

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, there is a need to further characterize pancreatic cancer 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.

Methods: Tobacco smoking habits and other relevant information were 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 pancreatic cancer risk by smoking characteristics and interactions with other pancreatic cancer risk factors. Fractional polynomials and restricted cubic splines were used to test for nonlinearity of the dose–response relationships and to analyze their shape.

Results: Relative to never-smokers, current smokers [OR = 1.72; 95% confidence interval (95% CI), 1.39–2.12], those inhaling into the throat (OR = 1.48; 95% CI, 1.11–1.99) or chest (OR = 1.33; 95%

CI, 1.12–1.58), and those using nonfiltered cigarettes (OR = 1.69; 95% CI, 1.10–2.61), were all at an increased pancreatic cancer risk. Pancreatic cancer risk was highest in current black tobacco smokers (OR = 2.09; 95% CI, 1.31–3.41), followed by blond tobacco smokers (OR = 1.43; 95% CI, 1.01–2.04). Childhood exposure to tobacco smoke relative to parental smoking was also associated with increased pancreatic cancer risk (OR = 1.24; 95% CI, 1.03–1.49). Dose–response relationships for smoking duration, intensity, cumulative dose, and smoking cessation were nonlinear and showed different shapes by tobacco type. Effect modification by family history of pancreatic cancer and diabetes was likely.

Conclusions: This study reveals differences in pancreatic cancer risk by tobacco type and other habit characteristics, as well as nonlinear risk associations.

Impact: This characterization of smoking-related pancreatic cancer risk profiles may help in defining pancreatic cancer high-risk populations.

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Introduction

Pancreatic cancer is one of the deadliest cancer types worldwide (5-year relative survival rate in the range 5%–15%; ref. 1). Disastrously, estimates of pancreatic cancer incidence are increasing both in United States and Europe (2). Despite the etiology of pancreatic cancer is relatively unknown, it is estimated that 10% to 30% of all pancreatic cancer cases are caused by smoking (3). Prevention of smoking is therefore a strong measure to reduce the burden of pancreatic cancer in the population.

Although the association between smoking and pancreatic cancer is well-established, a detailed characterization of tobacco smoking habits in relation to pancreatic cancer 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, were associated with an increase in pancreatic cancer risk (4). However, the authors assumed a linear trend for pancreatic cancer risk associated with increasing smoking exposure, a fact that was disputed by Zou and colleagues in an updated analysis combining 9,044 cases and 32,039 controls that showed a nonlinear dose–response relationship between several smoking characteristics and pancreatic cancer risk (5). In addition, the 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 pancreatic cancer risk levelled-off (6), shedding a different perspective on the dose–response relationship of smoking in relation to pancreatic cancer risk. However, in the aforementioned studies, an exploration of the shape of the association between smoking measures and pancreatic cancer risk was not further pursued. The shape of the dose–response relationship between cigarette smoking and pancreatic cancer risk was investigated in a recent meta-analysis of 38 case–control and 40 cohort studies (7). Risk patterns of pancreatic cancer in current versus smokers were compared in this study for smoking intensity and duration, ignoring the contribution to risk of former smokers. To understand multidimensional aspects of smoking in pancreatic cancer etiology, there is a need to provide consistent risk estimates for all smoking groups and to address the mutual influence of smoking intensity and duration.

Moreover, several aspects of tobacco smoking habits have not been considered until now. For instance, differences in pancreatic cancer risk by either black or blond tobacco use have not been explored despite the presumed differences in their chemical composition and damaging effects (8, 9). In fact, several studies have shown that black tobacco is associated with higher risk of bladder (8), colorectal (10), esophageal (11), and head-and-neck cancer (12, 13), than blond tobacco.

Therefore, we set out to investigate the association and dose–response relationship between tobacco smoking and pancreatic cancer risk in a large European population, considering every aspect of the smoking habit including use of black versus blond tobacco.

Materials and Methods

Study design and participants

The PanGenEU is an ongoing multicenter case–control study initiated in 2007, recruiting participants from six European countries (Germany, Ireland, Italy, Spain, Sweden, and United Kingdom) across 28 centers. Newly diagnosed patients with pancreatic cancer >18 years old and controls matched by age (± 10 years), gender, and geographical area were included if they had lived in the study area for at least 6 months. A rapid ascertainment approach was applied: pancreatic

cancer cases with a suspicion of the disease were recruited and remained in the study if the diagnosis was verified by the treating physician. Controls, sex-, age-, and centre-individually matched to cases, were mostly hospital-based and eligible if principal diagnosis at admission was unrelated to known risk factors of pancreatic cancer. Conditions of admission of controls are reported in Supplementary Materials and Methods. Population-based controls (Sweden and Ireland) were eligible if history of pancreatic cancer was absent. Participation rates were 86.3% for cases and 77.8% for controls. The study was approved by the IRB of all participant centers and all subjects gave written informed consent. More details of the study are provided elsewhere (14, 15).

Variables

Personal interviews to the study subjects were conducted by trained monitors using standardized protocols and questionnaires to obtain detailed information on lifetime smoking habits, among other pancreatic cancer risk factors. The smoking status of the participants was categorized into never-smokers if they smoked <100 cigarettes during their lifetime; occasional smokers if they smoked ≥ 1 cigarette/day for ≥ 6 months; former smokers if they quit smoking for >1 year; and current smokers otherwise (>100 cigarettes during lifetime without permanent smoking cessation). Information on smoking habits by tobacco type (only black, blond, or both) was only collected in the Spanish centers. 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, nonfiltered, 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 calculated as (cigarettes per day/20) \times smoking duration in years. Smoking variables by use of tobacco type were generated likewise. Environmental tobacco smoke (ETS) exposure during childhood was categorized according to the smoking status of the parents (none, one, or both).

Statistical analysis

Imputation of missing values, assumed to be at random, was performed using the Random Forest algorithm (R package missForest). Predictor variables such as center, country, and case–control status were kept in the imputation set. The performance of the imputation (Supplementary Table S1) was assessed by calculating the out of bag mean square error (OOB), representing the mean of squared differences between each observed value and its prediction, based on random forest trees ($n = 100$ was applied). The average OOB for all smoking variables was 5.27, with categorical variables presenting a markedly lower estimate (OOB = 0.04), indicating a better imputation performance of the latter. Use of unimputed data of all continuous variables, for which the proportion of missing values was relatively low (6.7%), was therefore deemed more appropriate for dose–response analyses. The performance of the imputation was also assessed with concordance rates between the observed and imputed data, considering a test dataset consisting of only subjects with complete data and missing values introduced by following the missingness rates of the original data. The concordance of all categorical variables was 94.4%.

Differences between cases and controls regarding smoking characteristics were evaluated by χ^2 and Student *t* test (or Kruskal–Wallis test, where appropriate). Unconditional logistic regression analysis

was performed to estimate OR and 95% confidence intervals (95% CI). Never-smokers were chosen as the reference category, except for the variables “age when last smoked” and “time since smoking cessation,” where current smokers were taken as the reference. Tertiles were created for the continuous variables based on the distribution of controls. A *P* value for trend was calculated by assuming ordinal variables in linear regression models. Age (≤ 54 , 55–64, 65–74, ≥ 75 years), gender, and country-adjusted models (aOR) were considered (Model 1). For the tobacco type-specific analyses within the Spanish PanGenEU study population, the same model was applied, but replacing country by region (East, Central, and Northern Spain). The attributable risk (AR) of smoking in relation to pancreatic cancer (population exposed: 59%) was calculated from the fitted multivariate adjusted logistic regression models (R packages *attrrisk* and *epiR*). Because heterogeneity by country ($P < 0.05$) was evident for all smoking variables (e.g., *P* value for interaction by smoking status = 0.007; Supplementary Fig. S1), random effects for country were applied in mixed effects models. Because of absence of heterogeneity by region in the Spanish study population, logistic regression models without random effects were considered.

The influence of confounding factors or effect modification on the association was assessed for several variables: gender (female, male), age (< 65 years, ≥ 65 years), obesity (body mass index > 30 : yes, no), diabetes (no, yes less than 2 years, yes more than 2 years), asthma (yes, no), chronic pancreatitis (yes, no), alcohol status/consumption (never, former, current), presence of periodontitis (yes, no) and recession (yes, no), educational level as a proxy for socioeconomic status (low, medium, high), and family history of pancreatic cancer (yes, no). Variables changing estimates by more than 10% or having a significant influence in the model (diabetes and family history of pancreatic cancer 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 (16). 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 (17, 18).

To test for interaction, a likelihood ratio (LR) test was performed comparing models with and without an interaction term between the smoking variables and the covariates (e.g., age, gender, BMI and obesity, diabetes, asthma, alcohol, periodontitis, recession, educational level, and family history of pancreatic cancer). Effect modification was tested further via stratified analyses. To assess interaction by time-related variables, we explored the combined effect of smoking duration and other smoking characteristics such as tobacco type on pancreatic cancer risk. Smoking duration was categorized into < 20 , 20 to 30, and ≥ 30 years of smoking and stratified further by tobacco type considering never-smokers as the reference category.

To assess the dose–response relationships, pancreatic cancer risk estimates were calculated per 1-unit of increase in continuous smoking exposure variables considering linear and nonlinear models if so indicated by fractional polynomials (R package *mfp*; ref. 19). In addition, restricted cubic splines were used to confirm nonlinear associations and for modelling the shape of the dose–response relationships (R package *splines*; ref. 20). Nonlinearity of the models was tested via the likelihood-ratio test comparing the model with and without restricted cubic splines. Knots were set at the 10%, 50%, and 90% percentile of the exposure distribution, as comparable results were obtained with five knots (21).

Sensitivity analyses were performed comparing the risk estimates in magnitude and trend regarding the unimputed and imputed data, and

the PanGenEU study population with and without Italy (since Italy provided cases only). As information bias could be induced by neglecting the quantity of smoking exposure, adjustment for cumulative dose (pack-years) was considered, thereby accounting for both smoking duration and smoking intensity. Additional adjustments were made also for smoking intensity and duration separately, to assess both the individual and joined effects of smoking characteristics independent of smoking duration and/or intensity. These adjustment variables were considered on the continuous scale and modeled as fractional polynomials to account for nonlinear effects. To further assess the performance of the restricted cubic splines, additional smoothing was applied by varying the degrees of freedom, allowing more flexibility into the model (22).

The threshold for statistical significance in two-sided tests was set at $P < 0.05$. Data were analyzed with R-project (version 3.4.1; ref. 23).

Results

Table 1 shows the characteristics of the 2,009 cases and 1,532 controls included in this analysis. The Spanish centers contributed the most to both cases ($N = 876$) and controls ($N = 762$). Pancreatic cancer cases presented more frequently with a family history of pancreatic cancer and a diagnosis of diabetes or chronic pancreatitis.

Table 2 shows pancreatic cancer risk associated with smoking characteristics. The prevalence of smoking was higher in cases (27.4%) than in controls (17.6%), with a corresponding aOR of 1.72 (95% CI, 1.39–2.12) for current smokers compared with never-smokers. Furthermore, a statistically significant increased trend ($P < 0.001$) in pancreatic cancer risk was observed for longer smoking duration, higher smoking intensity and higher cumulative dose. The use of nonfiltered cigarettes increased risk of pancreatic cancer more prominently (aOR = 1.69; 95% CI, 1.10–2.61), although use of filtered cigarettes was also associated with an increased pancreatic cancer risk (aOR = 1.25; 95% CI, 1.06–1.48). Marked increases in pancreatic cancer risk were also observed for inhalation into the throat (aOR = 1.48; 95% CI, 1.11–1.99) and chest (aOR = 1.33; 95% CI, 1.12–1.58). Childhood exposure to ETS by smoking parents (vs. nonparental exposure) was also associated with a 24% (95% CI, 1.03–1.49) increased pancreatic cancer risk. Risk for former smokers decreased progressively with longer time since smoking cessation when compared with current smokers (aOR for 14–28 years after cessation = 0.67; 95% CI, 0.51–0.88). A negative trend of the risk was also observed if compared with never-smokers (pancreatic cancer risk was diminished from 14 years of cessation), and when considering smoking cessation time at 5-year intervals (Supplementary Table S2). No significant associations between pancreatic cancer risk and pipe/cigar-use or other smoking variables were observed (Supplementary Table S3). Additional adjustment for diabetes and family history of pancreatic cancer led to minimal differences in risk estimates (Supplementary Table S3). Effect modification was apparent only for family history of pancreatic cancer and diabetes status (Supplementary Table S4), pointing towards a higher pancreatic cancer risk among current smokers with family history of the disease (aOR = 2.24; 95% CI, 0.66–7.61) and former smokers with diabetes (aOR = 1.44; 95% CI, 0.91–2.28; *P* value for interaction < 0.001).

Table 3 shows pancreatic cancer risk estimates by tobacco type in PanGenEU-Spain. Compared with never-smokers, pancreatic cancer risk was significantly increased for smokers of only black tobacco (aOR = 1.55; 95% CI, 1.13–2.12) and of both tobacco types (aOR = 1.58; 95% CI, 1.14–2.17). Considering smokers of only blond tobacco, pancreatic cancer risk tended to be increased (aOR = 1.23; 95% CI,

Table 1. Baseline characteristics of the PanGenEU study population (2,009 cases and 1,532 controls).

	PanGenEU			<i>P</i> ^a	PanGenEU - Spain			<i>P</i> ^a
	Cases (%)	Controls (%)			Cases (%)	Controls (%)		
Country				<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)			– –	– –		
Gender				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)		
Age				<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)		
BMI (kg/m ²)				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)		
Alcohol status ^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)		
Family history of PC				<0.001				<0.001
No	1,882 (93.7)	1,492 (97.4)			815 (93.00)	739 (97.0)		
Yes	127 (6.3)	40 (2.6)			61 (7.0)	23 (3.0)		
Ever been diagnosed with asthma				<0.001				0.014
No	1,878 (93.5)	1,374 (89.7)			817 (93.3)	684 (89.8)		
Yes	131 (6.5)	158 (10.3)			59 (6.7)	78 (10.2)		
Ever been diagnosed with diabetes				<0.001				<0.001
No	1,515 (75.4)	1,349 (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)		
Ever been diagnosed with chronic pancreatitis				0.004				0.460
No	1,990 (99.1)	1,530 (99.9)			871 (99.4)	760 (99.7)		
Yes	19 (0.9)	2 (0.1)			5 (0.6)	2 (0.3)		

Note: Descriptives are shown for the imputed baseline characteristics. Descriptives of the unimputed baseline characteristics can be found in Supplementary Table S9.

Abbreviations: BMI, body mass index; PC, pancreatic cancer.

^a χ^2 test applied to evaluate differences between the groups. Significance was set at $P < 0.05$.

^bLight drinker: 0–1 drink/day for men and women; moderate drinker: men: 1–5 drinks/day, women: 1–2.5 drinks/day; heavy drinker: men: ≥5 drinks/day, women: ≥2.5 drinks/day.

0.94–1.62), though without reaching statistical significance. When further stratifying by smoking status, a significant increase in risk was observed for current smokers of only black tobacco (aOR = 2.09; 95% CI, 1.31–3.41) and blond tobacco (aOR = 1.43; 95% CI, 1.01–2.04). Former smokers of only black tobacco were at increased, though milder, pancreatic cancer risk (aOR = 1.40; 95% CI, 0.98–1.99).

Table 4 shows the combined effect of smoking duration and type of tobacco on pancreatic cancer risk. Compared with never-smokers, smoking for ≥30 years of both tobacco types was associated with a higher pancreatic cancer risk than smoking only black or blond tobacco (aOR = 2.05; 95% CI, 1.25–3.36 and RERI = 0.206; 95% CI, –0.49–0.91).

Table 5 shows risk estimates for continuous smoking variables associated with pancreatic cancer. Nonlinear associations were evident for smoking duration and intensity, cumulative dose, time since cessation, and age at smoking initiation. Adjusted fractional poly-

nomials models suggested a statistically significantly higher pancreatic cancer risk per 1-unit increase in smoking duration, smoking intensity and cumulative dose, and decreasing pancreatic cancer risks for age at smoking initiation and time since smoking cessation. Linear associations were observed for other variables such as intensity of smoking cigars/pipes (data not shown). The restricted cubic splines approximating the shape of the dose–response relationships confirmed these nonlinear associations. Compared with never-smokers, smoking for >25 years (**Fig. 1A** and **B**) and smoking >20 cigarettes/day (**Fig. 1D** and **E**) was associated with a statistically significant increase of pancreatic cancer risk. Similarly, a cumulative dose of >14 pack-years was associated with increased pancreatic cancer risk (**Fig. 1C**). Visual inspection for smoking intensity and cumulative dose was suggestive of plateauing of pancreatic cancer risk, at approximately 27 cigarettes/day or pack-years. Concerning time since smoking cessation (**Fig. 1F–I**), and relative to current smokers, risk

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

	Cases (%)		Controls (%)		P^a	Unadjusted OR (95% CI)	Adjusted aOR (95% CI)
Smoking status (cigarettes)					<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)
							$P_{\text{trend}} < 0.001$
Smoking intensity in tertiles (cigarettes per day)					<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)
							$P_{\text{trend}} < 0.001$
Smoking duration in tertiles (years)					<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)
							$P_{\text{trend}} < 0.001$
Cumulative dose in tertiles (pack-years)					<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)
							$P_{\text{trend}} < 0.001$
Age at smoking initiation in tertiles (years)					<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)
							$P_{\text{trend}} = 0.010$
Inhalation					<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)
							$P_{\text{trend}} < 0.001$
Filter use					<0.001		
Never-smoker	759	(37.8)	690	(45.0)		1.00	1.00
Filtered only	1,042	(51.9)	706	(46.1)		1.34 (1.17-1.54)	1.25 (1.06-1.48)
Nonfiltered 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)
							$P_{\text{trend}} < 0.001$
ETS exposure during childhood					<0.001		
Both parents were never-smokers	420	(20.9)	391	(25.6)		1.00	1.00
One of the parents smoked	1,378	(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)
							$P_{\text{trend}} = 0.610$
Time since cessation in tertiles (years)					<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)		—	—
							$P_{\text{trend}} < 0.001$

Note: Risk estimates are shown for the imputed smoking variables. Risk estimates of the unimputed smoking variables can be found in Supplementary Table S5. 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.

Abbreviation: ETS, environmental tobacco smoke.

^a χ^2 test applied to evaluate differences between the groups. Significance was set at $P < 0.05$.

Table 3. Association between smoking variables and pancreatic cancer risk by tobacco type and smoking status in the PanGenEU-Spain study population (876 cases and 762 controls).

	Cases (%)		Controls (%)		P value ^a	Unadjusted OR (95% CI)	Adjusted aOR (95% CI)
Tobacco type					0.012		
Never-smoker	355	(40.5)	360	(47.2)		1.00	1.00
Smoker of black tobacco only	165	(18.8)	114	(15.0)		1.47 (1.11-1.94)	1.55 (1.13-2.12)
Smoker of blond tobacco only	204	(23.3)	182	(23.9)		1.14 (0.89-1.46)	1.23 (0.94-1.62)
Smoker of both tobacco types	152	(17.4)	106	(13.9)		1.45 (1.09-1.94)	1.58 (1.14-2.17)
Tobacco type by smoking status					0.028		
Never-smoker	369	(42.0)	377	(49.5)		1.00	1.00
Former							
Black tobacco	104	(11.9)	79	(10.4)		1.34 (0.97-1.87)	1.40 (0.98-1.99)
Blond tobacco	90	(10.3)	88	(11.5)		1.04 (0.75-1.45)	1.12 (0.79-1.57)
Both	76	(8.7)	58	(7.6)		1.34 (0.92-1.94)	1.44 (0.97-2.14)
Current							
Black tobacco	60	(6.8)	31	(4.1)		1.98 (1.26-3.16)	2.09 (1.31-3.41)
Blond tobacco	103	(11.8)	83	(10.9)		1.27 (0.92-1.75)	1.43 (1.01-2.04)
Both	74	(8.5)	46	(6.0)		1.64 (1.11-2.45)	1.81 (1.19-2.76)

Note: Risk estimates are shown for the imputed smoking variables. Adjusted model for age (≤ 54 , 55-64, 65-74, ≥ 75 years), gender (male, female), and region (East, Central, and Northern Spain).

^a χ^2 test applied to evaluate differences between the groups. Significance was set at $P < 0.05$.

appeared to decrease between 8 and 11 years of cessation and after around 18 years of cessation regardless of cumulative dose. In between these periods, the significant effect disappeared. By tobacco type, corresponding periods of significant decrease in pancreatic cancer risk were observed for black tobacco (after about 14 years since cessation) and for blond tobacco (between 2 and 8 years and after >20 years of cessation).

No relevant differences in the trend or magnitude of the estimates were found in sensitivity analyses (Supplementary Tables S3 and S5-S7), including further smoothing of the splines fit (Supplementary Fig. S2). In analyses adjusting for smoking intensity, risk estimates decreased in magnitude but showed a similar trend. By tobacco type, this adjustment did not affect either the associations nor the shapes of the relationships despite black tobacco smokers smoked heavier and for a longer time (Supplementary Table S8). Importantly, adjustment for smoking duration led to statistically nonsignificant risk estimates and change in the shape of the dose-response relationships (Supplementary Table S9). Joint effect analyses of smoking intensity and duration showed that long-lasting smoking together with intense

smoking increase pancreatic cancer risk, whereas for less intense smoking the association weakened (Supplementary Table S10).

Discussion

This study confirms that, in comparison to never-smokers, being a current smoker increases the risk of pancreatic cancer by 72%. In terms of AR, this study also endorses that around 16% (95% CI, 9.24-22.47) of all pancreatic cancer diagnoses could be avoided through tobacco preventive measures. A more detailed examination of smoking characteristics showed that the use of nonfiltered cigarettes, deep inhalation into the throat or chest, and exposure to tobacco smoke in the parental household were all associated with increased pancreatic cancer risk. Pancreatic cancer risk in black tobacco smokers was significantly higher compared with never-smokers, with blond tobacco smokers showing a less prominent risk pattern. Analysis of dose-response relationships corroborated that a higher smoking intensity, longer smoking duration, and increased levels of cumulative dose were associated further with an increased pancreatic cancer risk, whereas

Table 4. 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 (95%CI)	Case/Controls	aOR (95% CI)	Case/Controls	aOR (95% CI)	Case/Controls	aOR (95% CI)	Case/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

Note: 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 to 0.91.

Table 5. Nonlinear 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 LR test ^a P value	Fractional polynomials Formula resulting from the fractional polynomials ^b	aOR (95% CI) per 1-unit increase		
			Model 1	Model 2	Model 3
			aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Age at smoking initiation (years)	0.031	$(\frac{\text{smoke}_{\text{first}}+1}{10})^{-2}$	1.11 (1.04–1.20)	1.00 (0.89–1.11)	0.96 (0.87–1.07)
Age last smoked (years)	0.008	$(\frac{\text{smoke}_{\text{last}}+1}{10})^{0.5} + ((\frac{\text{smoke}_{\text{last}}+0.1}{10})^{0.5} \times \log(\frac{\text{smoke}_{\text{last}}+0.1}{10}))$	1.07 (1.04–1.10)	1.05 (1.00–1.11)	0.99 (0.93–1.06)
Smoking duration (years)	0.020	$(\frac{\text{duration}+0.1}{10})^3 + ((\frac{\text{duration}+0.1}{10})^3 \times \log(\frac{\text{duration}+0.1}{10}))$	1.04 (1.02–1.05)	1.03 (1.02–1.05)	N.A.
Smoking intensity (cigarettes per day)	0.001	$(\frac{\text{intensity}+0.2}{10})^{0.5}$	1.29 (1.18–1.45)	N.A.	1.04 (0.88–1.23)
Cumulative dose (pack-years)	0.000	$(\frac{\text{pack-years}+0.1}{10})^{0.5}$	1.24 (1.16–1.35)	N.A.	N.A.
Time since cessation (years) ^c	0.016	$(\frac{\text{cessation}+1}{10})^1 + (\frac{\text{cessation}+1}{10})^3$	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 ^{c,d}	0.073	$(\frac{\text{cessation}+1}{10})^1 + (\frac{\text{cessation}+1}{10})^3$	0.85 (0.74–0.96)	0.85 (0.73–0.96)	0.88 (0.66–1.11)

Note: 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, nonlinear).

Model 3: Model 1 plus additional adjustment for smoking duration (years, continuous, nonlinear).

Abbreviations: NA, not applicable; PC, pancreatic cancer.

^aLR 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%).

^bFractional polynomials adjusted for age (≤ 54 , 55–64, 65–74, ≥ 75 years), gender (male, female), and country (Spain, England, Germany, Ireland, Italy, Sweden).

^cNever-smokers were removed from time since cessation variables.

^dThe 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).

smoking cessation led to a gradual decline in pancreatic cancer risk, all in a nonlinear manner.

Our results are concordant with earlier studies on the same topic. Regarding the magnitude of pancreatic cancer risk associated with current versus never tobacco smoking, a meta-analysis and pooled analyses from the PanC4 and the Pancreatic Cancer Cohort Consortium showed similar estimates (RR = 1.74; 95% CI, 1.61–1.87; OR = 2.20; 95% CI, 1.71–2.83; and OR = 1.77; 95% CI, 1.38–2.26, respectively; refs. 4, 6, 24). Similarly, our study confirmed the trends and timing of tobacco smoking (4, 6), the excess risk conferred by tobacco smoking (4, 25, 26), the nonlinear tobacco–pancreatic cancer associations (5, 7), and risk due to childhood ETS (27). Compared with studies restricting ETS exposure to never-smokers, we also did not observe significant risk estimates (aOR = 1.24; 95% CI, 0.95–1.63; refs. 28, 29), suggesting that smokers, possibly more likely being exposed to childhood ETS, were driving this association in the overall analyses (aOR for current smokers exposed to parental smoking versus never smoking exposure = 2.01; 95% CI, 1.50–2.69). In contrast to the positive association between current cigar/pipe smokers and pancreatic cancer risk reported before (4, 30), we did not observe a significant associations in our study, probably due to low statistical power.

Effect-modification factors

The higher pancreatic cancer risk among smokers with family history of pancreatic cancer was previously described in our study population (14). Although statistical significance was not reached, former smoking diabetes patients tended to have a higher pancreatic cancer risk too. Were this true, lifestyle changes among diabetic

patients including smoking cessation, which in turn may lead to weight gain and insulin resistance (31, 32), might explain this finding. Previous studies suggested differences in smoking effects on pancreatic cancer risk by gender (5, 6), although they failed to demonstrate effect modification by this variable. Similarly, nonsignificant differences by gender were found in our study, which included a large female sample with a relatively high smoking prevalence.

Dose-response relationships

Nonlinear relationships of the association between smoking variables and pancreatic cancer risk were supported by both fractional polynomials and restricted cubic splines approaches. Because fractional polynomials in regression models become imprecise with small sample sizes (22), we based the dose–response curves on results derived from restricted cubic splines, which allow a more flexible modeling (33). Concordant with the observation of nonlinear associations for smoking duration, intensity, and cumulative dose, a plateauing in the dose–response relationship was apparent. This observed pattern was previously reported (5, 7), and could be attributed to the saturation of the detoxification processes of tobacco carcinogens in the body (34), or to a presumably weaker inhalation of tobacco smoke but stronger DNA repair efficiency among heavy smokers (35, 36), among other factors. Nonlinear associations for smoking cessation, with decreased pancreatic cancer risk after 20 years of smoking cessation, were also suggested (5) and confirmed by other studies (7). However, in these earlier studies, consideration was not given to the influence of smoking intensity and duration on these associations. Patterns in pancreatic cancer risk in our study changed after adjusting for smoking duration

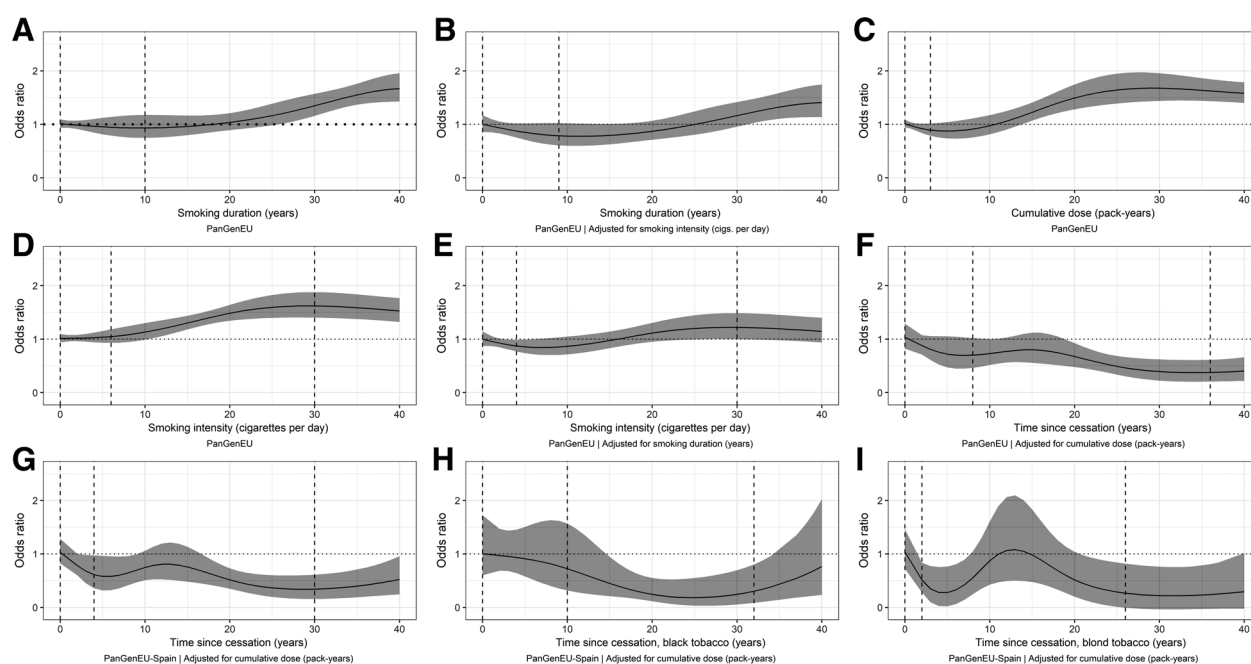


Figure 1.

A–I, Dose–response relationships between several smoking variables and the risk of pancreatic cancer, depicted by restricted cubic splines (RCS) 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). RCS are shown for the unimputed smoking variables, and additional adjustment variables were modeled as fractional polynomials to account for nonlinear effects. The spline curve is shown as a black trend line, and 95% CIs are shadowed in gray. 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). **H,** Time since cessation in years for smokers of only black tobacco (PanGenEU-Spain), adjusted for cumulative dose (pack-years). **I,** Time since cessation in years for smokers of only blond tobacco (PanGenEU-Spain), adjusted for cumulative dose (pack-years).

mainly, whereby the magnitude of the risk estimates was affected (Supplementary Table S9).

Black versus blond tobacco use

Compared with never-smokers, black tobacco smokers showed a significantly higher pancreatic cancer risk, this tobacco type appearing to be more harmful than blond tobacco. This result is consistent with the few studies that examined the association between smoking by tobacco type in bladder (8, 37, 38) and other cancers (10–13). Smoking both black and blond tobacco for a long time (≥ 30 years) tended to be related to higher pancreatic cancer risk, this also being shown in previous studies on tobacco smoking and bladder cancer (8).

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 (39), whereas blond tobacco may mostly consist of late-stage carcinogens (37). It is conceivable that the two tobacco types contribute to pancreas carcinogenesis through different mechanisms: black tobacco may predominantly cause DNA mutations whereas blond tobacco may preferentially act through epigenetic changes, as has been shown for LINE-1 (9). As a consequence, an immediate and significantly higher increase in pancreatic cancer risk could be expected in black tobacco smokers, whereas blond tobacco might need a longer time to trigger pancreatic cancer development. This may also imply that following smoking cessation of blond tobacco pancreatic cancer 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 (40). For black tobacco, instead, the pancreatic cancer risk reduction effects might not take place or might require longer since smoking cessation. Our results support these hypotheses to some extent. Compared with never-smokers, not only did black tobacco smoking have a more detrimental effect on pancreatic cancer 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 in some (37, 38), but not all (8), studies. Among blond tobacco smokers, the trend towards a reduction in pancreatic cancer risk became evident shortly after smoking cessation (Supplementary Table S9). The shape of dose–response curves supported the aforementioned trends, specifically regarding smoking cessation. 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 risk levels more akin to never-smokers likely due to desaturation of detoxification routes of tobacco-carcinogens (5, 41), the second showing risks leveling-off after approximately 20 years of smoking cessation, once alteration of DNA methylation levels of key genes regain the state of normalcy.

Among the limitations of the study, stratifying by tobacco type might have underpowered the analyses to detect any differences. As in any other study, subgroup analyses and multiple statistical tests are prone to chance findings due to increased type I error. Also, we could not consider potential differences in the content of carcinogens because we lacked information on tobacco brands, likely to contain varying amounts of heavy metals (42) and other carcinogens (39). Residual confounding can be therefore expected, also due to lack of, or imprecise, information on other relevant data such as ETS in adulthood. Extensive efforts have been made to adjust for as much confounding as possible, thereby alleviating the bias to the highest extent possible. Moreover, differential misclassification of the exposure due to recall bias of smoking habits among either the cases or controls is possible, or because use of only black or blond tobacco smoking might not have been reliably reported. Therefore, mixed effects due to alternate use of both tobacco types cannot be ruled out. We considered only smokers of black or blond tobacco to keep the effects by tobacco type separate, and considered switching from one type to the other in the group of users of both tobacco types.

Major strengths of the study are the large number of pancreatic cancer cases representing a European-wide pancreatic cancer population and the degree of detail in the information collected about smoking habits. This allowed us to undertake exhaustive and solid analyses considering many aspects of the habit in relation to pancreatic cancer risk. In fact, this is the first study assessing pancreatic cancer risk by black and blond tobacco. Also, as a novelty, the shapes of dose-response relationships have been fully characterized using different modeling strategies to account for nonlinear effects of smoking on pancreatic cancer risk.

In conclusion, findings of this study support and add to the previous evidence that smoking increases pancreatic cancer risk and demonstrates, for the first time, that both blond and black tobacco smoke are key in pancreatic cancer etiology, although probably acting through different genetic mechanisms. Considering these smoking-related pancreatic cancer risk profiles may help to refine the definition of high-risk pancreatic cancer population towards screening interventions implementation. Future studies should confirm our findings on type of tobacco and shed light on the mechanisms underlying their differential association with pancreatic cancer risk.

Disclosure of Potential Conflicts of Interest

M. Hidalgo is a consultant for Agenus, Pharmacy, InxMed, Tolero, and Takeda; reports receiving a commercial research grant from Bioline; and has ownership

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interest (including patents) in Agenus, Pharmacy, and BioOncotech. No potential conflicts of interest were disclosed by the other authors.

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