.07) | 0.99 | (0.91-1.07) | 0.99 | (0.92-1.08) |
| 33 | <b>Intensity of smoking cigars (cigars per week)</b>             | 1.00 | (0.99-1.02) | 1.01 | (0.94-1.10) | 1.02 | (0.94-1.10) | 1.02 | (0.94-1.10) | 1.01 | (0.94-1.09) |
| 34 | <b>Intensity of smoking pipes (pipes per week)</b>               | 1.00 | (0.99-1.01) | 1.00 | (0.92-1.08) | 1.00 | (0.93-1.09) | 1.00 | (0.93-1.09) | 1.00 | (0.92-1.09) |

PC: pancreatic cancer; ETS: environmental tobacco smoke.

Results are shown for the categorical, imputed smoking variables, and for the continuous, unimputed smoking variables.

Model 1: adjusted for age (≤ 54, 55-64, 65-74, ≥75 years), gender (male, female) and country (Spain, England, Germany, Ireland, Italy, Sweden);

Model 1a: Model 1 plus additional adjustment for smoking intensity (cigarettes per day, continuous, non-linear);

Model 1b: Model 1 plus additional adjustment for smoking duration (years, continuous, non-linear);

Model 1c: Model 1 plus additional adjustment for smoking intensity (cigarettes per day, continuous, non-linear) and smoking duration (years, continuous, non-linear);

Model 1d: Model 1 plus additional adjustment for cumulative dose (pack-years, continuous, non-linear).

<sup>1</sup> Chi-square test applied to evaluate differences between the groups. Significance was set at p<0.05.

<sup>2</sup> Type of tobacco was only collected for Spain.

<sup>3</sup> Type of pipe was not collected for Ireland.

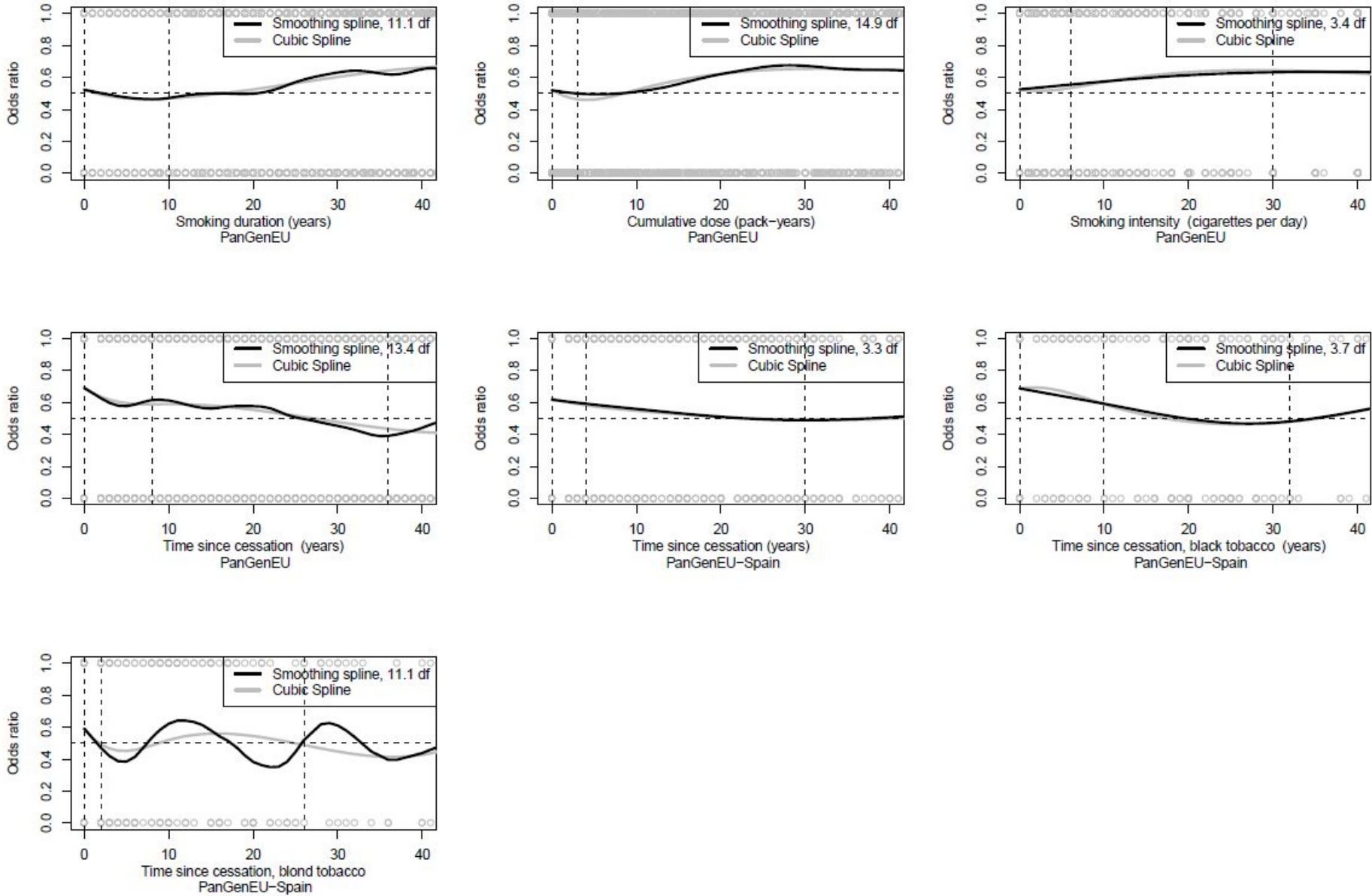
**Supplementary Table 13:** Combined effects of smoking intensity and duration in the PanGenEU study population (2,009 cases and 1,532 controls).

|   | Cases (%)  | Controls (%) | Model 1<br>OR (95% CI)  |
|---|------------|--------------|-------------------------|
| Never smokers                             | 759 (37.8) | 690 (45.0)   | 1.00 (Ref.)             |
| <b>Low intensity &amp; high duration</b>  | 120 (6.0)  | 79 (5.2)     | <b>1.18 (0.84-1.13)</b> |
| Moderate intensity & high duration        | 182 (9.1)  | 102 (6.7)    | 1.54 (1.15-2.07)        |
| <b>High intensity &amp; high duration</b> | 179 (8.9)  | 96 (6.3)     | <b>1.78 (1.32-2.39)</b> |
| Low intensity & moderate duration         | 141 (7.0)  | 118 (7.7)    | 1.18 (0.87-1.61)        |
| Moderate intensity & moderate duration    | 241 (12.0) | 96 (6.3)     | 2.25 (1.67-3.02)        |
| High intensity & moderate duration        | 95 (4.7)   | 67 (4.4)     | 1.18 (0.81-1.70)        |
| Low intensity & low duration              | 128 (6.4)  | 146 (9.5)    | 0.78 (0.58-1.06)        |
| Moderate intensity & low duration         | 110 (5.5)  | 89 (5.8)     | 1.08 (0.76-1.54)        |
| High intensity & low duration             | 54 (2.7)   | 49 (2.7)     | 1.01 (0.65-1.58)        |

Model 1: adjusted for age, sex and country.

Low, moderate and high levels of smoking intensity and smoking duration were based on tertiles, as reported in the article.

**Figure 1 (A-G):** Dose-response relationships between several smoking variables and the risk of PC, depicted by restricted cubic splines with knots at 10%, 50% and 90%, represented as dashed, vertical lines. Not adjusted for age, gender and country (for the PanGenEU study population) or region (for the PanGenEU-Spain study population) or smoking intensity or duration. Splines are shown for the unimputed data. The spline curve with smoothing applied is shown as a black trend line, the original spline curve is shown as a reference in grey. The dashed horizontal black line represents the reference odds ratio of 1.



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