

Circulating plasma phospholipid fatty acids and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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Abstract

Background. Epidemiological data support a role for fatty acids (FAs) in pancreatic cancer (PC) development, but their effects may differ depending on specific FA class. To date, no study has explored the association between biomarkers of FAs and PC risk within a prospective cohort setting.

Methods. A case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study was conducted to assess the association between plasma phospholipid FAs and the risk of PC, as well as their interaction with stearoyl-CoA desaturase-1 (*SCD-1*) polymorphisms. The FA composition was measured by gas chromatography in plasma samples collected at recruitment from 375 PC cases and their matched controls. Multivariable conditional logistic regression models were used to estimate relative risk of PC across tertiles of FAs. Models were adjusted for BMI, total energy intake, height, alcohol intake, history of diabetes mellitus, tobacco smoking status, years of education, and physical activity.

Results. Statistically significant inverse associations were found between PC incidence and levels of saturated heptadecanoic acid (OR_{T3-T1} [odds ratio for highest versus lowest tertile]=0.63; 95%CI[confidence interval]=0.41–0.98; $P_{trend}=0.036$), n-3 polyunsaturated α -linolenic acid ($OR_{T3-T1}=0.60$; 95%CI=0.39–0.92; $P_{trend}=0.02$) and docosapentaenoic acid ($OR_{T3-T1}=0.52$; 95%CI=0.32–0.85; $P_{trend}=0.008$). Among current smokers, the long-chain n-6/n-3 polyunsaturated fatty acid (PUFA) ratio was positively associated with PC risk ($OR_{T3-T1}=3.40$; 95% CI 1.39–8.34; $P_{trend}=0.007$), while inverse associations emerged for docosahexaenoic acid ($OR_{T3-T1}=0.31$; 95%CI=0.13–0.76; $P_{trend}=0.009$) and total n-3 PUFAs ($OR_{T3-T1}=0.26$; 95%CI=0.11–0.62; $P_{trend}=0.002$). None of these associations were significant among non-smokers ($P_{interaction}\leq 0.01$). Results were robust to a range of sensitivity analyses.

Conclusions. Higher circulating levels of saturated fatty acids (SFAs) with an odd number of carbon atoms and n-3 PUFAs may reduce the risk of PC. The influence of some FAs on the development of PC may depend on gender or smoking status.

Keywords: biomarkers; plasma phospholipids; fatty acids; tobacco smoking; *SCD-1* polymorphism; pancreatic cancer.

Abbreviations: *SCD-1* (stearoyl-CoA desaturase-1); FA (fatty acid); SFA (saturated fatty acid); MUFA (monounsaturated fatty acid); PUFA (polyunsaturated fatty acid); TFA (*trans* fatty acid); PC (pancreatic cancer); SNP (single nucleotide polymorphism); EPIC (European Prospective Investigation into Cancer and Nutrition); OR (odds ratio); CI (confidence intervals).

Introduction

Pancreatic cancer (PC) occurs prevalently in developed regions and approximately 104,000 new cases were diagnosed in Europe in 2012 ¹. The late and unspecific symptoms of the disease and the lack of effective screening tests result in extremely poor prognosis ². In addition, PC is the only major neoplasm showing an unfavorable mortality trend in both sexes over the last few decades in Europe ³.

Several factors have been linked with the risk of PC, including tobacco smoking, alcohol, chronic pancreatitis, history of diabetes, obesity, family history of PC, and some common genetic variants ⁴⁻⁶. A role for dietary fat and FAs in PC has also been suggested by experimental evidence ⁷⁻¹¹, but previous epidemiological studies of dietary FA intake have produced inconclusive results ¹²⁻¹⁵.

The inconsistency between epidemiological findings may be due to methodological limitations of dietary questionnaires ^{16,17}, while no study to date has explored the relationship between circulating concentrations of FAs and PC risk. The use of biomarkers may offer a more valid estimation on the contribution of FAs to the etiology of PC ¹⁸. The FA composition of plasma phospholipids reflects medium-term intake of some FAs ^{19,20}, particularly of those not endogenously synthesized ^{21,22}. Furthermore, the ratio of MUFAs to SFAs (also known as desaturation index) measured in blood phospholipids is used as surrogate marker of the activity of hepatic stearoyl-CoA desaturase-1 (*SCD-1*), a key enzyme in the synthesis of MUFAs from SFAs ^{23,24} and previously associated with cancer mortality ²⁵.

We conducted a case-control study nested within the longitudinal European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to estimate the association of specific plasma phospholipid levels of relevant FAs and PC risk. In addition, we used the desaturation index and *SCD-1* gene polymorphisms (rs3071 and rs3793767) as indices of endogenous MUFA synthesis ^{23,26} to investigate the association between fat metabolism and pancreatic carcinogenesis.

Methods

Study design

The EPIC cohort includes 521,330 participants recruited between 1992 and 2000 from 23 centers in 10 European countries to investigate the relationship between diet, lifestyle and genetic factors and the incidence of cancer and other chronic diseases ²⁷. The study design, recruitment procedures and data collection have been described previously ²⁸. Briefly, socio-demographic, lifestyle and dietary data were collected at enrolment from all study participants by administration of country-specific questionnaires. Baseline anthropometric measurements and peripheral blood samples were also collected. Procedures for sample collection, processing and storage are described in detail elsewhere ²⁹. All participants signed an informed consent for the use of their blood samples and data. The EPIC study was approved by the Ethical Review Board of the IARC and those of all national recruiting centres.

Outcome assessment

Participants were followed from the date of enrolment until first cancer diagnosis, death, emigration or end of the follow-up period, whichever occurred first (last updated: 2015). Incident PC cases were identified through population cancer registries (Italy except Naples, the Netherlands, Norway, Spain, Sweden and the United Kingdom) or a combination of methods including health insurance records, cancer and pathology registries, and active follow-up in three countries (France, Germany, Greece and Naples). Mortality data were collected from cancer and mortality registries at the regional or national level.

In the present study, 61.2% of PC cases were confirmed by histological or cytological examination, whereas the remaining 38.8% were diagnosed through clinical observation, imaging results, autopsy, or death certificate. Clinical and tumour characteristics were defined according to the codes of the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Diagnosis of cancer cases in EPIC was based on the 3rd revision of the International

Classification of Diseases for Oncology (ICD-O-3). Mortality data were coded according to the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10). The most common histological subtype of PC was adenocarcinoma (77.6%), while the less common endocrine form accounted for less than 1%. The remaining PC cases were of unknown (21.3%) or mixed (0.8%) origin.

Lifestyle data collection

Participants completed a baseline lifestyle questionnaire providing information on reproductive history, use of oral contraceptives and hormonal replacement therapy, education, socio-economic status, occupation, family history of cancer, history of previous illness (i.e., diabetes), physical activity, dietary intake, alcohol consumption and smoking status in the year prior to enrolment date ²⁹.

Selection of study subjects

Of 521,330 subjects (aged 35-70 y) recruited in the EPIC study, the current analysis excluded subjects with prevalent cancer at any anatomic site (n=23,785) or those lost to follow-up (n=4365). A total of 1013 incident PC cases were identified after a median follow-up of 14.9 years.

A nested case-control study was initially designed with 417 eligible cases who provided a blood sample and completed the lifestyle and dietary questionnaires at recruitment. Each case was individually matched to one control subject (ratio 1:1) using an incidence density sampling approach while fulfilling the following matching criteria: study center, sex, age at blood collection (\pm 3 months), date and time at blood collection, length of follow-up, fasting status and, for women, use of pill/hormonal replacement treatment. After exclusion of subjects with inadequate FA measurements and incomplete pairs, 375 cases with PC (153 men and 222 women) and 375 controls were available for analysis.

Fatty acid quantification

Gas chromatography was used to determine plasma phospholipid concentrations of sixty FAs from short-chain SFAs to long-chain PUFAs, including fifteen *trans* fatty acids (TFAs) from industrial processes and natural animal sources^{30,31}. Briefly, total lipids were extracted from plasma samples (200 µl) with chloroform-methanol 2:1 (vol/vol) containing antioxidant butylated hydroxytoluene and L-A-phosphatidylcholine-dimyristoyl-d54 as an internal standard. Phospholipids were purified by adsorption chromatography on SPE columns, and then converted to their methyl esters (FAMES) at room temperature using Meth-Prep II reagent. FAMES were extracted in hexane and transferred to small vials until being injected into the gas chromatograph (Agilent 7890A GC). The Select for FAME Capillary GC Columns (Agilent) were used for separation of FAMES. Samples from cases and control subjects were processed in the same batch, and laboratory staff was blinded to any participant characteristics. Identification of individual FAMES was obtained by comparison with the relative retention time of commercially available pure standard mixtures (Sigma, St. Louis, MO). The relative amount of each FA was expressed as percentage of total FAs and as absolute plasma concentration (µmol/l) based on the amount of the internal standard.

The within-day coefficients of variation (CVs), which were calculated using standard quality control samples as previously described³⁰, ranged from 0.29% to 9.34%. All laboratory analyses were performed at the International Agency for Research on Cancer (Lyon, France).

Using concentrations of individual FAs, we calculated the plasma phospholipid percentage of the following groups: SFAs (10:0, 12:0, 14:0, 15:0, 16:0, 17:0, 18:0, 20:0, 22:0, 24:0), *cis* MUFAs (15:1, 17:1, 18:1n-5/7/9, 16:1n-7/9, 14:1n-5, 20:1n-9, 22:1n-9, 24:1n-9), *cis* n-6 PUFAs (18:2n-6, 18:3n-6, 20:2n-6, 20:3n-6, 20:4n-6, 22:4n-6, 22:5n-6), *cis* n-3 PUFAs (18:3n-3, 18:4n-3, 20:3n-3, 20:4n-3, 20:5n-3, 22:5n-3, 22:6n-3, 24:5n-3, 24:6n-3), long-chain n-6/n-3 PUFA ratio, ruminant TFAs (16:1n-7t/9t, 18:1n-7t, 9c11t, 10t12c) and industrial TFAs (18:1n-8t/9t/12t, 18:2n-6t, 18:3n-3t). The desaturation indexes as the ratio of oleic acid (18:1n-9) to stearic acid (18:0) (DI₁₈) and the ratio of palmitoleic acid (16:1n-7) to palmitic acid (16:0) (DI₁₆) were also computed²³.

SNP selection and genotyping

Determination of the genotype status was performed for two candidate single nucleotide polymorphisms (SNPs) in the *SCD1* locus (rs3071 and rs379367) previously associated with changes in desaturation index and cancer death^{25,26}.

Genomic DNA from study participants was extracted from a 0.5 ml aliquot of buffy coat, which had been kept frozen since blood collection and processing³². All DNA samples were extracted at IARC by use of the Gentra Autopure LS DNA preparation platform (Gentra Systems, Minneapolis, USA).

Genetic analyses were performed at Institut Curie (Genetic Epidemiology of Cancers team, U900) using TaqMan pre-designed SNP genotyping assays (Applied Biosystems, Foster City, CA, USA). The fluorescence reading and allelic discrimination analyses were performed with the Applied Biosystems ABI PRISM 7900HT Sequence detection system. DNA from study participants was randomized on plates, and all samples were analysed simultaneously.

For quality control purposes, duplicates of 10% of the samples were interspersed throughout the plates and >99% consistency was achieved. The call rate was 98.5% for rs3071 and 97.0% for rs379367. The quality of the genotype data was assessed by testing for Hardy-Weinberg equilibrium (HWE) using the chi-squared distribution among controls. No deviation from HWE was observed (P=0.87 for rs3071 and P=0.10 for rs379367 in controls).

Statistical methods

Baseline lifestyle and dietary characteristics of cases and control individuals were compared using paired t-test for continuous variables, and the Chi-squared test from unadjusted conditional logistic regression for categorical variables. All missing values were excluded from these calculations. Distributions of plasma phospholipid FAs were log natural transformed. Geometric means (\pm SD) of plasma phospholipid FAs expressed as percentage and absolute concentration (μ mol/l) were presented for descriptive purposes.

Multivariable conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) according to percentage of FAs assessed continuously (log transformed) and as tertiles based on the distribution in controls (the lowest tertile was used as the

reference category). Tests for linear trend were performed by entering the median value of each tertile as continuous term in the multivariable models. Analyses were also stratified by gender because of experimental evidence of the effect of sex hormones on plasma phospholipid FA composition ³³. We used a chi-squared statistic to test for heterogeneity between genders comparing the deviations of logistic beta-coefficients observed in each subgroup relative to the overall beta-coefficient.

All multivariable models were adjusted for an *a priori* set of confounding factors that included BMI, total energy intake, height, alcohol intake (as continuous variables), history of diabetes mellitus (yes; no; 14.7% unknown), smoking status (never smokers; former smokers; current smokers; 1.5% unknown), socioeconomic status (none or primary school; secondary school; higher education; 3.7% unknown), and physical activity (inactive; moderately inactive; moderately active; active; 2.4% unknown, according to the Cambridge Physical Activity Index). Unknown categories of the above-mentioned variables were included in the models using indicator variables. There were only modest differences in results between models with and without adjustment for potential confounders, and only adjusted models are presented. Simultaneous adjustment for FAs that share common food sources was also performed to assess their independent effects.

Additive and dominant models were used for modeling the association between the *SCD-1* SNPs and PC risk. Each SNP was coded as 0, 1 and 2 according to the number of minor alleles carried. Homozygosity for the common allele was used as the reference category. Test for trend was conducted by modelling the genotypes as equally spaced integer weights and entering the variable as continuous term in the model. Linkage disequilibrium between the two SNPs was assessed with the r^2 measure using Haploview 4.2 ³⁴.

Subgroup analyses were conducted by median level of BMI or alcohol intake and by smoking status (never; ever). Multivariable unconditional logistic regression models were used to prevent loss of study subjects as individuals were not matched for the above-mentioned risk factors. Tests for interaction between plasma phospholipid FAs as continuous variables and potential risk factors as dichotomous variables were computed by including a cross-product term in the multivariable model and evaluating the influence of this term by a likelihood ratio test.

Sensitivity analyses excluding cases with blood samples drawn less than two years before diagnosis, subjects with the non-adenocarcinoma subtype, or subjects with a history of diabetes mellitus were performed. Models were further adjusted for biomarkers of hyperinsulinemia (C-peptide; a biomarker of endogenous insulin secretion ³⁵) and glycosylated hemoglobin (HbA1c; a stable and long-term marker for glucose, independent of fasting status ³⁶) measured at recruitment in 320 and 344 study subjects, respectively.

Statistical tests were two-sided, and P values below 0.05 were considered statistically significant. All analyses were performed using STATA 12.1 (StataCorp. 2011, Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

Baseline characteristics of study participants by case-control status are summarized in Table 1. The mean lag time between blood collection and PC diagnosis was 7.1 (± 3.6) years. Cases were significantly more likely to be smokers at recruitment compared to controls ($P=0.001$). Among women, significantly higher weight ($P=0.003$), BMI ($P=0.02$), waist to hip ratio ($P=0.017$) and tobacco use ($P=0.008$) were observed in cases than controls (Supplementary Table 1). The two investigated *SCD-1* SNPs were in high linkage disequilibrium among controls ($r^2=0.83$), and the minor allele frequency was 28.4% for rs3071 and 31.3% for rs3793767 (data not shown).

The baseline distribution of plasma phospholipid FAs in cases and controls is presented in Table 2. Palmitic acid (16:0) and linoleic acid (18:2n-6) represented almost half of the total measured FAs, and the addition of stearic acid (18:0), oleic acid (18:1n-9) and arachidonic acid (20:4n-6) accounted for more than 80% of the total FA fraction. Each of the remaining FAs were found at proportions below 5%.

Table 3 presents overall and gender-stratified risk estimates by tertiles of plasma phospholipid FAs expressed as percentage of total FAs. In overall analysis, we found a significant inverse association between heptadecanoic acid (17:0) and PC risk ($OR_{T3-T1}=0.63$; 95% CI=0.41–0.98; $P_{trend}=0.036$). This association was also when heptadecanoic acid levels were expressed as a continuous variable (OR per 1% increase=0.32; 95% CI=0.13–0.82; data not shown). Concentrations of pentadecanoic acid (15:0) were also inversely associated with the risk of PC, albeit the risk estimate did not quite attain statistical significance ($OR_{T3-T1}=0.63$; 95% CI=0.38–1.04; $P_{trend}=0.058$). In gender-stratified analysis, evidence of association was found between conjugated linoleic acid (9c11t+10t12c) and reduced PC risk among women ($OR_{T3-T1}=0.37$; 95% CI=0.17–0.81; $P_{trend}=0.008$), and between total industrial TFAs and higher risk among men ($OR_{T3-T1}=3.00$; 95% CI=1.13–7.99; $P_{trend}=0.029$). Heterogeneity by sex was borderline significant for both conjugated linoleic acid ($P_{heterogeneity}=0.056$) and significant for industrial TFAs ($P_{heterogeneity}=0.030$).

Among individual *cis* n-3 PUFAs, α -linolenic acid (18:3n-3; $OR_{T3-T1}=0.60$; 95% CI=0.39–0.92; $P_{trend}=0.02$) and docosapentaenoic acid (22:5n-3; $OR_{T3-T1}=0.52$; 95% CI=0.32–0.85; $P_{trend}=0.008$) were

significantly inversely associated with PC risk, while there was no evidence of association for total *cis* n-3 PUFAs (Table 3). The inverse relationship between α -linolenic acid and PC risk was also significant in the continuous model (OR per 1% increase=0.59; 95%CI=0.38–0.92; data not shown). There was no statistically significant difference between genders for the associations of either α -linolenic acid ($P_{\text{heterogeneity}}=0.773$) or docosapentaenoic acid ($P_{\text{heterogeneity}}=0.147$) with PC risk, although both FAs conferred a significantly reduced risk among women (OR_{T3-T1}=0.55; 95%CI=0.31–0.99; $P_{\text{trend}}=0.043$ for 18:3n-3; OR_{T3-T1}=0.36; 95%CI=0.18–0.74; $P_{\text{trend}}=0.004$ for 22:5n-3).

In the smoking-stratified analysis, we observed that several FAs were significantly associated with PC risk among smokers only. Specifically, the long-chain n-6/n-3 PUFA ratio was positively associated with PC risk (OR_{T3-T1}=3.40; 95%CI=1.39–8.34; $P_{\text{trend}}=0.007$), while docosahexaenoic acid (22:6n-3; OR_{T3-T1}=0.31; 95%CI=0.13–0.76; $P_{\text{trend}}=0.009$) and total *cis* n-3 PUFAs (OR_{T3-T1}=0.26; 95%CI=0.11–0.62; $P_{\text{trend}}=0.002$) were inversely associated with PC risk. None of these FAs were significantly associated with PC risk among non-smokers ($P_{\text{interaction}}\leq 0.01$; Supplementary Table 3).

We found no evidence of association between the investigated *SCD-1* SNPs (rs3071 and rs3793767) and PC risk in both the additive and dominant models ($P\geq 0.374$; Table 4). In addition, neither SNP significantly modified the associations between the desaturation indexes (DI₁₆ and DI₁₈) and PC assuming the dominant model ($P_{\text{interaction}}\geq 0.129$; Table 5). Adjusted mean percentage of DI₁₆ was significantly lower in homozygous carriers of the minor allele for both rs3071 (2.49; $P=0.006$) and rs3793767 (2.58; $P=0.033$) compared with carriers of the common allele (2.74 and 2.73, respectively), suggesting an effect of genetic variation on the activity or expression of *SCD-1*. A borderline significant inverse relationship between DI₁₈ and rs3071 (0.70 vs. 0.75; $P=0.040$) was also observed (data not shown).

In sensitivity analyses, the risk estimates did not substantially alter when analyses were restricted to the adenocarcinoma subtype of PC (n=291). The associations between individual FAs and PC risk did not differ following adjustment for C-peptide or HbA1c levels (data not shown). In addition, exclusion of subjects with blood HbA1c levels $\geq 6.5\%$ (n=32) or those with a history of diabetes mellitus (n=51) did not materially change the risk estimates. Mutual adjustment for FAs that share common food

sources did not substantially modify the risk estimates (data not shown). Exclusion of cases with blood samples drawn less than two years before diagnosis of PC (n=42) did not change the risk estimates (data not shown).

Discussion

In this prospective analysis of prediagnostic plasma phospholipid FA levels and PC development, we found evidence of significantly reduced risk of PC among subjects with higher levels of saturated heptadecanoic acid (17:0) and pentadecanoic acid (15:0), as well as with *cis* n-3 polyunsaturated α -linolenic acid (18:3n-3) and docosapentaenoic acid (22:5n-3). In gender-stratified analysis, industrial TFAs were positively associated with PC risk among men, while conjugated linoleic acids conferred a significantly reduced risk among women. Finally, there was a significantly higher risk of PC associated with the long-chain n-6/n-3 PUFA ratio among smokers, whereas no association emerged among non-smokers.

SFAs comprised of an odd number of carbon atoms (15:0 and 17:0) cannot be synthesized *de novo* and are primarily derived from ruminant products ³⁷. Several cross-sectional studies performed in the EPIC cohort reported a positive correlation between plasma phospholipid levels of pentadecanoic acid and heptadecanoic acid and dairy products intake ^{38,39}. Our results support the hypothesis that consumption of FAs from dairy products is associated with decreased risk of PC, although the association may be attributed to other constituents of dairy products such as calcium ⁴⁰ and vitamin D ⁴¹. Experimental studies are needed to clarify the independent effect of these fatty acids on PC risk.

The polyunsaturated α -linolenic acid (18:3n-3) is an essential n-3 PUFA primarily found in green leafy vegetables, seed and vegetable oils, nuts and meat. Intake of α -linolenic acid has not been linked to PC risk in prospective studies based on dietary questionnaires ^{12,13,15,42}, which might be a result of poor assessment ¹⁷. We found no evidence of association between total n-3 PUFAs and PC risk, which is in line with results from a meta-analysis of prospective studies based on dietary questionnaires ⁴³. However, when we estimated the risk by individual n-3 PUFA isomers, a significant inverse association emerged for docosapentaenoic acid. Since docosapentaenoic acid is a minor constituent of the diet, previous epidemiological studies based on self-reported dietary intake were unable to measure the availability of this compound in foods. A study on the effect of individual n-3 PUFAs on human colorectal carcinoma cells reported strong anti-proliferative and pro-apoptotic effects of this FA isomer

⁴⁴. More extensive research is required to elucidate the role of docosapentaenoic acid in pancreatic carcinogenesis.

Tobacco-specific nitrosamines have been shown to induce pancreatic tumors in animal models ^{45,46}, and the carcinogenic effect of these compounds was increased when animals were fed with a high-fat diet ⁴⁷. The n-3 and n-6 PUFAs have opposing effects in modulating signal transduction and gene expression involved in systemic inflammation ⁴⁸. Our finding of a statistically significant interaction between the long-chain n-6/n-3 PUFA ratio and smoking status might be due to the ability of these FAs and smoking-derived compounds to modulate the same inflammatory pathways that promote pancreatic carcinogenesis ⁴⁹. Experimental studies are needed to investigate the role of FAs in the susceptibility to tobacco-related carcinogens.

The gender-specific associations between TFAs, conjugated linoleic acids and PC risk that were found in our analysis may reflect differences in hormone levels and dietary patterns between men and women ⁵⁰. However, the sample size may have been insufficient to detect a convincing statistical heterogeneity between genders, and study populations with a larger number of cases or a wider intake of these FAs might be required to confirm our findings.

Strengths of this study are the prospective and multi-center study design, the ability to distinguish various FA isomers, the relatively long follow-up time and the detailed information on lifestyle factors. The study also had some limitations including the low statistical power for SNP-biomarker interaction analyses, the lack of information on family history of PC, and the single collection of blood samples at baseline. However, a previous study in a population of healthy women has shown high reliability of serum phospholipid FA levels from samples collected over time ⁵¹.

In conclusion, this study based on biomarkers of FA exposure provides support for a possible protective effect of specific FA isomers present in dairy products, seeds and marine foods on the development of PC. In addition, we found evidence of potential interactions of specific FAs with gender or smoking status on the risk of PC. Our findings support the conclusions of the WCRF Pancreatic Cancer 2012 Report ⁵² and highlight the role of individual FA isomers in PC susceptibility. Finally, the present study shows the importance of using plasma and genetic biomarkers as objective measures of

FA profile, and opens towards a more accurate methodological approach in future epidemiological studies on the association between FAs and PC risk.

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Table 1. Baseline characteristics of study population*

	Controls (n=375)	Cases (n=375)	P value [†]
Sex, n (%)			
Men	153 (40.8%)	153 (40.8%)	-
Women	222 (59.2%)	222 (59.2%)	-
Mean age (y) at			
Blood collection	57.44 ± 8.28	57.44 ± 8.30	-
Diagnosis		64.59 ± 8.87	-
Anthropometric measures			
Mean adult weight (kg)	72.62 ± 14.11	74.35 ± 13.50	0.087
Mean adult height (cm)	165.19 ± 8.95	165.93 ± 8.84	0.251
Mean body mass index (kg/m ²)	26.55 ± 4.43	26.99 ± 4.40	0.18
Waist to hip ratio	0.87 ± 0.10	0.88 ± 0.09	0.261
Nutrient intake			
Total energy intake (kcal)	2064.96 ± 598.26	2069.97 ± 666.98	0.914
Alcohol intake (g/d) [‡]	16.17 ± 22.05	16.56 ± 21.27	0.823
History of diabetes mellitus, n (%)			0.631
No	292 (77.9)	297 (79.2)	
Yes	27 (7.2)	24 (6.4)	
Unknown [‡]	56 (14.9)	54 (14.4)	
Smoking status, n (%)			0.001
Never smokers	183 (48.8)	164 (43.7)	
Former smokers	123 (32.8)	100 (26.7)	
Current smokers	65 (17.3)	104 (27.7)	
Unknown [‡]	4 (1.1)	7 (1.9)	
Physical activity, n (%)			0.743
Inactive	41 (10.9)	38 (10.1)	
Moderately inactive	118 (31.5)	107 (28.5)	
Moderately active	184 (49.1)	191 (50.9)	
Active	24 (6.4)	29 (7.7)	
Unknown [‡]	8 (2.1)	10 (2.7)	
Years of education, n (%)			0.062
Low	150 (40.0)	175 (46.7)	
Medium	146 (38.9)	120 (32.0)	
High	67 (17.9)	64 (17.1)	
Unknown [‡]	12 (3.2)	16 (4.3)	
SCD-1 rs3071, n (%)			0.732
A/A	185 (51.4)	170 (48.0)	
A/C	147 (40.1)	147 (41.5)	
C/C	29 (7.9)	31 (8.8)	
Unknown [‡]	6 (1.6)	6 (1.7)	
Paired trend test [§]			0.442
Minor allele (C) [‡]	205 (28.4)	209 (30.0)	

SCD-1 rs3793767, n (%)			0.571
C/C	175 (47.7)	162 (45.8)	
C/T	142 (38.7)	148 (41.8)	
T/T	41 (11.2)	32 (9.0)	
Unknown [‡]	9 (2.4)	12 (3.39)	
Paired trend test [§]			0.573
Minor allele (T) [‡]	224 (31.3)	212 (31.0)	

*Data are presented as means (\pm SD) or proportions (percentages).

†Statistical significance for differences between cases and control individuals was tested using paired t-test for continuous variables and the Chi-squared test from unadjusted conditional logistic regression for categorical variables. P-values were not computed for matching factors.

‡Among consumers only.

§P-trend calculated by unadjusted conditional logistic regression models.

‡Unknown subjects were excluded from calculations.

‡Alleles given in brackets (most>less frequent allele).

Table 2. Baseline plasma proportions and levels of fatty acids in the study population*

	Controls (n=375)		Cases (n=375)	
	Percentage [†]	Level (μmol/l)	Percentage [†]	Level (μmol/l)
Saturated fatty acids				
15:0 (pentadecanoic acid)	0.14 ± 1.74	8.93 ± 1.82	0.14 ± 1.67	8.71 ± 1.79
16:0 (palmitic acid)	25.06 ± 1.07	1588.61 ± 1.22	25.07 ± 1.07	1592.48 ± 1.24
17:0 (heptadecanoic acid)	0.37 ± 1.23	21.55 ± 1.28	0.35 ± 1.23	20.84 ± 1.28
18:0 (stearic acid)	14.07 ± 1.09	785.46 ± 1.24	14.04 ± 1.09	785.29 ± 1.26
<i>Cis</i> monounsaturated fatty acids				
16:1n-7 (palmitoleic acid)	0.67 ± 1.40	39.18 ± 1.56	0.70 ± 1.44	41.26 ± 1.62
18:1n-9 (oleic acid)	10.47 ± 1.21	577.18 ± 1.34	10.61 ± 1.22	585.99 ± 1.36
<i>Trans</i> monounsaturated fatty acids				
18:1n-9t/12t (elaidic acid)	0.25 ± 1.89	11.38 ± 2.00	0.26 ± 1.86	11.57 ± 1.91
18:1n-7t (vaccenic acid)	0.16 ± 1.88	7.09 ± 1.82	0.16 ± 1.87	7.03 ± 1.78
<i>Cis</i> n-6 polyunsaturated fatty acids				
18:2n-6 (linoleic acid)	22.07 ± 1.17	1224.16 ± 1.91	21.91 ± 1.16	1217.31 ± 1.26
18:3n-6 (γ-linolenic acid)	0.11 ± 1.57	6.08 ± 1.86	0.11 ± 1.55	6.22 ± 1.70
20:3n-6 (di-homo-γ-linolenic acid)	3.39 ± 1.28	197.62 ± 1.40	3.48 ± 1.26	203.44 ± 1.39
20:4n-6 (arachidonic acid)	10.78 ± 1.22	601.36 ± 1.31	10.78 ± 1.21	602.38 ± 1.32
Conjugated linoleic acids				
9c11t + 10t12c	0.19 ± 1.77	11.34 ± 1.86	0.19 ± 1.67	11.07 ± 1.79
<i>Cis</i> n-3 polyunsaturated fatty acids				
18:3n-3 (α-linolenic acid)	0.19 ± 1.55	11.25 ± 1.65	0.18 ± 1.52	10.60 ± 1.65
20:5n-3 (eicosapentaenoic acid)	1.05 ± 1.75	53.83 ± 1.85	1.03 ± 1.73	53.00 ± 1.84
22:5n-3 (docosapentaenoic acid)	1.02 ± 1.29	48.53 ± 1.40	0.99 ± 1.27	47.00 ± 1.40
22:6n-3 (docosahexaenoic acid)	4.55 ± 1.35	262.65 ± 1.41	4.55 ± 1.37	263.01 ± 1.43
Groupings				
Total saturated fatty acids	40.05 ± 1.03	2431.01 ± 1.21	40.00 ± 1.03	2433.91 ± 1.24
Total <i>cis</i> monounsaturated fatty acids	13.09 ± 1.19	717.05 ± 1.33	13.27 ± 1.19	728.71 ± 1.35

Total <i>cis</i> n-6 polyunsaturated fatty acids	37.71 ± 1.10	2103.94 ± 1.23	37.66 ± 1.09	2106.18 ± 1.23
Total <i>cis</i> n-3 polyunsaturated fatty acids	7.06 ± 1.30	389.75 ± 1.39	6.98 ± 1.32	386.83 ± 1.41
Long-chain n-6/n-3 PUFA ratio	2.23 ± 1.42	2.28 ± 1.43	2.27 ± 1.41	2.31 ± 1.41
Total <i>trans</i> ruminant fatty acids	0.73 ± 1.48	40.39 ± 1.53	0.73 ± 1.47	40.27 ± 1.50
Total <i>trans</i> industrial fatty acids	0.41 ± 1.69	18.64 ± 1.82	0.41 ± 1.63	18.89 ± 1.73
Desaturation index				
DI₁₆ (16:1n-7c/16:0)	0.03 ± 1.37	0.02 ± 1.37	0.03 ± 1.40	0.03 ± 1.41
DI₁₈ (18:1n-9c/18:0)	0.74 ± 1.26	0.73 ± 1.26	0.76 ± 1.26	0.75 ± 1.26

*Geometric means (±SD) of plasma fatty acids are presented.

†Relative amount expressed as percentage of total fatty acids.

Table 3. Multivariable odds ratios (ORs) and 95% confidence intervals (95% CIs) for plasma phospholipid fatty acids (percentage of total fatty acids) associated with pancreatic cancer risk*

Plasma phospholipid fatty acids	Tertiles of plasma phospholipid fatty acids‡			P-trend#	P-heterogeneity†
	T1 (Ref)	T2	T3		
Saturated fatty acids					
15:0 (pentadecanoic acid)					0.691
Total	1.00	0.88 (0.56; 1.37)	0.63 (0.38; 1.04)	0.058	
Men	1.00	1.14 (0.58; 2.26)	0.78 (0.34; 1.77)	0.523	
Women	1.00	0.79 (0.46; 1.37)	0.62 (0.34; 1.15)	0.132	
16:0 (palmitic acid)					0.756
Total	1.00	0.71 (0.47; 1.06)	1.05 (0.69; 1.59)	0.787	
Men	1.00	0.74 (0.39; 1.42)	1.06 (0.50; 2.22)	0.871	
Women	1.00	1.21 (0.69; 2.11)	1.25 (0.70; 2.20)	0.466	
17:0 (heptadecanoic acid)					0.547
Total	1.00	0.56 (0.37; 0.84)	0.63 (0.41; 0.98)	0.036	
Men	1.00	0.49 (0.25; 0.95)	0.84 (0.41; 1.71)	0.523	
Women	1.00	0.63 (0.37; 1.05)	0.60 (0.34; 1.06)	0.075	
18:0 (stearic acid)					0.580
Total	1.00	0.89 (0.60; 1.31)	0.92 (0.61; 1.38)	0.686	
Men	1.00	0.59 (0.32; 1.09)	1.13 (0.57; 2.25)	0.798	
Women	1.00	1.37 (0.79; 2.37)	0.87 (0.49; 1.52)	0.578	
Cis monounsaturated fatty acids					
16:1n-7 (palmitoleic acid)					0.723
Total	1.00	1.08 (0.71; 1.64)	1.17 (0.77; 1.79)	0.461	
Men	1.00	1.12 (0.60; 2.09)	1.35 (0.65; 2.81)	0.425	
Women	1.00	1.04 (0.57; 1.87)	1.13 (0.63; 2.02)	0.662	
18:1n-9 (oleic acid)					0.642
Total	1.00	1.33 (0.90; 1.95)	1.10 (0.71; 1.69)	0.561	
Men	1.00	1.35 (0.73; 2.48)	0.78 (0.38; 1.61)	0.655	

Women	1.00	1.17 (0.71; 1.91)	1.03 (0.59; 1.81)	0.848	
<i>Trans</i> monounsaturated fatty acids					
18:1n-9t/12t (elaidic acid)					0.409
Total	1.00	1.12 (0.73; 1.71)	1.24 (0.72; 2.15)	0.439	
Men	1.00	1.20 (0.62; 2.34)	1.74 (0.74; 4.12)	0.218	
Women	1.00	1.14 (0.67; 1.94)	1.03 (0.49; 2.15)	0.894	
18:1n-7t (vaccenic acid)					0.860
Total	1.00	0.94 (0.61; 1.45)	1.12 (0.66; 1.89)	0.648	
Men	1.00	0.87 (0.42; 1.78)	1.38 (0.53; 3.62)	0.547	
Women	1.00	1.39 (0.78; 2.46)	1.24 (0.64; 2.39)	0.577	
<i>Cis</i> n-6 polyunsaturated fatty acids					
18:2n-6 (linoleic acid)					0.088
Total	1.00	1.01 (0.70; 1.47)	0.93 (0.61; 1.43)	0.768	
Men	1.00	1.21 (0.62; 2.37)	1.67 (0.79; 3.55)	0.178	
Women	1.00	0.82 (0.50; 1.35)	0.73 (0.42; 1.27)	0.254	
18:3n-6 (γ-linolenic acid)					0.195
Total	1.00	0.96 (0.65; 1.44)	1.10 (0.71; 1.69)	0.692	
Men	1.00	1.07 (0.59; 1.93)	1.74 (0.85; 3.57)	0.156	
Women	1.00	0.85 (0.49; 1.46)	0.90 (0.50; 1.63)	0.721	
20:3n-6 (di-homo-γ-linolenic acid)					0.717
Total	1.00	1.03 (0.69; 1.55)	1.14 (0.75; 1.73)	0.534	
Men	1.00	1.15 (0.61; 2.17)	1.30 (0.69; 2.44)	0.416	
Women	1.00	1.14 (0.65; 1.99)	1.12 (0.64; 1.95)	0.725	
20:4n-6 (arachidonic acid)					0.201
Total	1.00	0.86 (0.58; 1.28)	1.14 (0.76; 1.71)	0.534	
Men	1.00	1.29 (0.70; 2.38)	0.80 (0.41; 1.57)	0.535	
Women	1.00	0.74 (0.43; 1.27)	1.48 (0.86; 2.56)	0.197	
Conjugated linoleic acids					
9c11t + 10t12c					0.056
Total	1.00	0.80 (0.52; 1.25)	0.70 (0.42; 1.16)	0.175	

Men	1.00	1.01 (0.51; 1.98)	1.02 (0.48; 2.15)	0.958	
Women	1.00	0.74 (0.38; 1.43)	0.37 (0.17; 0.81)	0.008	
<i>Cis</i> n-3 polyunsaturated fatty acids					
18:3n-3 (α -linolenic acid)					0.773
Total	1.00	0.69 (0.46; 1.03)	0.60 (0.39; 0.92)	0.020	
Men	1.00	0.64 (0.32; 1.27)	0.63 (0.33; 1.20)	0.152	
Women	1.00	0.46 (0.27; 0.79)	0.55 (0.31; 0.99)	0.043	
20:5n-3 (eicosapentaenoic acid)					0.174
Total	1.00	0.73 (0.50; 1.09)	0.71 (0.48; 1.07)	0.091	
Men	1.00	0.54 (0.28; 1.05)	1.08 (0.57; 2.07)	0.875	
Women	1.00	0.74 (0.44; 1.25)	0.58 (0.33; 1.02)	0.057	
22:5n-3 (docosapentaenoic acid)					0.147
Total	1.00	0.76 (0.48; 1.21)	0.52 (0.32; 0.85)	0.008	
Men	1.00	0.54 (0.25; 1.15)	0.72 (0.32; 1.60)	0.553	
Women	1.00	0.83 (0.45; 1.53)	0.36 (0.18; 0.74)	0.004	
22:6n-3 (docosahexaenoic acid)					0.932
Total	1.00	0.81 (0.55; 1.20)	1.14 (0.76; 1.72)	0.506	
Men	1.00	0.81 (0.43; 1.51)	1.01 (0.53; 1.93)	0.949	
Women	1.00	1.07 (0.64; 1.80)	0.99 (0.57; 1.72)	0.949	
Groupings					
Total saturated fatty acids					0.791
Total	1.00	0.99 (0.67; 1.48)	0.99 (0.62; 1.59)	0.977	
Men	1.00	0.94 (0.48; 1.83)	1.11 (0.48; 2.58)	0.824	
Women	1.00	1.15 (0.67; 1.98)	1.27 (0.68; 2.37)	0.451	
Total <i>cis</i> monounsaturated fatty acids					0.339
Total	1.00	1.27 (0.87; 1.86)	1.07 (0.70; 1.64)	0.701	
Men	1.00	1.26 (0.69; 2.29)	0.61 (0.29; 1.30)	0.307	
Women	1.00	1.03 (0.61; 1.74)	1.07 (0.63; 1.84)	0.800	
Total <i>cis</i> n-6 polyunsaturated fatty acids					0.776
Total	1.00	0.87 (0.60; 1.26)	0.87 (0.58; 1.30)	0.474	

Men	1.00	0.65 (0.33; 1.28)	0.83 (0.41; 1.72)	0.629	
Women	1.00	0.99 (0.62; 1.60)	0.95 (0.56; 1.61)	0.860	
Total <i>cis</i> n-3 polyunsaturated fatty acids					0.694
Total	1.00	0.58 (0.39; 0.86)	0.92 (0.62; 1.35)	0.692	
Men	1.00	0.66 (0.35; 1.24)	0.96 (0.50; 1.84)	0.966	
Women	1.00	0.50 (0.30; 0.84)	0.82 (0.49; 1.38)	0.491	
Long-chain n-6/n-3 PUFA ratio					0.232
Total	1.00	0.87 (0.59; 1.30)	1.02 (0.68; 1.54)	0.928	
Men	1.00	0.89 (0.49; 1.62)	0.69 (0.35; 1.34)	0.276	
Women	1.00	0.96 (0.56; 1.64)	1.19 (0.67; 2.11)	0.567	
Total <i>trans</i> ruminant fatty acids					0.531
Total	1.00	0.92 (0.60; 1.41)	0.84 (0.50; 1.42)	0.520	
Men	1.00	1.02 (0.49; 2.14)	1.12 (0.46; 2.72)	0.817	
Women	1.00	0.99 (0.57; 1.71)	0.77 (0.39; 1.52)	0.460	
Total <i>trans</i> industrial fatty acids					0.030
Total	1.00	1.32 (0.86; 2.02)	1.07 (0.62; 1.84)	0.728	
Men	1.00	1.32 (0.60; 2.93)	3.00 (1.13; 7.99)	0.029	
Women	1.00	1.06 (0.60; 1.86)	0.73 (0.33; 1.58)	0.485	
Desaturation index					
DI₁₆ (16:1n-7c/16:0)					0.698
Total	1.00	1.27 (0.85; 1.90)	1.09 (0.70; 1.70)	0.752	
Men	1.00	1.08 (0.57; 2.01)	1.10 (0.53; 2.28)	0.793	
Women	1.00	1.76 (0.99; 3.13)	1.41 (0.77; 2.61)	0.348	
DI₁₈ (18:1n-9c/18:0)					0.501
Total	1.00	1.07 (0.72; 1.57)	1.18 (0.78; 1.79)	0.438	
Men	1.00	1.23 (0.68; 2.23)	1.22 (0.59; 2.54)	0.529	
Women	1.00	0.74 (0.43; 1.29)	0.93 (0.54; 1.61)	0.768	

*Conditional logistic regression adjusted for body mass index, height, history of diabetes mellitus, smoking status, alcohol intake, years of education, and physical activity. Cases are individually matched to controls for study center, sex, age at blood collection (± 3 months), date and time at blood collection, length of follow-up, fasting status and, for women, use of pill/hormonal replacement treatment.

‡Cut-points of tertiles determined on control individuals.

≠Obtained by modelling the cut-points of tertiles as continuous variable.

†Tests of heterogeneity between ORs in men and in women based on Chi-squared statistics calculated as the deviations of logistic beta-coefficients observed in each of the subgroups relative to the overall beta-coefficient.

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for association between *SCD-1* genotypes and pancreatic cancer risk*

Additive model	Genotypic groups[‡]			P_{add}[§]
	0	1	2	
rs3071				
Controls/cases (n) [†]	175/165	138/145	27/30	
OR (95% CI)	1 (ref)	1.12 (0.81; 1.55)	1.17 (0.67; 2.03)	0.442
rs3793767				
Controls/cases (n) [†]	170/159	132/145	30/28	
OR (95% CI)	1 (ref)	1.19 (0.85; 1.66)	1.00 (0.56; 1.79)	0.573
Dominant model	0	1 or 2		P_{dom}[§]
rs3071				
Controls/cases (n) [†]	175/165	165/175		
OR (95% CI)	1 (ref)	1.13 (0.83; 1.53)		0.438
rs3793767				
Controls/cases (n) [†]	170/159	162/173		
OR (95% CI)	1 (ref)	1.15 (0.84; 1.59)		0.374

*Unconditional logistic regression adjusted for sex and age at blood collection.

[‡]SNPs are coded as 0, 1 and 2 according to the number of minor alleles a participant carries.

[§]**P_{add}**, P for trend or P for the additive model; **P_{dom}**, P value for the dominant model.

[†]Cases are individually matched to controls for study center, sex, age at blood collection (\pm 3 months), date and time at blood collection, length of follow-up, fasting status and, for women, use of pill/hormonal replacement treatment.

Table 5. Multivariable odds ratios (OR) and 95% confidence intervals (95% CI) for association between percentage of desaturation index and pancreatic cancer risk stratified by SCD-1 genotypes*

SCD-1 genotypes [†]	Tertiles of desaturation indexes [‡]			P-trend [§]	P interaction [§]
	T1 (Ref)	T2	T3		
DI₁₆ (16:1n-7cis/16:0)					0.130
rs3071 AA					
Controls/cases (n)	62/37	62/77	61/56		
OR (95% CI)	1 (ref)	2.40 (1.35; 4.27)	1.73 (0.95; 3.16)	0.104	
rs3071 AC+CC					
Controls/cases (n)	60/63	59/56	57/59		
OR (95% CI)	1 (ref)	0.98 (0.57; 1.70)	1.29 (0.75; 2.21)	0.354	
DI₁₈ (18:1n-9cis/18:0)					0.174
rs3071 AA					
Controls/cases (n)	62/47	62/58	61/65		
OR (95% CI)	1 (ref)	1.14 (0.66; 1.99)	1.34 (0.77; 2.34)	0.294	
rs3071 AC+CC					
Controls/cases (n)	59/65	59/42	58/71		
OR (95% CI)	1 (ref)	0.93 (0.54; 1.61)	0.96 (0.56; 1.65)	0.894	
DI₁₆ (16:1n-7cis/16:0)					0.129
rs3793767 CC					
Controls/cases (n)	59/36	58/73	58/53		
OR (95% CI)	1 (ref)	2.42 (1.34; 4.37)	1.77 (0.94; 3.31)	0.099	
rs3793767 CT+TT					
Controls/cases (n)	62/58	61/58	60/64		

OR (95% CI)	1 (ref)	1.16 (0.68; 1.98)	1.23 (0.72; 2.12)	0.449
DI₁₈ (18:1n-9cis/18:0)				0.168
rs3793767 CC				
Controls/cases (n)	59/47	58/51	58/64	
OR (95% CI)	1 (ref)	1.05 (0.59; 1.86)	1.31 (0.75; 2.29)	0.339
rs3793767 CT+TT				
Controls/cases (n)	62/67	61/48	60/65	
OR (95% CI)	1 (ref)	1.03 (0.60; 1.76)	0.96 (0.56; 1.63)	0.874

*Unconditional logistic regression adjusted for matching variables (sex, age at blood collection, date and time at blood collection, fasting status, pill/hormone replacement treatment), body mass index, height, history of diabetes mellitus, tobacco smoking, alcohol, years of education, physical activity.

‡Cut points of tertiles determined on control individuals in each genotypic group separately.

†The dominant model was assumed for SNP effect.

≠Obtained by modeling the cut points of tertiles as continuous variable.

§Obtained by modeling the interaction term between plasma phospholipid FAs as continuous variable and genotypic groups.

Supplementary Table 1. Baseline characteristics of the study population by gender*

	Males			Females		
	Controls (n=153)	Cases (n=153)	P value†	Controls (n=222)	Cases (n=222)	P value†
Mean age (y) at						
Blood collection	56.44 ± 8.32	56.48 ± 8.36	0.971	58.13 ± 8.20	58.11 ± 8.21	0.973
Diagnosis		63.38 ± 8.62			65.42 ± 8.97	
Anthropometric measures						
Mean adult weight (kg)	81.40 ± 12.25	80.37 ± 11.18	0.446	66.58 ± 11.99	70.20 ± 13.41	0.003
Mean adult height (cm)	171.82 ± 6.81	172.37 ± 7.50	0.500	160.62 ± 7.23	161.50 ± 6.70	0.184
Mean body mass index (kg/m ²)	27.55 ± 3.71	27.06 ± 3.47	0.230	25.86 ± 4.75	26.93 ± 4.96	0.020
Waist to hip ratio	0.96 ± 0.06	0.95 ± 0.06	0.669	0.80 ± 0.07	0.82 ± 0.07	0.017
Nutrient intake						
Energy intake (kcal)	2314.86 ± 604.54	2410.08 ± 678.00	0.197	1892.29 ± 530.13	1837.10 ± 550.20	0.283
Alcohol intake (g/d)‡	23.94 ± 28.35	26.12 ± 26.54	0.510	9.76 ± 11.65	9.15 ± 11.55	0.624
History of diabetes mellitus, n (%)			0.493			1
No	119 (77.8)	116 (75.8)		178 (80.2)	176 (79.3)	
Yes	13 (8.5)	16 (10.5)		11 (5.0)	11 (5.0)	
Unknown#	21 (13.7)	21 (13.7)		33 (14.9)	35 (15.8)	
Smoking status, n (%)			0.070			0.008
Never smokers	48 (31.4)	43 (28.1)		135 (60.8)	121 (54.5)	
Former smokers	66 (43.1)	53 (34.6)		57 (25.7)	47 (21.2)	
Current smokers	36 (23.5)	52 (34.0)		29 (13.1)	52 (23.4)	
Unknown#	3 (2.0)	5 (3.3)		1 (0.5)	2 (0.9)	
Physical activity, n (%)			0.295			0.668
Inactive	29 (19.0)	20 (13.1)		12 (5.4)	18 (8.1)	
Moderately inactive	50 (32.7)	46 (30.1)		68 (30.6)	61 (27.5)	
Moderately active	61 (39.9)	67 (43.8)		123 (55.4)	124 (55.9)	
Active	9 (5.9)	16 (10.5)		15 (6.8)	13 (5.9)	
Unknown#	4 (2.6)	4 (2.6)		4 (1.8)	6 (2.7)	

Years of education, n (%)			0.125			0.180
Low	53 (34.6)	67 (43.8)		97 (43.7)	108 (48.7)	
Medium	59 (38.6)	49 (32.0)		87 (39.2)	71 (32.0)	
High	39 (25.5)	32 (20.9)		28 (12.6)	32 (14.4)	
Unknown [‡]	2 (1.3)	5 (3.3)		10 (4.5)	11 (5.0)	
SCD-1 rs3071, n (%)			0.935			0.387
A/A	62 (41.3)	67 (47.2)		113 (52.1)	95 (44.8)	
A/C	62 (41.3)	54 (38.0)		80 (36.9)	94 (44.3)	
C/C	22 (14.7)	15 (10.6)		19 (8.8)	17 (8.0)	
Unknown [‡]	4 (2.7)	6 (4.2)		5 (2.3)	6 (2.8)	
Paired trend test [§]			0.726			0.174
Minor allele (A>C) [‡]	106 (36.3)	84 (30.9)		118 (27.8)	128 (31.1)	
SCD-1 rs3793767, n (%)			0.745			0.169
C/C	69 (46.0)	68 (47.9)		116 (53.5)	102 (48.1)	
C/T	61 (40.7)	56 (39.4)		86 (39.6)	91 (42.9)	
T/T	17 (11.3)	15 (10.6)		12 (5.5)	16 (7.6)	
Unknown [‡]	3 (2.0)	3 (2.1)		3 (1.4)	3 (1.4)	
Paired trend test [§]			0.458			0.151
Minor allele (C>T) [‡]	95 (32.3)	86 (30.9)		110 (25.7)	123 (29.4)	

*Data are presented as means (±SD) or proportions (percentages).

†Statistical significance for differences between cases and control individuals was tested using paired t-test for continuous variables and the Chi-squared test from unadjusted conditional logistic regression for categorical variables. P-value was not computed for matching factors.

‡Among consumers only.

§P-trend calculated by unadjusted conditional logistic regression models.

‡Unknown subjects are excluded from calculations.

‡Alleles given in brackets (most>less frequent allele).

Supplementary Table 2. Multivariable odds ratios (ORs) and 95% confidence intervals (95% CIs) for association between plasma phospholipid fatty acid (percentage of total fatty acids) and pancreatic cancer risk stratified by levels of BMI at recruitment*

Plasma phospholipid fatty acids	Tertiles of plasma phospholipid fatty acids [†]			P-trend [‡]	P interaction [§]
	T1 (Ref)	T2	T3		
Saturated fatty acids					
15:0 (pentadecanoic acid)					0.030
BMI <26.1 kg/m ² ‡	1 (ref)	0.92 (0.55; 1.56)	0.61 (0.35; 1.09)	0.109	
BMI ≥26.1 kg/m ²	1 (ref)	1.98 (1.18; 3.34)	1.43 (0.81; 2.52)	0.189	
16:0 (palmitic acid)					0.634
BMI <26.1 kg/m ²	1 (ref)	0.70 (0.40; 1.23)	1.40 (0.81; 2.44)	0.221	
BMI ≥26.1 kg/m ²	1 (ref)	1.05 (0.61; 1.80)	1.07 (0.62; 1.87)	0.805	
17:0 (heptadecanoic acid)					0.040
BMI <26.1 kg/m ²	1 (ref)	0.67 (0.38; 1.17)	0.62 (0.35; 1.08)	0.084	
BMI ≥26.1 kg/m ²	1 (ref)	0.60 (0.34; 1.05)	0.70 (0.41; 1.20)	0.181	
18:0 (stearic acid)					0.287
BMI <26.1 kg/m ²	1 (ref)	0.74 (0.43; 1.25)	0.79 (0.46; 1.36)	0.387	
BMI ≥26.1 kg/m ²	1 (ref)	1.21 (0.71; 2.06)	0.84 (0.47; 1.50)	0.550	
Cis monounsaturated fatty acids					
16:1n-7 (palmitoleic acid)					0.321
BMI <26.1 kg/m ²	1 (ref)	1.08 (0.63; 1.83)	1.08 (0.62; 1.88)	0.798	
BMI ≥26.1 kg/m ²	1 (ref)	0.99 (0.58; 1.68)	1.31 (0.77; 2.25)	0.319	
18:1n-9 (oleic acid)					0.655
BMI <26.1 kg/m ²	1 (ref)	0.92 (0.54; 1.58)	1.06 (0.61; 1.84)	0.838	
BMI ≥26.1 kg/m ²	1 (ref)	1.74 (1.03; 2.93)	1.26 (0.74; 2.17)	0.402	
Trans monounsaturated fatty acids					
18:1n-9t/12t (elaidic acid)					0.843
BMI <26.1 kg/m ²	1 (ref)	0.91 (0.53; 1.56)	1.16 (0.64; 2.13)	0.649	
BMI ≥26.1 kg/m ²	1 (ref)	0.75 (0.43; 1.30)	1.21 (0.66; 2.21)	0.590	
18:1n-7t (vaccenic acid)					0.103

BMI <26.1 kg/m ²	1 (ref)	0.94 (0.54; 1.63)	0.83 (0.45; 1.52)	0.541	
BMI ≥26.1 kg/m ²	1 (ref)	0.89 (0.53; 1.49)	1.27 (0.72; 2.23)	0.448	
<i>Cis</i> n-6 polyunsaturated fatty acids					
18:2n-6 (linoleic acid)					0.916
BMI <26.1 kg/m ²	1 (ref)	0.98 (0.57; 1.67)	0.77 (0.44; 1.34)	0.353	
BMI ≥26.1 kg/m ²	1 (ref)	1.20 (0.72; 2.01)	0.87 (0.51; 1.50)	0.644	
18:3n-6 (γ-linolenic acid)					0.028
BMI <26.1 kg/m ²	1 (ref)	0.95 (0.56; 1.62)	1.16 (0.68; 1.98)	0.588	
BMI ≥26.1 kg/m ²	1 (ref)	0.94 (0.56; 1.57)	0.99 (0.58; 1.68)	0.951	
20:3n-6 (di-homo-γ-linolenic acid)					0.143
BMI <26.1 kg/m ²	1 (ref)	1.23 (0.72; 2.10)	1.39 (0.80; 2.41)	0.247	
BMI ≥26.1 kg/m ²	1 (ref)	1.03 (0.60; 1.77)	1.01 (0.59; 1.72)	0.980	
20:4n-6 (arachidonic acid)					0.828
BMI <26.1 kg/m ²	1 (ref)	1.02 (0.59; 1.77)	1.49 (0.87; 2.53)	0.133	
BMI ≥26.1 kg/m ²	1 (ref)	0.74 (0.43; 1.28)	0.82 (0.48; 1.41)	0.502	
Conjugated linoleic acids					
9c11t + 10t12c					0.716
BMI <26.1 kg/m ²	1 (ref)	0.97 (0.57; 1.65)	0.89 (0.51; 1.56)	0.692	
BMI ≥26.1 kg/m ²	1 (ref)	0.90 (0.53; 1.54)	0.94 (0.51; 1.74)	0.809	
<i>Cis</i> n-3 polyunsaturated fatty acids					
18:3n-3 (α-linolenic acid)					0.959
BMI <26.1 kg/m ²	1 (ref)	0.65 (0.39; 1.09)	0.58 (0.33; 1.03)	0.052	
BMI ≥26.1 kg/m ²	1 (ref)	0.82 (0.48; 1.40)	0.89 (0.51; 1.57)	0.647	
20:5n-3 (eicosapentaenoic acid)					0.444
BMI <26.1 kg/m ²	1 (ref)	0.65 (0.39; 1.10)	0.81 (0.47; 1.38)	0.383	
BMI ≥26.1 kg/m ²	1 (ref)	0.87 (0.52; 1.45)	0.75 (0.44; 1.29)	0.304	
22:5n-3 (docosapentaenoic acid)					0.932
BMI <26.1 kg/m ²	1 (ref)	0.69 (0.41; 1.17)	0.54 (0.30; 0.98)	0.04	
BMI ≥26.1 kg/m ²	1 (ref)	0.69 (0.40; 1.18)	0.67 (0.37; 1.18)	0.16	
22:6n-3 (docosahexaenoic acid)					0.726

BMI <26.1 kg/m ²	1 (ref)	1.04 (0.61; 1.80)	1.05 (0.61; 1.81)	0.862	
BMI ≥26.1 kg/m ²	1 (ref)	0.77 (0.44; 1.32)	1.33 (0.80; 2.23)	0.248	
Grouping					
Total saturated fatty acids					0.065
BMI <26.1 kg/m ²	1 (ref)	1.10 (0.63; 1.90)	1.36 (0.78; 2.40)	0.273	
BMI ≥26.1 kg/m ²	1 (ref)	0.78 (0.46; 1.32)	0.76 (0.44; 1.31)	0.308	
Total <i>cis</i> monounsaturated fatty acids					0.653
BMI <26.1 kg/m ²	1 (ref)	0.98 (0.57; 1.67)	1.14 (0.66; 1.97)	0.645	
BMI ≥26.1 kg/m ²	1 (ref)	2.19 (1.28; 3.75)	1.56 (0.90; 2.70)	0.141	
Total <i>cis</i> n-6 polyunsaturated fatty acids					0.874
BMI <26.1 kg/m ²	1 (ref)	0.84 (0.49; 1.44)	0.88 (0.51; 1.53)	0.665	
BMI ≥26.1 kg/m ²	1 (ref)	0.76 (0.46; 1.29)	0.68 (0.40; 1.16)	0.151	
Total <i>cis</i> n-3 polyunsaturated fatty acids					0.988
BMI <26.1 kg/m ²	1 (ref)	0.67 (0.39; 1.15)	0.87 (0.51; 1.48)	0.568	
BMI ≥26.1 kg/m ²	1 (ref)	0.74 (0.44; 1.26)	1.07 (0.64; 1.79)	0.802	
Long-chain n-6/n-3 PUFA ratio					0.924
BMI <26.1 kg/m ²	1 (ref)	1.01 (0.58; 1.74)	1.22 (0.70; 2.12)	0.482	
BMI ≥26.1 kg/m ²	1 (ref)	0.89 (0.53; 1.51)	0.88 (0.52; 1.50)	0.648	
Total <i>trans</i> ruminant fatty acids					0.370
BMI <26.1 kg/m ²	1 (ref)	0.90 (0.52; 1.55)	0.73 (0.41; 1.30)	0.288	
BMI ≥26.1 kg/m ²	1 (ref)	1.11 (0.65; 1.87)	1.25 (0.69; 2.25)	0.464	
Total <i>trans</i> industrial fatty acids					0.829
BMI <26.1 kg/m ²	1 (ref)	1.22 (0.71; 2.12)	1.18 (0.66; 2.13)	0.574	
BMI ≥26.1 kg/m ²	1 (ref)	1.10 (0.65; 1.87)	1.06 (0.57; 1.95)	0.830	
Desaturation index					
DI₁₆ (16:1n-7c/16:0)					0.311
BMI <26.1 kg/m ²	1 (ref)	1.09 (0.64; 1.87)	1.26 (0.73; 2.18)	0.395	

BMI ≥ 26.1 kg/m ²	1 (ref)	1.53 (0.90; 2.59)	1.57 (0.90; 2.73)	0.115	0.447
DI₁₈ (18:1n-9c/18:0)					
BMI <26.1 kg/m ²	1 (ref)	0.86 (0.49; 1.48)	1.25 (0.73; 2.14)	0.415	
BMI ≥ 26.1 kg/m ²	1 (ref)	1.63 (0.96; 2.77)	1.40 (0.81; 2.41)	0.237	

*Unconditional logistic regression adjusted for matching variables (sex, age at blood collection, data and time at blood collection, fasting status, pill/hormone replacement treatment), body mass index, height, history of diabetes mellitus, tobacco smoking, alcohol intake, years of education, physical activity.

†Cut-points of tertiles determined on control individuals.

‡Median level of BMI determined on control individuals.

§Obtained by modelling the cut-points of tertiles as continuous variable.

§Obtained by modelling the interaction term between plasma phospholipid FAs and BMI as continuous variables.

Supplementary Table 3. Multivariable odds ratios (ORs) and 95% confidence intervals (95% CIs) for association between plasma phospholipid fatty acid (percentage of total fatty acids) and pancreatic cancer risk stratified by smoking status at recruitment*

Plasma phospholipid fatty acids	Tertiles of plasma phospholipid fatty acids [†]			P-trend [‡]	P interaction [§]
	T1 (Ref)	T2	T3		
Saturated fatty acids					
15:0 (pentadecanoic acid)					0.551
Non-smokers‡	1 (ref)	1.15 (0.76; 1.72)	0.79 (0.49; 1.28)	0.386	
Current smokers	1 (ref)	0.69 (0.31; 1.54)	0.90 (0.36; 2.23)	0.743	
16:0 (palmitic acid)					0.509
Non-smokers	1 (ref)	0.94 (0.62; 1.44)	1.05 (0.68; 1.62)	0.831	
Current smokers	1 (ref)	0.68 (0.28; 1.68)	1.18 (0.53; 2.64)	0.617	
17:0 (heptadecanoic acid)					0.394
Non-smokers	1 (ref)	0.61 (0.40; 0.93)	0.72 (0.46; 1.15)	0.147	
Current smokers	1 (ref)	1.15 (0.51; 2.56)	0.58 (0.23; 1.47)	0.289	
18:0 (stearic acid)					0.988
Non-smokers	1 (ref)	0.87 (0.57; 1.33)	0.93 (0.60; 1.44)	0.761	
Current smokers	1 (ref)	1.38 (0.62; 3.10)	0.84 (0.35; 2.02)	0.755	
Cis monounsaturated fatty acids					
16:1n-7 (palmitoleic acid)					0.639
Non-smokers	1 (ref)	1.07 (0.71; 1.63)	1.21 (0.79; 1.85)	0.385	
Current smokers	1 (ref)	1.61 (0.68; 3.79)	2.01 (0.87; 4.68)	0.109	
18:1n-9 (oleic acid)					0.305
Non-smokers	1 (ref)	1.15 (0.76; 1.73)	0.97 (0.63; 1.48)	0.887	
Current smokers	1 (ref)	1.55 (0.67; 3.58)	1.93 (0.82; 4.53)	0.136	
Trans monounsaturated fatty acids					
18:1n-9t/12t (elaidic acid)					0.622
Non-smokers	1 (ref)	1.00 (0.64; 1.55)	1.01 (0.63; 1.63)	0.970	
Current smokers	1 (ref)	2.78 (1.16; 6.70)	3.27 (1.21; 8.84)	0.023	
18:1n-7t (vaccenic acid)					0.914

Non-smokers	1 (ref)	1.07 (0.70; 1.64)	1.13 (0.71; 1.79)	0.604	
Current smokers	1 (ref)	1.25 (0.55; 2.88)	1.18 (0.50; 2.78)	0.693	
<i>Cis</i> n-6 polyunsaturated fatty acids					
18:2n-6 (linoleic acid)					0.695
Non-smokers	1 (ref)	0.72 (0.47; 1.09)	0.72 (0.47; 1.10)	0.120	
Current smokers	1 (ref)	2.55 (1.10; 5.89)	1.68 (0.70; 4.06)	0.279	
18:3n-6 (γ -linolenic acid)					0.089
Non-smokers	1 (ref)	0.99 (0.65; 1.51)	0.91 (0.61; 1.38)	0.674	
Current smokers	1 (ref)	0.79 (0.34; 1.83)	1.40 (0.65; 3.02)	0.399	
20:3n-6 (di-homo- γ -linolenic acid)					0.314
Non-smokers	1 (ref)	1.24 (0.81; 1.89)	1.30 (0.84; 2.03)	0.242	
Current smokers	1 (ref)	0.85 (0.36; 1.98)	1.30 (0.57; 3.00)	0.519	
20:4n-6 (arachidonic acid)					0.997
Non-smokers	1 (ref)	0.85 (0.55; 1.30)	1.17 (0.77; 1.77)	0.428	
Current smokers	1 (ref)	1.30 (0.56; 3.01)	1.20 (0.50; 2.88)	0.689	
Conjugated linoleic acids					
9c11t + 10t12c					0.661
Non-smokers	1 (ref)	0.84 (0.55; 1.28)	0.77 (0.48; 1.22)	0.259	
Current smokers	1 (ref)	1.91 (0.85; 4.33)	1.63 (0.60; 4.40)	0.304	
<i>Cis</i> n-3 polyunsaturated fatty acids					
18:3n-3 (α -linolenic acid)					0.692
Non-smokers	1 (ref)	0.82 (0.54; 1.24)	0.75 (0.48; 1.15)	0.183	
Current smokers	1 (ref)	0.82 (0.35; 1.89)	0.62 (0.25; 1.52)	0.295	
20:5n-3 (eicosapentaenoic acid)					0.138
Non-smokers	1 (ref)	0.80 (0.53; 1.22)	0.96 (0.63; 1.45)	0.833	
Current smokers	1 (ref)	0.83 (0.38; 1.83)	0.37 (0.16; 0.89)	0.034	
22:5n-3 (docosapentaenoic acid)					0.405
Non-smokers	1 (ref)	0.96 (0.63; 1.47)	0.61 (0.38; 0.98)	0.046	
Current smokers	1 (ref)	0.98 (0.43; 2.25)	0.72 (0.29; 1.75)	0.469	
22:6n-3 (docosahexaenoic acid)					0.002

Non-smokers	1 (ref)	0.93 (0.60; 1.43)	1.43 (0.95; 2.17)	0.074	
Current smokers	1 (ref)	0.49 (0.21; 1.14)	0.31 (0.13; 0.76)	0.009	
Grouping					
Total saturated fatty acids					0.410
Non-smokers	1 (ref)	1.24 (0.81; 1.88)	1.08 (0.69; 1.69)	0.736	
Current smokers	1 (ref)	0.70 (0.30; 1.61)	0.94 (0.41; 2.16)	0.897	
Total <i>cis</i> monounsaturated fatty acids					0.401
Non-smokers	1 (ref)	1.06 (0.70; 1.60)	0.98 (0.64; 1.50)	0.941	
Current smokers	1 (ref)	1.88 (0.80; 4.37)	1.70 (0.72; 4.02)	0.249	
Total <i>cis</i> n-6 polyunsaturated fatty acids					0.300
Non-smokers	1 (ref)	0.89 (0.59; 1.33)	0.68 (0.44; 1.05)	0.087	
Current smokers	1 (ref)	0.73 (0.32; 1.67)	1.41 (0.63; 3.18)	0.401	
Total <i>cis</i> n-3 polyunsaturated fatty acids					0.003
Non-smokers	1 (ref)	0.76 (0.49; 1.17)	1.34 (0.89; 2.02)	0.140	
Current smokers	1 (ref)	0.41 (0.18; 0.93)	0.26 (0.11; 0.62)	0.002	
Long-chain n-6/n-3 PUFA ratio					0.010
Non-smokers	1 (ref)	0.88 (0.58; 1.34)	0.79 (0.52; 1.22)	0.291	
Current smokers	1 (ref)	1.81 (0.75; 4.38)	3.40 (1.39; 8.34)	0.007	
Total <i>trans</i> ruminant fatty acids					0.525
Non-smokers	1 (ref)	0.92 (0.60; 1.41)	0.89 (0.56; 1.40)	0.608	
Current smokers	1 (ref)	2.21 (0.94; 5.15)	1.00 (0.40; 2.50)	0.929	
Total <i>trans</i> industrial fatty acids					0.583
Non-smokers	1 (ref)	1.09 (0.71; 1.68)	0.88 (0.55; 1.42)	0.605	
Current smokers	1 (ref)	1.53 (0.65; 3.58)	2.04 (0.79; 5.23)	0.139	
Desaturation index					
DI₁₆ (16:1n-7c/16:0)					0.708
Non-smokers	1 (ref)	1.14 (0.75; 1.73)	1.17 (0.76; 1.80)	0.471	
Current smokers	1 (ref)	1.81 (0.79; 4.14)	1.79 (0.76; 4.20)	0.186	
DI₁₈ (18:1n-9c/18:0)					0.398

Non-smokers	1 (ref)	1.02 (0.67; 1.55)	1.06 (0.70; 1.62)	0.770
Current smokers	1 (ref)	1.32 (0.55; 3.18)	2.80 (1.18; 6.64)	0.017

*Unconditional logistic regression adjusted for matching variables (sex, age at blood collection, data and time at blood collection, fasting status, pill/hormone replacement treatment), body mass index, height, history of diabetes mellitus, tobacco smoking, alcohol intake, years of education, physical activity.

†Cut-points of tertiles determined on control individuals in each genotypic group separately.

‡Non-smokers included former and never smokers.

§Obtained by modelling the cut-points of tertiles as continuous variable.

§Obtained by modelling the interaction term between plasma phospholipid FAs as continuous variable and smoking status as dichotomous variable.

