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Childhood and adulthood passive and active smoking, and the ABO group as risk factors for pancreatic cancer in women

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Abstract

Objectives: Active smoking and the A blood group are associated with pancreatic adenocarcinoma (PC) risk. However, potential interactions between those risk factors and the role of passive smoking have been little investigated. We aimed to explore specific and joint associations of passive and active smoking, and effect modification by the ABO blood group in French women.

Methods: The study included 96,594 women from the E3N prospective cohort, mean age: 49 years (SD 6.7). Information on active and passive smoking was reported at inclusion and throughout follow-up. Cases were classified according to the International Classification of Diseases 10. Associations with passive and active smoking and effect modification by the ABO blood group were investigated with multivariable Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: During a 24-year median follow-up, 346 incident PC cases were identified. Current smoking compared with never and former smoking (HR 1.51 [95% CI 1.08–2.10]), and passive smoking in childhood compared with no childhood exposure (HR 1.47 [95% CI 1.08–2.00]) were associated with increased PC risk, but not passive exposure in adulthood (HR 1.16 [95% CI 0.91–1.47]). Exposure to both passive smoking in childhood and current smoking was associated with a stronger risk (HR 2.80 [95% CI 1.42–5.52]) than exposure to both current smoking and passive smoking only in adulthood (HR 1.68 [95% CI 1.10–2.57]) compared with neither passive nor active smoking. Associations between active smoking and PC risk were strongest in the O or B groups, while associations with passive smoking were strongest in the A or AB blood groups, but the interaction terms were not statistically significant.

Conclusions: Both current smoking and passive smoking in childhood were associated with PC risk, with a maximal risk of current smokers exposed to passive

Anne-Laure Vedie and Nasser Laouali are considered as co-first authors.

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smoking during childhood. Possible interactions between blood groups and active or passive smoking must be investigated in a larger series.

KEYWORDS

blood groups, cohort, epidemiology, pancreas cancer, passive smoking, risk factor, tobacco

INTRODUCTION

Pancreatic adenocarcinoma, with an estimated 466,003 deaths in 2020 worldwide, is the seventh leading cause of cancer-related mortality according to the International Agency for Research on Cancer.¹ In France, the incidence of PC was 14,461 in 2020, and PC accounted for 9060 deaths.¹ Despite a relatively low incidence rate, PC has a high mortality rate due to low 5-year survival rates, below 8%, and up to 80% of patients with already distant metastases at the time of diagnosis.² In France, between 1982 and 2012, age-standardized incidence rates increased from 4.8 to 9.6 per 100,000 in men, and from 2.3 to 6.8 in women.³ Mortality rates reported in 2012 tended to be stable in men but to increase in women.³ Hence, there is a strong interest in identifying modifiable risk factors that may help understand the fundamentals of PC pathophysiology, especially in women, in view of prevention strategies.

Although the underlying causes of PC remain largely unknown, several risk factors including lifestyle behaviors⁴⁻⁷ have been suggested in addition to advanced age. Becker et al.,⁸ estimated 10% of inter-individual variability to be due to genetic factors, leaving a large proportion related to modifiable risk factors. Among them, tobacco use is, to the present knowledge, the most important one. Indeed, a recent review by Subhan et al.⁹ showed that smoking is a strong risk factor for PC, leading to progressive fibrosis of the pancreatic glandular tissue and stroma. However, the potential effect of passive smoking has been little investigated so far, especially regarding passive smoking in childhood. Over the past decades, the ABO blood groups have been the most studied non-modifiable risk factor, with consistent reports of an increased PC risk associated with the A blood group, whereas the O blood group was associated with a lower risk. Results were less consistent regarding the B and AB blood groups¹⁰⁻¹³; those groups have been associated with increased PC risk in Western populations but not in Chinese or Japanese populations.¹³ Few studies have specifically focused on women, and to our knowledge, no study has explored potential interactions between blood groups and smoking in relation to PC risk.

Therefore, based on the detailed information on active and passive smoking in adulthood and passive smoking in childhood in the large *Etude Epidémiologique auprès de femmes de l'Education Nationale* (E3N) cohort study, we investigated associations between active and passive smoking and PC risk, and potential interactions between smoking and the ABO blood groups.

Key Summary

Summarize the established knowledge on this subject

- Active smoking and the A group have been associated with pancreatic adenocarcinoma (PC) risk.
- Limited studies have explored the role of passive smoking, especially in childhood, and the joint effect of passive and active smoking on PC risk.
- No study has explored the potential interactions between smoking and blood group on PC risk.

What are the significant and/or new findings of this study?

- Our findings suggest that women with passive smoking experience, especially in childhood, are at a higher PC risk compared with women who have never experienced passive smoking.
- The PC risk was maximal for current smokers exposed to passive smoking during childhood.
- While we confirmed that the A or AB blood groups are associated with higher PC risk compared to O or B blood groups, associations between active smoking and PC risk were strongest in O or B groups, but associations with passive smoking were strongest in A or AB blood groups.

METHODS

Study population and follow-up

The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) Statement is reported in Supplementary Table S1.

The E3N study is a large ongoing French prospective cohort of women set up in France in 1990. The study was approved by the French National Commission for Data Protection and Privacy (clinicaltrials.gov identifier: NCT03285230). All participants signed informed consent in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (*Commission Nationale Informatique et Libertés*). The detailed protocol has been described elsewhere.¹⁴ Briefly, 98,995 women born between 1925 and 1950 from the French national health insurance plan for teachers and co-workers, the *Mutuelle Générale de l'Education Nationale* (MGEN), were enrolled in the cohort through a self-administered questionnaire; they

were subsequently followed every 2–3 years on health and lifestyle aspects. Furthermore, the health insurance plan provided data on outpatient reimbursements for health expenditures since 1 January 2004 for each cohort member. The average response rate to any follow-up questionnaire was 83%, with a total loss to follow-up since 1990 below 3%.

Eligible participants ($n = 98,995$) were those who completed the inclusion questionnaire sent in 1990. The study aimed to investigate incident first primary pancreatic adenocarcinomas. Indeed, most prospective studies on any cancer type restrict cases to first primary cases since the treatment of a preceding cancer or post-cancer changes in life habits could affect the etiology of a second cancer. We therefore excluded all prevalent cases of PC, women with unknown date of diagnosis ($n = 3$), and those who did not complete any follow-up questionnaire after the baseline questionnaire ($n = 2368$). Including prevalent cases in the analysis would introduce a reverse causality bias and the prospective design of this study required the information on the date of diagnosis. In addition, we excluded women with a pancreatic tumor of uncertain status regarding malignancy or whether primary or secondary ($n = 3$), and women with a non-pancreatic cancer synchronous with the PC or prevalent ($n = 27$). We restricted the study to the first primary pancreatic adenocarcinoma and therefore excluded benign cystic pancreatic lesions such as IPMN, neuroendocrine tumors, and pancreatic metastases of other cancers. The final study population included 96,594 women (Figure 1). Follow-up started in 1990 and ended in 2014 (the latest date of cancer case ascertainment in the E3N cohort).

Incident pancreatic cancer ascertainment

Pancreatic adenocarcinoma cases were identified from information provided in each follow-up questionnaire, which inquired about any cancer occurrence (including the date of diagnosis and site), next-of-kin spontaneous reports, and the national cause-of-death registry. Medical and pathology records were obtained for part of the incident PC cases. PC cases of all grades were considered. For cases identified only from the national cause-of-death registry ($N = 108$), dates of diagnosis were imputed 275 days before death (median survival time observed among deceased PC cases with available date of diagnosis).

Active and passive smoking status

At inclusion and throughout the follow-up period, information on tobacco smoking was reported on all questionnaires, and included the following categories: never smoker, former smoker, and current smoker. Former smokers and never smokers were grouped as non-smokers given their similar risk of PC observed in preliminary analyses (Supplementary Table S2) and in a previous study.¹⁵ For the passive smoking status in childhood, women were asked the following question at inclusion: “When you were a child, did you stay in a smoky room?”. Answer modalities were “never”, “do not remember”,

“rarely”, “occasionally (a few hours a week)”, “a few hours a day”, or “several hours a day”. Women were considered exposed to passive smoking in childhood if the answers were “a few hours a day”, or “several hours a day”. Passive smoking exposure in adulthood was assessed at inclusion by asking the women to sum up their time spent at home or outside the home during the day in a room while someone was smoking. Women were considered exposed if they were exposed for at least 1 hour a day.

Covariates

All variables were obtained at baseline in 1990 and, when possible, updated during follow-up. Self-reported height and weight were used to calculate the Body Mass Index (BMI). In the E3N cohort, self-reported anthropometry was considered reliable from a validation study.¹⁶ In all models, BMI was included as a time-dependent ordinal qualitative variable (5 kg/m² increments). The level of recreational physical activity (Metabolic Equivalent of Task hours per week, METs-h/week) was considered as continuous. We considered three categories for education level (undergraduate or less, graduate - used as the reference - and, postgraduate or more). The ascertainment of type 2 diabetes has been described in detail elsewhere.¹⁷ Briefly, diabetes cases were identified via questionnaires through self-reporting of diabetes, diabetes drugs, and hospitalizations for diabetes, and then through the files of drugs reimbursed by the medical insurance between January 2004 and February 2012. We considered the diabetes status as yes/no used as the reference, the status being updated throughout the follow-up. The A, B, AB, and O blood groups were reported in the second questionnaire (1992). Few cases were blood group AB ($N = 19$). Since in preliminary analyses, the association of blood group AB with PC risk was in the same direction as that of blood group A, the two blood groups were subsequently grouped together. The same applied to blood group B ($N = 21$), which was grouped with blood group O (Supplementary Table S3). Therefore, for all analyses, we considered the O or B blood groups versus the A or AB blood groups.

Statistical analyses

Baseline characteristics of the study population, overall and according to the active smoking status, were reported as mean (SD) for continuous variables and as number (percentage) for categorical variables.

We used Cox proportional hazards models with age as the time scale to estimate hazards ratios (HRs) and 95% confidence intervals (CIs). Participants were followed from age at baseline until age at PC diagnosis, death, the last follow-up, or end of the follow-up period (2014), whichever occurred first. The main exposure variables were active smoking (current vs. never or former, used as the reference), passive smoking in childhood (yes/no – used as the reference), passive smoking in adulthood (yes/no - used as the reference), and the ABO blood groups (A or AB vs. O or B - used as the reference). In

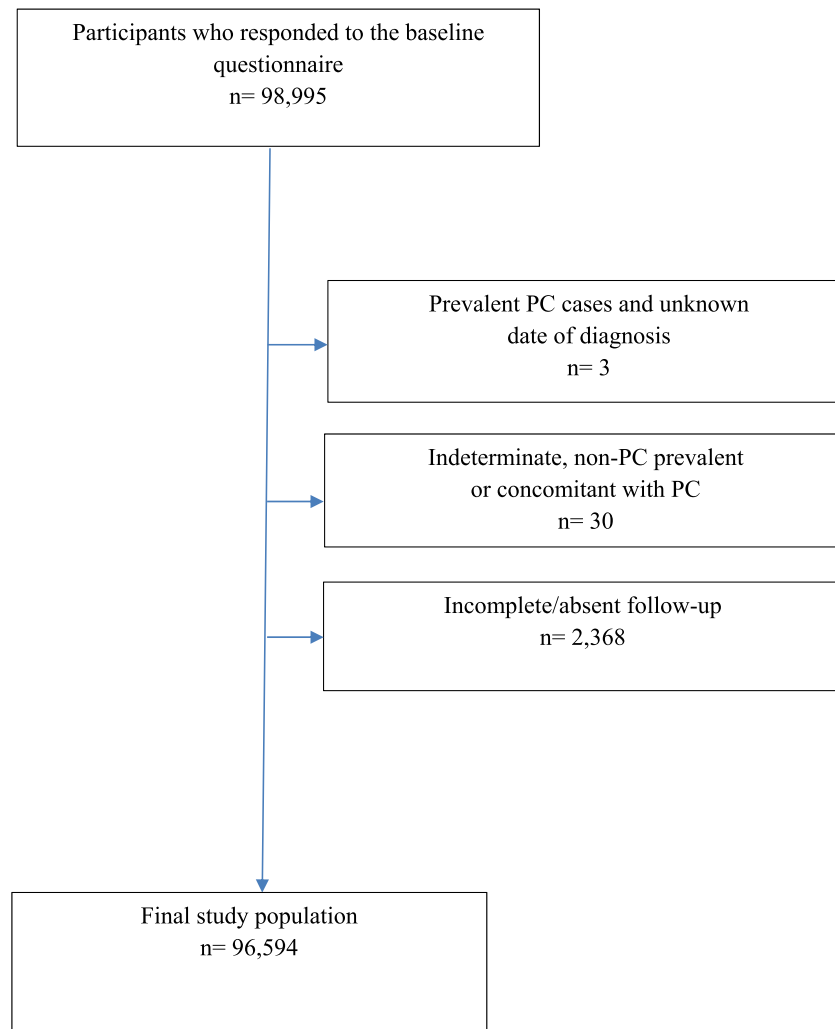


FIGURE 1 Flowchart of the population for analysis.

addition, we further considered the joint association of active and passive smoking (never or former smoker, with no passive smoking in childhood or adulthood used as the reference) with PC risk. Three models were presented for each analysis of smoking status: the first model was adjusted for age (time-scale) and stratified by birth generation by 5-year categories (<1930, [1930–1935], [1935–1940], [1940–1945], and ≥ 1945); the second one was further adjusted for time-dependent type 2 diabetes status and BMI; the third one was further adjusted for physical activity at baseline and level of education. For the ABO blood group analyses, the model included the following variables: age (as the time-scale), stratified by birth generation by 5-year categories, active smoking, passive smoking, body mass index (5 kg/m^2), and history of diabetes. The selection of potential confounders was done a priori, based on the known risk factors of PC and associations with the smoking status.

We additionally investigated the effect modification by blood group type (O-B vs. A-AB) in the sub-sample of participants with blood group data ($N = 88,051$). We performed stratified analyses by blood groups O or B, and A or AB, and tested a potential interaction

by including in the model an interaction term between the smoking status and blood groups.

Missing values were <5% for all adjustment variables, and therefore imputed with the median and mode for quantitative and qualitative variables, respectively, or with the latest information provided in the follow-up questionnaires for the variables considered as time-dependent.

All tests were two-sided, with statistical significance set at $p < 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 presents the baseline characteristics of the study, overall and according to the active smoking status. During 2,110,739 person-years of follow-up (median 24 years), a total of 346 (0.36%) incident PC cases were identified. The population mean (SD) age at baseline was 49.0 (6.7) years. Compared to nonsmokers or former

TABLE 1 Baseline characteristics of participants, overall and according to the active smoking status (N = 96,594).

	Smoking status			Global p-value
	All (N = 96,594)	Never or former smoker (N = 82,153)	Current smoker (N = 14,441)	
Pancreatic cancer				0.0022
No	96,248 (99.6)	81,879 (99.7)	14,369 (99.5)	
Yes	346 (0.4)	274 (0.3)	72 (0.5)	
Age (in years) (N = 96,594)	49.4 (6.7)	49.7 (6.7)	48.0 (6.1)	<0.0001
Birth generation				<0.0001
<1930	7578 (7.9)	6904 (8.4)	674 (4.7)	
(1930; 1935)	12,503 (12.9)	11,169 (13.6)	1334 (9.1)	
(1935; 1940)	18,308 (19.0)	15,946 (19.4)	2362 (16.4)	
(1940; 1945)	23,322 (24.1)	19,599 (23.9)	3723 (25.8)	
≥1945	34,883 (36.1)	28,535 (34.7)	6348 (44.0)	
Blood type				0.4119
O	37,996 (39.3)	32,348 (39.4)	5648 (39.1)	
A	39,273 (40.7)	33,407 (40.7)	5866 (40.6)	
B	7468 (7.7)	6326 (7.6)	1142 (7.9)	
AB	3314 (3.4)	2845 (3.5)	469 (3.3)	
Missing	8543 (8.9)	7227 (8.8)	1316 (9.1)	
Body Mass Index (kg/m ²) (N = 96,594)	22.6 (3.2)	22.7 (3.2)	22.3 (3.2)	<0.0001
Body Mass Index (5 kg/m ²)				<0.0001
<20.0	17,237 (17.9)	14,051 (17.1)	3186 (22.1)	
(20.0; 25.0)	62,008 (64.2)	52,953 (64.5)	9055 (62.7)	
(25.0; 30.0)	14,318 (14.8)	12,524 (15.2)	1794 (12.4)	
≥30.0	3031 (3.1)	2625 (3.2)	406 (2.8)	
Passive smoking in childhood				<0.0001
No	73,279 (75.9)	62,576 (76.2)	10,703 (74.1)	
Yes	12,850 (13.3)	10,821 (13.1)	2029 (14.1)	
Missing	10,465 (10.8)	8756 (10.7)	1709 (11.8)	
Passive smoking in adulthood				<0.0001
No	47,311 (49.0)	43,837 (53.4)	3474 (24.1)	
Yes	49,283 (51.0)	38,316 (46.6)	10,967 (75.9)	
Passive smoking				<0.0001
No passive smoking or, status of passive smoking in childhood unknown and no passive smoking in adulthood	41,805 (43.3)	38,731 (47.1)	3074 (21.2)	
In childhood	12,850 (13.3)	10,821 (13.2)	2029 (14.1)	
In adulthood only or status of passive smoking in childhood unknown but passive smoking in adulthood	41,939 (43.4)	32,601 (39.7)	9338 (64.7)	
History of diabetes				0.2584
No	95,859 (99.2)	81,517 (99.2)	14,342 (99.3)	
Yes	735 (0.8)	636 (0.8)	99 (0.7)	

TABLE 1 (Continued)

	Smoking status			Global <i>p</i> -value
	All (<i>N</i> = 96,594)	Never or former smoker (<i>N</i> = 82,153)	Current smoker (<i>N</i> = 14,441)	
Education level				<0.0001
Undergraduate or less	12,944 (13.4)	11,433 (13.9)	1511 (10.5)	
Graduate	67,167 (69.5)	57,300 (69.8)	9867 (68.3)	
Postgraduate or more	16,483 (17.1)	13,420 (16.3)	3063 (21.2)	
Physical activity (in METs-h/w) (<i>N</i> = 96,594)	41.0 (26.9)	41.1 (26.9)	40.4 (26.6)	0.0024
Physical activity (in METs-h/w)				0.0011
<25.06	23,736 (24.6)	20,003 (24.4)	3733 (25.9)	
(25.06; 35.06)	23,190 (24.0)	19,782 (24.1)	3408 (23.5)	
(35.06; 51.56)	25,416 (26.3)	21,639 (26.3)	3777 (26.2)	
≥51.56	24,252 (25.1)	20,729 (25.2)	3523 (24.4)	

Note: *N* (%) and *p*-value of Khi-2 test for categorical variables. Mean (STD) and logistic regression test for continuous variables.

Abbreviations: kg/m², kilograms by the square meter; METs-h/w, Metabolic Equivalent of Task hours per week.

smokers, current smokers were more likely to be passive smokers in childhood and adulthood, and to have higher educational levels. They were younger and less likely to be overweight or obese (Table 1).

Active and passive smoking status, ABO blood group, and pancreatic cancer risk

The associations between active and passive smoking, the ABO blood groups, and PC risk are presented in Table 2. In the fully adjusted model, compared with nonsmokers, current smokers were at an increased risk of PC (HR 1.51 [95% CI 1.08, 2.10]). When considering passive smoking in childhood and adulthood, we observed an increased risk of women exposed in childhood (HR 1.47 [95% CI 1.08, 2.00]) and a slightly higher risk, although non-statistically significant, for passive exposure in adulthood (HR 1.16 [95% CI 0.91, 1.47]) compared to women who did not experience passive smoking in childhood or adulthood.

The joint associations of active and passive smoking with PC risk are presented in Table 3. In the fully adjusted model, compared with nonsmokers with no passive smoking in childhood or adulthood, the risk was maximal for current smokers exposed to passive smoking during childhood (HR 2.80 [95% CI 1.42, 5.52]). In contrast, the risk was more limited and not statistically significant in current smokers never exposed to passive smoking (HR 1.30 [95% CI 0.57, 2.95]), but the population was small. The risk was intermediate for current smokers with adulthood exposure to passive smoking (HR 1.68 [95% CI 1.10, 2.57]). Never or past smokers with childhood exposure to passive smoking were also at an intermediate increased risk (HR 1.41 [95% CI 1.01, 1.96]).

Compared with the O or B group, women in the A or AB group were at an increased risk of PC (HR 1.31 [95% CI 1.03, 1.68]).

Active and passive smoking status, and pancreatic cancer risk stratified by blood group type

Table 4 shows the association between smoking status and PC risk stratified by blood group. In the fully adjusted model, the risk of PC associated with current smoking was observed only in women with the O or B blood group (HR 2.39 [95% CI 1.50, 3.81]) but not in women with the A or AB blood group (HR 1.19 [95% CI 0.71, 1.98]). However, the test for interaction between smoking status and blood group on the risk of PC was borderline significant (*p* = 0.0533). In the opposite, the risk associated with passive smoking during childhood was slightly stronger and statistically significant in women with the A or AB blood group (HR 1.72 [95% CI 1.12, 2.65]) compared to those in the O or B blood group (HR 1.39 [95% CI 0.84, 2.28]). However, the interaction term was not statistically significant (*p* = 0.7524).

DISCUSSION

Using a large sample of French adult women, we confirmed that current smokers were at a higher risk of PC compared with nonsmokers and former smokers. We also observed that women with passive smoking experience in childhood and adulthood were at higher risk of PC compared with women who had never experienced passive smoking. Most importantly, we found that the risk was maximal (2.8 times higher than for unexposed women) for current smokers who had also been exposed to passive smoking during childhood. In addition, we found that the A or AB blood groups were associated with a higher PC risk than the O or B blood groups. Although the interaction terms were not statistically significant, the risk associated with current smoking was observed only in women of the O or B groups, while passive smoking exposures were associated

TABLE 2 Associations between active and passive smoking status, ABO blood groups, and pancreatic cancer risk (N = 96,594 for smoking and 83,840 for blood groups).

	Number (%) non-cases N = 96,248	Number (%) cases N = 346	M1		M2	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Smoking status				0.0157		0.0163
Never or past smoker	87,554 (90.97)	305 (88.15)	Reference		Reference	
Current smoker	8694 (9.03)	41 (11.85)	1.51 (1.08; 2.11)		1.51 (1.08; 2.10)	
Passive smoking				0.0481		0.0506
No passive smoking, or status of passive smoking in childhood unknown, and no passive smoking in adulthood	38,774 (40.29)	131 (37.86)	Reference		Reference	
In childhood	12,791 (13.29)	59 (17.05)	1.47 (1.08; 2.01)		1.47 (1.08; 2.00)	
In adulthood only or status of passive smoking in childhood unknown but passive smoking in adulthood	44,683 (46.42)	156 (45.09)	1.16 (0.92; 1.48)		1.16 (0.91; 1.47)	
Blood group ^a				0.0283		
O or B	43,215 (51.71)	117 (44.83)	Reference			
A or AB	40,364 (48.29)	144 (55.17)	1.31 (1.03; 1.68)			

Note: M1: Adjusted for age (as the time-scale), Body Mass Index (5 kg/m²), history of diabetes (no, yes), stratified by birth generation (<1930, [1930; 1935], [1935; 1940], [1940; 1945], ≥1945). M2: M1 + education levels (undergraduate or less, graduate, postgraduate or more), physical activity (in METs-h/w). The numbers specified in "Number of non-cases" and "Number of cases" are given at the end of the follow-up.

^aM1 was adjusted for age (as the time-scale), stratified by birth generation (<1930, [1930; 1935], [1935; 1940], [1940; 1945], ≥1945), active smoking status, passive smoking status, Body Mass Index (5 kg/m²), and history of diabetes (no, yes).

TABLE 3 Joint associations of active and passive smoking status with pancreatic cancer (N = 96,594).

	Number (%) non-cases N = 96,248	Number (%) cases N = 346	M1		M2	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Passive smoking				0.0119		0.0122
Never or past smoker and no passive smoking	37,232 (38.68)	125 (36.13)	Reference		Reference	
Never or past smoker, and passive smoking in childhood	11,524 (11.97)	50 (14.45)	1.44 (1.04; 2.00)		1.41 (1.01; 1.96)	
Never or past smoker, and passive smoking in adulthood	38,798 (40.31)	130 (37.57)	1.19 (0.93; 1.53)		1.16 (0.91; 1.49)	
Current smoker and no passive smoking	1542 (1.60)	6 (1.73)	1.29 (0.57; 2.92)		1.30 (0.57; 2.95)	
Current smoker and passive smoking in childhood	1267 (1.32)	9 (2.60)	2.77 (1.40; 5.46)		2.80 (1.42; 5.52)	
Current smoker and passive smoking in adulthood	5885 (6.11)	26 (7.51)	1.68 (1.09; 2.57)		1.68 (1.10; 2.57)	

Note: M1: Adjusted for age (as the time-scale), Body Mass Index (5 kg/m²), history of diabetes (no, yes), stratified by birth generation (<1930, [1930; 1935], [1935; 1940], [1940; 1945], ≥1945). M2: M1 + education levels (undergraduate or less, graduate, postgraduate or more), physical activity (in METs-h/w). The numbers specified in "Number of non-cases" and "Number of cases" are given at the end of the follow-up.

with increased risks only in the A or AB groups. Given the present concern about the rise in the incidence of PC in most developed countries, and the extremely low survival rate for this cancer type, the risks observed in this study may translate into a significant burden for society in terms of the number of early deaths and of financial costs of treatments.

Our findings on smoking and PC risk are consistent with previous population-based studies showing that current and passive smoking were associated with an increased risk of PC.^{9,18-22} A recent meta-analysis on the association between smoking and PC risk found a higher risk for current smokers than non-smokers.²³ Similarly, large-scale studies from Europe²⁴ and Asia²⁵ showed that smoking is

TABLE 4 Associations between smoking status and pancreatic cancer risk stratified by blood group type (N = 88,051).

	O or B				A or AB				p-homogeneity (p-interaction)
	Number (%) non-cases	Number (%) cases	HR (95% CI)	p-value	Number (%) non-cases	Number (%) cases	HR (95% CI)	p-value	
	N = 45,333	N = 131			N = 42,412	N = 175			
Smoking status				0.0002				0.5102	
Never or past smoker	41,258 (91.01)	108 (82.44)	Reference		38,602 (91.02)	158 (90.29)	Reference		
Current smoker	4075 (8.99)	23 (17.56)	2.39 (1.50; 3.81)		3810 (8.98)	17 (9.71)	1.19 (0.71; 1.98)		0.0465
p-interaction (blood type * smoking status)									(0.0533)
Passive smoking				0.3662				0.0369	
No passive smoking, or status of passive smoking in childhood unknown, and no passive smoking in adulthood	18,137 (40.01)	51 (38.93)	Reference		16,816 (39.65)	60 (34.29)	Reference		
In childhood	6017 (13.27)	23 (17.56)	1.39 (0.84; 2.28)		5714 (13.47)	32 (18.29)	1.72 (1.12; 2.65)		0.5227
In adulthood only, or status of passive smoking in childhood unknown but passive smoking in adulthood	21,179 (46.72)	57 (43.51)	1.00 (0.68; 1.48)		19,882 (46.88)	83 (47.43)	1.37 (0.97; 1.92)		0.2398
p-interaction (blood type * passive smoking)									(0.7524)

Note: Adjusted for age (as the time-scale), stratified by birth generation (<1930, [1930; 1935], [1935; 1940], [1940; 1945], ≥1945) + Body Mass Index (5 kg/m²), history of diabetes (no, yes), education levels (undergraduate or less, graduate, postgraduate or more), physical activity (in METs-h/w). The numbers specified in "Number of non-cases" and "Number of cases" are given at the end of the follow-up.

associated with a 2-fold increased risk of PC. Our findings of a 1.5-fold increased PC risk in women is consistent with the fact that in our population of women born 1925–1950 and with a higher education level than in the overall population, the smoking intensity was moderate; thus, risks associated with smoking could become higher in younger generations. Concerning passive smoking, few epidemiological studies have assessed the association of childhood and adulthood exposures with the risk of PC.^{24,26} The findings were summarized in a meta-analysis by Zhou et al.²⁷; Overall, exposure to environmental tobacco smoking during childhood was not associated with the risk of PC (three prospective and two retrospective studies; summary relative risk 1.12). In addition, no association was found with exposure to environmental tobacco smoking during adulthood at home (five prospective and three retrospective studies; summary relative risk 1.23)

or at work (one prospective and two retrospective studies; summary relative risk 0.94). In contrast, we found that women with passive smoking experience in childhood and adulthood were at a higher risk of PC. In the opposite to active smoking, that generation could have been more strongly exposed to passive smoking, especially during childhood, since there was little knowledge at that time of the potential dangers of passive exposure to smoking, and male smoking was more common nowadays. Our results are in line with two previous studies that reported an increased risk of PC in case of exposure in childhood²⁸ and adulthood. Also, a large study in a European population showed that early childhood exposure and passive smoking in the workplace increased the risk of PC.²⁹ As discussed by Zhou et al.,²⁷ there are very few prospective studies exploring the potential role of passive smoking on PC. PC is a non-frequent disease, and

retrospective case-control studies were commonly used to investigate risk factors, the approach being substantially more cost- and time-effective compared to prospective studies. However, retrospective studies have numerous limitations, including the use of proxy data for exposure ascertainment, and the potential for recall and selection biases. Differences in the findings between studies could be explained by heterogeneity in exposure assessment as well as the number of covariates considered in model adjustment that were widely different from one study to another. For example, some studies only adjusted for age,³⁰ while others adjusted for a large number of potential confounders.²⁸

Some previous studies have investigated the association of the ABO blood groups with PC risk.^{13,16,31} They consistently showed associations between A or non-O groups and PC risk, in agreement with our findings. A population study conducted in Spain showed a higher risk of PC among individuals with blood group A.³² Additionally, a combined, prospective cohort study of over 107,000 US health professionals observed that blood groups A, B, and AB were associated with an overall increased risk of PC.³¹ We are not aware of any previous study that investigated potential interactions between blood groups and smoking with regard to PC risk. Although not statistically significant, potentially because of limited power due to small numbers of cases in some exposure categories, our data suggest that current smoking could be mostly deleterious in the O or B groups, while the opposite could be observed regarding passive smoking. Although those results should be interpreted with caution, they suggest different mechanisms regarding the relationship between active and passive smoking, and PC risk.

The ABO blood groups are genetically determined, and therefore not a modifiable risk factor as are smoking or other lifestyle-related factors. The risk of PC for individuals with blood group A has been replicated in several studies. As a possible mechanism, genome-wide association studies have identified an association between single-nucleotide polymorphisms (rs505922) in the ABO gene and PC risk³³ as well as plasma markers of inflammation^{34,35} suggesting a link between chronic inflammatory states and PC, and raising the possibility that blood group antigens may alter the systemic inflammatory response. Alternatively, the association might involve ABO glycosyltransferase enzymes, which participate in malignant cell immunosurveillance as well as cellular membrane signaling modifications and intercellular adhesion during tumorigenesis.³⁶ The mechanisms involved in the association between smoking and PC risk have been extensively described and summarized in a review by Pandol et al.³⁷; Different from the ABO groups, smoking does not cause genetic alterations of the genes known to be mutated in PC, suggesting that smoking enhances the risk of PC through mechanisms other than genetic mutations.^{38,39} A role of cadmium, a heavy metal mostly provided by smoking in the absence of professional hazards, has been suggested since it tends to accumulate in the pancreas and has been associated with several cancer sites including PC (<https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100C-8.pdf>). A study has reported a significant increase in the infiltration of macrophages into neoplastic lesions in mice treated with chemical compounds of

tobacco.⁴⁰ Chronic inflammation has also been suggested as the underlying mechanism. Since passive exposure in childhood occurs early in life, an initiation effect can be suggested, while active smoking in adulthood would rather be related to carcinogenesis promotion or progression, the more so that ex-smokers do not seem to be at a specific risk. To our knowledge, no study has evaluated the interaction between blood groups and smoking status on the risk of developing PC. The reason why chronic inflammation should mostly occur in O or B groups in case of active smoking or in A and AB groups in case of passive exposure needs further investigation, if such associations are confirmed in larger studies.

The strengths of our study include the prospective nature with long follow-up, a large sample size of PC-free participants at baseline, and minimal loss to follow-up. The availability of comprehensive data at baseline and updated along follow-up permitted adjustment for the main potential confounders. However, some limitations should be considered. First, like with all observational studies, we cannot infer causality. Second, there is the possibility that unmeasured confounders, such as specific environmental factors, may have influenced our findings. Third, the date of diagnosis of some cases ($N = 108$) identified from the French causes of death database was not known and was imputed. We considered the 275th day before death as the date of diagnosis, which represents the median survival time observed among deceased PC cases with available date of diagnosis. Fourth, our study population was exclusively composed of women. This could limit the external validity of our findings toward men if sex-specific biological factors influence PC risk. Fifth, the use of self-reported questionnaires to assess the smoking status could lead to misclassification of exposure. However, because of the prospective design, the potential bias would be nondifferential, thus only potentially reducing the strength of the association. Moreover, in our study, information on tobacco smoking was collected at inclusion and updated throughout the follow-up period, at each follow-up questionnaire, which increases the reliability of the reported smoking status. Finally, our findings in a cohort of rather well-educated women from the French education system may not be generalized to the overall French population.

In conclusion, our study showed that women with both passive smoking in childhood, and current active smoking were at a very high risk of PC compared to women that were never or past smokers with no passive exposure in childhood or adulthood. We confirmed that women of the A or AB blood groups were at a higher risk than those with non-A blood group alleles, and we suggest that they could be at the highest risk when exposed to passive smoking. In the opposite, active smoking could be mostly deleterious in those with no A allele, that is, of O or B blood groups. Those results should prompt similar investigations in other populations and, if confirmed, should encourage animal and cell studies to understand the underlying mechanisms.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the study findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

INFORMED CONSENT

The study was approved by the French National Commission for Data Protection and Privacy (clinicaltrials.gov identifier: NCT03285230). All participants signed informed consent in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (*Commission Nationale Informatique et Libertés*). The study was conducted following the Helsinki Declaration.

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