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ORIGINAL ARTICLE

Pancreatic cancer risk is modulated by inflammatory potential of diet and ABO genotype: a consortia-based evaluation and replication study

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Abstract

Diets with high inflammatory potential are suspected to increase risk for pancreatic cancer (PC). Using pooled analyses, we examined whether this association applies to populations from different geographic regions and population subgroups with varying risks for PC, including variation in ABO blood type. Data from six case–control studies (cases, *n* = 2414; controls, *n* = 4528) in the Pancreatic Cancer Case–Control Consortium (PanC4) were analyzed, followed by replication in five nested case–control studies (cases, *n* = 1268; controls, *n* = 4215) from the Pancreatic Cancer Cohort Consortium (PanScan). Two polymorphisms in the ABO locus (rs505922 and rs8176746) were used to infer participants' blood types. Dietary questionnaire-derived nutrient/food intake was used to compute energy-adjusted dietary inflammatory index (E-DII®) scores to assess inflammatory potential of diet. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable-adjusted logistic regression. Higher E-DII scores, reflecting greater inflammatory potential of diet, were associated with increased PC risk in PanC4 [OR_{Q5} versus $_{Q1}$=2.20, 95% confidence interval (CI) = 1.85–2.61, $P_{trend} < 0.0001$; $OR_{continuous}$ = 1.20, 95% CI = 1.17–1.24], and PanScan (OR_{Q5} versus $_{Q1}$ = 1.23, 95% CI = 0.92–1.66, P_{trend} = 0.008; $OR_{continuous}$ = 1.09, 95% CI = 1.02–1.15). As expected, genotype-derived non-O blood type was associated with increased PC risk in both the PanC4 and PanScan studies. Stratified analyses of associations between E-DII quintiles and PC by genotype-derived ABO blood type did not show interaction by blood type ($P_{interaction}$ = 0.10 in PanC4 and $P_{interaction}$=0.13 in PanScan). The results show that consuming a pro-inflammatory diet and carrying non-O blood type are each individually, but not interactively, associated with increased PC risk.

Abbreviations

BMI	body mass index
CI	confidence interval
DHQ	diet history questionnaire
E-DII	energy-adjusted dietary inflammatory index
FFQ	food frequency questionnaire
IL	interleukin
OR	odds ratio
PanC4	Pancreatic Cancer Case–Control Consortium
PanScan	Pancreatic Cancer Cohort Consortium
PC	pancreatic cancer
TNF	tumor necrosis factor

Introduction

Pancreatic cancer (PC) is a major cause of cancer-related death in developed countries (1,2). In the United States, PC has surpassed breast cancer to become the fourth leading cause of cancer death in men and women combined, with a 5-year survival of only 8% (3). Established risk factors for PC include a positive family history of PC, cigarette smoking, pre-existing diabetes mellitus, non-O ABO blood type, chronic pancreatitis and obesity (2,4,5). Because of the extremely poor prognosis of PC, identifying additional modifiable risk factors for PC is crucial for prevention efforts (2). Epidemiological studies suggest that diet plays a plausible role in PC development (6,7). However, the association between dietary habits and PC is unclear, partly because diet is a complex exposure and its impact is probably most relevant a decade or more before PC diagnosis. Additionally, the assessment of individual dietary components or single nutrients in relation to PC risk, which has yielded mixed results (7–10), does not reflect the overall quality of a person's diet; the absence of this information could obscure important clues about the role of whole diet on PC risk.

Approaches that assess the whole diet have the potential to take into account interactions between dietary components and can provide insight into whether certain food patterns foster favorable or deleterious changes in the intermediate pathway(s) of a disease process (11). On this premise, the dietary inflammatory index (DII®) was developed and construct-validated as a tool to assess inflammatory potential of the diet (12,13). The DII scores up to 45 dietary components based on evidence from published literature showing whether each component increases, decreases or has no relationship to the following circulating inflammatory biomarkers: interleukin 1 beta (IL-1β), IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (12). The inflammatory potential of a person's diet is determined by summing inflammatory index scores across the dietary components. Based on the DII, two previous studies reported increased PC risk for individuals with greater dietary inflammatory potential (14,15); however, questions remain as to the validity and consistency of the association, and applicability of the findings to populations from different geographic regions and population subgroups with varying environmental and genetic risks for PC.

ABO blood type is an established genetic risk factor for PC, and is determined by the *ABO* gene, located on chromosome 9q34.1 (5,16–18). *ABO* encodes glycosyltransferase enzymes that catalyze the attachment of specific carbohydrate molecules to the H antigen (19). The association of ABO blood type with PC risk was first reported in 1960, with nearly consistent results from studies published since then (18). Individuals with type O blood have a lower risk of developing PC than those with blood types A, B or AB (18). Variation in ABO blood type has been associated also with varying levels of circulating inflammatory markers (e.g. intercellular adhesion molecule-1, E-selectin and TNF-a) (20–23), suggesting that inflammation may link ABO blood type to PC risk. It is therefore plausible that ABO blood type might act in concert with modifiable inflammation modulators, such as cigarette smoking or pro-inflammatory diet, to increase PC risk further.

The primary aim of this study was to examine the association between dietary inflammatory potential, as measured by the DII, and PC risk in a large, multicenter, pooled analysis of individual-level data from six studies in the Pancreatic Cancer Case–Control Consortium (PanC4), followed by replication of findings in five nested case–control studies from the Pancreatic Cancer Cohort Consortium (PanScan). The secondary aim was to investigate whether an association between a pro-inflammatory dietary pattern and PC is modulated by known risk factors of PC, including ABO blood type and cigarette smoking. All initial

analyses were performed using data from the retrospective case–control studies in PanC4, followed by replication using data from the prospective cohorts in PanScan.

Materials and methods

For the initial analyses, data on 2450 individuals with incident PC (cases) and 4562 non-cancer controls were obtained directly from PanC4 investigators at Mayo Clinic (14), University of Minnesota (UMN) (24), MD Anderson Cancer Center (MDACC) (25), University of California, San Francisco (UCSF) (26), Yale University (16) and Milan and Pordenone provinces in Italy (27). The cases and controls were obtained through collaboration in PanC4 (28,29). The data from the PanC4 studies were combined into a single dataset following a standardized process for data harmonization (29). For the replication analyses, we obtained prospectively collected dietary data and covariates on 1271 incident PC cases matched to 4249 controls by PanScan investigators (28,30,31) from the following studies: Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (32); Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial (33); New York University Women's Health Study (NYU-WHS) (34); European Prospective Investigation into Cancer and Nutrition (EPIC) (35); and Shanghai Men's and Women's Health Study (SMWHS) (36). At a minimum, all of the PanScan studies matched controls to cases based on year of birth (in 5-year groups), sex and self-reported race/ethnicity. Some performed more robust matching for age, such as age at baseline or age at blood draw (5-year age groups) and/or additional matching for smoking, date or time of day of fasting blood draw and years of follow-up (37). Data from the PanScan studies also were harmonized following a standardized protocol (37) and combined into a single data set for analysis. Detailed descriptions of each study, including recruitment periods, recruitment methods and design are provided in Supplementary Tables 1 and 2, available at *Carcinogenesis* Online. Structured questionnaires were administered in each study to collect health-related information that included demographics, personal and family health history, smoking history and anthropometry. Summaries of the data obtained from each study are provided in Supplementary Tables 3 and 4, available at *Carcinogenesis* Online. All participating studies previously received ethics approval from their respective Institutional Review Board (IRB). Additional approval was obtained from the Mayo Clinic IRB for the pooled analyses.

Data received from the PanC4 studies included information on age at diagnosis or recruitment (controls); sex; race/ethnicity; usual adult weight and height; smoking status (never, former, current and number of cigarettes smoked per day, and smoking duration for former and current smokers); personal history of diabetes (yes, no); and first-degree family history of PC (yes/no). For this study, participants who reported smoking <100 cigarettes in their lifetime were considered non-smokers. Pack-years of smoking were calculated by multiplying the number of packs smoked per day (20 cigarettes per pack) by the number of years of smoking. Usual adult height and weight were used to calculate body mass index (BMI) in kg/m^2. One of the PanC4 studies (UMN) did not have information on height or weight; therefore, we created a separate category for participants with missing information on BMI, and BMI was categorized as <25, 25–29, ≥30 kg/m^2 and unknown. Data obtained from the PanScan studies included previously harmonized data on age and date of PC diagnosis for cases, BMI, smoking status, pack-years of smoking, personal history of diabetes and first-degree family history of PC. The data were categorized similarly for the PanC4 and the PanScan studies for analyses (Supplementary Tables 3 and 4, available at *Carcinogenesis* Online).

Assessment of ABO blood type

One tag single nucleotide polymorphism (SNP, rs505922) and one functional SNP (rs8176746) in the *ABO* locus were used to infer participants' blood types. Four of the PanC4 studies (Mayo, MDACC, UCSF and Yale) had the genotype data required to identify ABO blood type, and while all five PanScan studies had genotype data, not all individuals in the studies had the *ABO* SNP data (Supplementary Tables 3 and 4, available at *Carcinogenesis* Online). All participants who had *ABO* SNP data were genotyped in either the PanScan I or PanScan II GWAS (28,30) or the PanC4 GWAS (38). The genotyping methods and quality control measures have been published (28,30,38). The T allele of rs505922 tags the O blood type, while the A allele of rs8176746 determines the B blood type, and a haplotype of the two SNPs identifies the A blood type (39). Thus, participants who carry both the TT genotype of rs505922 and the CC genotype of rs8176746 were coded as having type O blood, and all others were coded as having a non-O blood type, as has been done previously (17,18,39).

Dietary assessment

Diet was assessed in each study with validated food frequency questionnaires (FFQ) (14,16,24–27,32,34–36) or diet history questionnaires (DHQ) (33). All of the dietary instruments used in the participating studies were designed to measure usual dietary habits; however, the periods of diet assessment differed among studies, particularly among the PanC4 studies (Supplementary Tables 5 and 6, available at *Carcinogenesis* Online). Three of the PanC4 studies (UMN, MDACC and UCSF) adapted the Willett FFQ (40), which asked participants to recall their dietary intake in the 12 months prior to diagnosis or recruitment (controls) and included questions about usual frequency of intake. In the UMN study, the Willett FFQ was modified slightly to include foods common in the upper Midwestern region of the United States (24). The FFQ used in the Italian study asked about dietary habits in the 2 years prior to diagnosis or recruitment and included questions on usual frequency and usual portion size (27). In the Mayo and Yale studies, cases and controls were asked to recall their usual dietary intake in the previous 5 years or during the previous 1–5 years, respectively. In the Mayo study, there was an additional question asking if participants had changed their diet in the last 5 years; those who indicated they had changed their diet were excluded from the analyses. Both the Mayo and Yale studies included questions on intake frequency but did not ask about portion size; thus, portion size was assumed to be medium intake for all items. The dietary instruments used in the PanScan studies asked participants to recall intake in the 12 months prior to enrollment and asked about usual portion size and frequency of intake. Some of the PanScan studies collected additional follow-up dietary information; however, only the baseline dietary data were used in this study. In both PanC4 and PanScan, participants' usual nutrient intake from various foods was estimated in each study by linking the FFQ or DHQ responses to regionally appropriate nutrient databases. Dietary supplement use was not assessed in the present analysis.

Calculation of the E-DII Score

Food and nutrient estimates obtained from the dietary questionnaires were used to calculate energy-adjusted DII (E-DII) scores (41). In brief, the DII classifies an individual's diet from the extremes of anti-inflammatory to pro-inflammatory, with the ability to adapt to various populations across the globe. The DII scores are based on information derived from a review of 1943 studies published between 1950 and 2010, which assessed the associations of various dietary factors on six commonly studied inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-1, TNF-α and C-reactive protein. Scores were assigned to each DII component (i.e. food parameter) based on the overall evidence from the publications indicating whether that food parameter increased (+1), decreased (–1) or had no effect (0) on the six inflammatory biomarkers. In total, 45 food parameters that included various micro- and macronutrients and whole foods were identified in the search and scored (41). After weighting by study design, adjusting for the size of the literature pool, and calculating z scores for intake of the food parameters compared with mean energy-adjusted global intakes (based on standard intake of 1000 kcal), all food parameter-specific DII scores were summed to derive an overall E-DII score for each participant, with higher E-DII scores reflecting a more pro-inflammatory diet (42).

Among the PanC4 studies, UMN had the largest number of food parameters (n = 30) used for calculating the E-DII and Yale had the least number (n = 18) (Supplementary Table 5, available at *Carcinogenesis* Online). Altogether, the PanC4 studies provided 35 unique food parameters out of the 45 parameters included in the development of the DII. Of the 35 unique food parameters derived from FFQs used in the PanC4 studies, nine were pro-inflammatory and were assigned positive inflammatory scores based on the E-DII scoring algorithm (carbohydrate, cholesterol, energy [calories], iron, protein, saturated fat, total fat, trans fat and vitamin B_{12}); 26 were assigned negative inflammatory scores (alcohol, anthocyanidins, β-carotene, caffeine, fiber, flavan-3-ol, flavones, flavonol,

flavonones, isoflavones, magnesium, monounsaturated fatty acids, niacin, omega 3 fatty acids, omega 6 fatty acids, polyunsaturated fatty acids, riboflavin, selenium, tea, thiamin, vitamins A, B_6, C, D and E and zinc). For the PanScan studies, EPIC's FFQ had the largest number of food parameters (n = 36) available for calculation of the E-DII, while NYU-WHS had the fewest (n = 19) (Supplementary Table 6, available at *Carcinogenesis* Online). Of thirty-nine unique food parameters derived from the dietary questionnaires used in the PanScan studies, nine were assigned positive inflammatory scores (carbohydrate, cholesterol, energy, iron, protein, saturated fat, total fat, trans fat and vitamin B_{12}), and 30 were assigned negative inflammatory scores (alcohol, anthocyanidins, b-carotene, caffeine, fiber, flavan-3-ol, flavones, flavonol, flavanone, folate, folic acid, garlic, isoflavones, magnesium, monounsaturated fatty acids, niacin, omega 3 fatty acid, omega 6 fatty acid, onions, polyunsaturated fatty acids, riboflavin, selenium, tea, thiamin, vitamins A, B_6, C, D, and E and zinc).

Exclusions

From the 2450 PC cases and 4562 controls in the PanC4 studies, we excluded participants whose FFQ responses resulted in implausible values for energy intake (<500 or >6000 kcal/day for men, 22 cases and 19 controls; <600 or >5000 kcal/day for women, 14 cases and 15 controls), leaving 2414 cases and 4528 controls for the PanC4 analyses. From the 1271 PC cases and 4249 controls in PanScan, we excluded individuals with implausibly high or low levels of energy intake (men, 2 cases and 29 controls; women, 1 case and 5 controls), leaving 1268 cases and 4215 controls for the PanScan analyses. Further details are provided in Supplementary Tables 7 and 8, available at *Carcinogenesis* Online.

Statistical analysis

Initial analyses were performed using the PanC4 studies, followed by replication analysis using the PanScan studies. For both PanC4 and PanScan, means and proportions were used to compare cases and controls on demographic, lifestyle and clinical characteristics. Unconditional logistic regression was used to calculate study-specific and pooled odds ratios (ORs) and their 95% CIs. The pooled analyses were performed by combining individual-level data from each study into a single, harmonized dataset. Before performing pooled analyses, we examined between-study heterogeneity using likelihood ratio X^2 statistics between logistic regression models with and without multiplicative interaction terms. We first examined the association between ABO blood type and PC risk in each study by comparing participants with non-O blood type to those with type O blood (referent group). The following pre-determined risk factors of PC were included in the model: age (continuous), sex, race (White, other), self-reported history of diabetes (yes, no), first-degree family history of PC (yes, no), BMI (< 25, 25–29, ≥30 kg/m^2, unknown) and pack-years of smoking within smoking category (never, former with <15 pack-years, former with ≥15 pack-years, current with <15 pack-years, current with ≥15 pack-years). All participants in the ATBC trial were current smokers and all had data on pack-years of smoking; thus, smoking was categorized as current with <15 pack-years versus current with ≥15 for this study. In addition to the covariates listed above, additional adjustment for study site was performed in the pooled analyses for the PanC4 and PanScan studies, separately. Results were plotted for visual comparison among studies.

The association between E-DII scores and PC risk was examined in two ways. First, the E-DII scores were modeled as a continuous variable for study-specific and pooled analyses, and results were plotted for visual comparison. We then categorized the E-DII scores into quintiles based on sex-specific control distribution categorized separately in each study. The sex- and study-specific quintiles were then pooled from each study into a single data set for the pooled analyses. In modeling the E-DII quintiles, we used the lowest quintile as the referent group to estimate ORs and 95% CIs for the higher quintiles. All E-DII association analyses were adjusted for the above-listed risk factors, with additional adjustment for study site in the pooled analyses. We also examined whether the association between E-DII quintiles and PC was homogenous across strata of selected risk factors of PC: smoking status (never, former, current), ABO blood type (O, non-O), age (< 65, ≥65 years), sex, race (White, other), BMI (<25, ≥25 kg/m^2, unknown), personal history of diabetes (yes, no) and first-degree family history of PC (yes, no). We examined also interaction between the E-DII and these risk factors (e.g. continuous E-DII variable [or E-DII quintile] by age group) using likelihood ratio X^2-tests. Further, we adjusted for pack-years of smoking (continuous) among former and current smokers in the stratified analysis by smoking status.

Results

Characteristics of the incident PC cases and controls included in the analyses are presented in Tables 1 and 2 for the six PanC4 and the five PanScan studies, respectively. The 2414 cases and 4528 controls in the PanC4 studies were roughly similar in distributions of age, sex and race, but the cases were more frequently obese than the controls (BMI ≥30 kg/m^2, 22% versus 18%) (Table 1). Higher proportions of current smokers and individuals with personal histories of diabetes or first-degree family histories of PC were noted for cases compared with controls. In the PanScan studies, the 1268 cases were, on average, older than the 4215 controls (67 versus 63 years, respectively) at baseline (Table 2). The cases had also higher percentages of women, racial minorities, current smokers and a slightly greater percentage of individuals with personal histories of diabetes than controls, but the cases and controls did not differ substantially regarding family history of PC.

Associations of non-O blood type and continuous E-DII variable, and PC risk

As shown in Figure 1, participants in the PanC4 studies with non-O blood type had increased PC risk compared with those with blood type O. Nearly all the study-specific ORs for the four PanC4 studies with genotype data showed a directionally consistent association, with the exception of MDACC. In the pooled analysis of the PanC4 studies, having a non-O blood type was associated with a 28% increased PC risk (pooled $OR_{non\text{-}O}$ versus $_O$ = 1.28, 95% CI = 1.13–1.44; $P_{heterogeneity}$ = 0.34). Similar results were observed for individuals in the PanScan studies with genotype data (cases n = 723, controls n = 772; pooled $OR_{non\text{-}O}$ versus $_O$ = 1.36, 95% CI = 1.07–1.75; $P_{heterogeneity}$ = 0.55) (Figure 2).

The E-DII scores in the pooled PanC4 data (cases and controls combined) ranged from a maximum anti-inflammatory score of −5.51 to a maximum pro-inflammatory score of 5.07, with mean of −0.86 (standard deviation [SD], 1.87) (Supplementary Table 5, available at *Carcinogenesis* Online). For the PanScan studies, the E-DII scores in the pooled data ranged from −5.58 to 5.45, with a mean (SD) of −0.17 (1.72) (Supplementary Table 6, available at *Carcinogenesis* Online). All of the PanC4 studies showed similar positive associations between a continuous E-DII score variable and PC risk (Figure 3), with an overall 20% increase in risk for every 1.87 unit increment (corresponding to the SD) in E-DII score (pooled $OR_{continuous}$ = 1.20, 95 % CI = 1.17–1.24, $P_{heterogeneity}$ = 0.78). None of the individual PanScan studies showed a statistically significant association between continuous E-DII score and PC risk; but the pooled analysis showed a significant association with a significantly smaller estimated magnitude of risk ($OR_{continuous}$ = 1.09, 95 % CI = 1.02–1.15, $P_{heterogeneity}$ = 0.05) (Figure 4); difference in effect estimate between-consortium, P-value = 0.0047.

We also evaluated an *a priori* hypothesis that an association between the E-DII scores and PC risk might reflect reverse causation, wherein subclinical PC may cause individuals to consume more easily digestible pro-inflammatory foods (e.g. diets rich in carbohydrate and fat). The possibility of reverse causation was examined by excluding cases diagnosed <2 years after recruitment into the PanScan studies. The results from this restricted pooled analysis (cases n = 1115; controls, n = 4215) is very similar to the results of the overall pooled analysis in

Table 1. Characteristics of participants in the six retrospective case–control studies from the Pancreatic Cancer Case–Control Consortium (PanC4)

	Case (*N* = 2414)		Control (*N* = 4528)	
Study	*N*	%	*N*	%
Mayo	925	38.3	1976	43.6
UMN	185	7.7	548	12.1
MDACC	388	16.1	426	9.4
UCSF	262	10.9	283	6.3
Yale	332	13.8	643	14.2
Italy	322	13.3	652	14.4
Age, years				
<49	179	7.4	422	9.3
49–54	210	8.7	427	9.4
55–59	308	12.8	610	13.5
60–64	408	16.9	695	15.3
65–69	425	17.6	771	17.0
70–74	408	16.9	806	17.8
≥75	476	19.7	797	17.6
Mean (SD)	65.1 (10.4)		64.3 (10.7)	
Sex				
Men	1357	56.2	2452	54.2
Women	1057	43.8	2076	45.8
Race				
Non-Hispanic White	2316	95.9	4417	97.5
Other	98	4.1	111	2.5
BMI, kg/m^2				
<25	790	32.7	1375	30.4
25–29	902	37.4	1714	37.9
≥30	535	22.2	829	18.3
Unknown[a]	187	7.7	610	13.5
Smoking status				
Never	943	39.1	2343	51.7
Former	1031	42.7	1749	38.6
Current	440	18.2	436	9.6
Pack-years of smoking within smoking category				
Never smoker	943	39.1	2343	51.7
Former				
<15 pack-years	368	15.2	768	17.0
≥15 pack-years	663	27.5	981	21.7
Current				
<15 pack-years	77	3.2	94	2.1
≥15 pack-years	363	15.0	342	7.6
	Case (*N* = 2414)		Control (*N* = 4528)	
Personal history of diabetes	*N*	%	*N*	%
No	1814	75.1	4068	89.8
Yes	579	24.0	460	10.2
Unknown	21	0.9	0	0.0
First-degree family history of PC				
No	2247	93.1	4347	96.0
Yes	159	6.6	165	3.6
Unknown	8	0.3	16	0.4

[a]Information on body mass index (BMI) was not collected in the UMN study (*n* = 733). The remaining (*n* = 64) were missing from other studies.
Abbreviations: Mayo, Mayo Clinic, MDACC, MD Anderson Cancer Center; PC, pancreatic cancer, UCSF, University of California, San Francisco; UMN, University of Minnesota; Yale, Yale University.

Table 2. Characteristics of participants in the five prospective studies from the Pancreatic Cancer Cohort Consortium (PanScan)

	Case (*N* = 1268)		Control (*N* = 4215)	
Cohort	*N*	%	*N*	%
ATBC	322	25.4	427	10.1
EPIC	533	42.0	381	9.0
NYU-WHS	11	0.9	13	0.3
PLCO	212	16.7	3313	78.6
SMWHS	190	15.0	81	1.9
Age, years				
<49	28	2.2	58	1.4
49–54	65	5.1	172	4.1
55–59	129	10.2	998	23.7
60–64	240	18.9	1357	32.2
65–69	276	21.8	1064	25.7
70–74	288	22.7	538	12.8
≥75	242	19.1	28	0.7
Mean (SD)	67.2 (8.3)		62.7 (5.9)	
Sex				
Men	889	70.1	3726	88.4
Women	379	29.9	489	11.6
Race				
Non-Hispanic White	1050	82.8	4049	96.1
Other	218	17.2	166	3.9
BMI, kg/m^2				
<25	497	39.2	1234	29.3
25–29.9	543	42.8	2019	47.9
≥30	218	17.2	929	22.0
Unknown	10	0.8	33	0.8
Smoking status				
Never	447	35.3	1543	36.6
Former	247	19.5	1860	44.1
Current	562	44.3	806	19.1
Unknown	12	0.9	6	0.1
Pack-years of smoking within smoking category				
Never smoker	447	35.3	1543	36.6
Former				
<15 pack-years	133	10.5	602	14.3
≥15 pack-years	114	9.0	1258	29.8
Current				
<15 pack-years	105	8.3	82	1.9
≥15 pack-years	457	36.0	724	17.2
Unknown	12	0.9	6	0.1
	Case (*N* = 1268)		Control (*N* = 4215)	
Personal history of diabetes	*N*	%	*N*	%
No	1088	85.8	3836	91.0
Yes	121	9.5	337	8.0
Unknown	59	4.7	42	1.0
First-degree family history of PC				
No	590	46.5	3656	86.7
Yes	24	1.9	70	1.7
Unknown	654	51.6	489	11.6

ATBC, alpha-tocopherol, Beta-Carotene Cancer Prevention Trial; EPIC, European Prospective Investigation into Cancer and Nutrition; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SMWHS, Shanghai Men's and Women's Health Study.

PanScan ($OR_{continuous}$ = 1.09, 95% CI=1.03–1.17, $P_{heterogeneity}$ = 0.05). Because Asian diets are substantially different from Western diets, we performed a separate subanalysis that excluded the SMWHS data; the association remained essentially the same but with significant heterogeneity between studies (cases *n* = 1078; controls *n* = 4134; $OR_{continuous}$ = 1.11, 95% CI = 1.04–1.19; $P_{heterogeneity}$ = 0.02). The SMWHS data were included in remaining analyses. In a *post hoc* sensitivity analysis, we examined

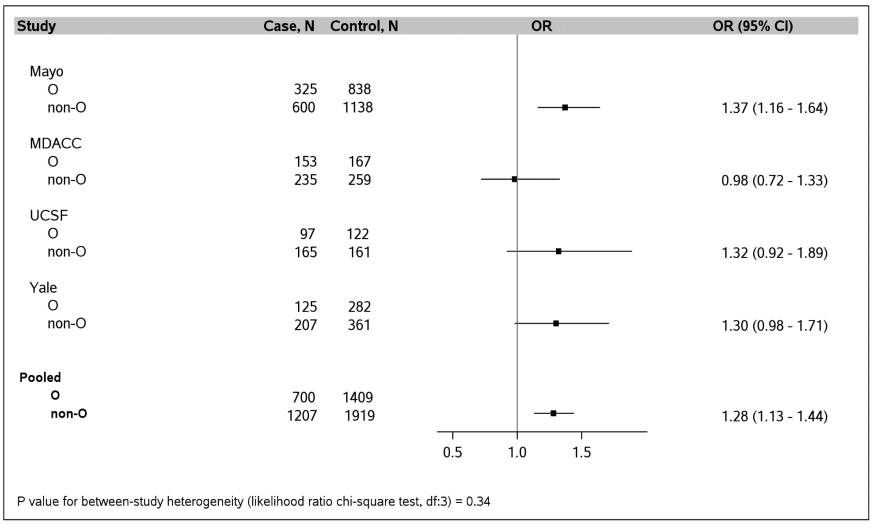

Figure 1. Non-O blood type is associated with increased pancreatic cancer risk compared with blood type O in the Pancreatic Cancer Case–Control (PanC4) studies, after adjusting for age (continuous), sex, race (White, other), personal history of diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (<25, 25-29, ≥30 kg/m^2, unknown), pack-years of smoking within smoking category (never, former with <15 pack-years, former with ≥15 pack-years, current with <15 pack-years, current with ≥15 pack-years), and with additional adjustment for study site (Mayo, MDACC, UCSF, Yale) in the pooled estimate. Genotype data were not available in the UMN and the Italian studies. Mayo, Mayo Clinic; MDACC, MD Anderson Cancer Center; UCSF, University of California at San Francisco; Yale, Yale University.

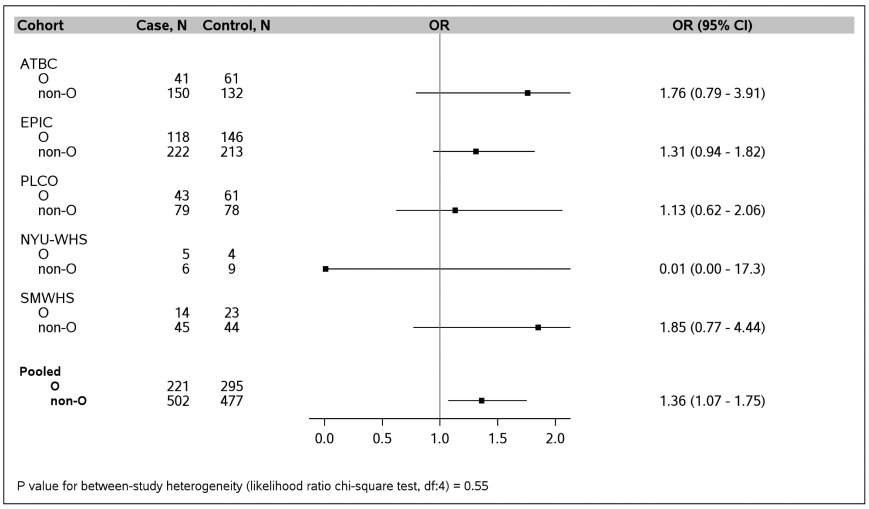

Figure 2. Increased odds of pancreatic cancer risk among individuals with non-O blood type compared with those with blood type O in the Pancreatic Cancer Cohort Consortium (PanScan) studies, after adjusting for age (continuous), sex, race (White, other), personal history of diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (<25, 25–29, ≥30 kg/m^2, unknown), pack-years of smoking within smoking category (never, former with <15 pack-years, former with ≥15 pack-years, current with <15 packyears, current with ≥15 pack-years), and with additional adjustment for study site (ATBC, EPIC, PLCO, NYUWHS and SMWHS) in the pooled estimate. Analyses were restricted to individuals with genotype data. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial; EPIC, European Prospective Investigation into Cancer and Nutrition; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SMWHS, Shanghai Men's and Women's Health Study.

the association between continuous E-DII variable and PC risk (1) with and without additional adjustment for alcohol intake and (2) with exclusion of alcohol from calculation of the E-DII but adjusted for alcohol intake in the model; the results did not differ materially from the results presented above (data not presented).

Associations of E-DII quintiles and stratified analyses by risk factors of PC

The E-DII scores were categorized into quintiles separately in each individual study based on sex-specific control distribution and then pooled after the sex- and study-specific categorization for analyses in PanC4 and PanScan, separately. For the PanC4 studies, we found a dose-dependent association between increasing E-DII quintiles and PC risk (OR_{Q5} versus $_{Q1}$ = 2.20, 95% CI = 1.85–2.61, P_{trend} < 0.001) (Table 3). Results from stratified analysis by smoking status in PanC4 showed a consistent pattern of increasing PC risk across quintiles of the E-DII in strata of never, former and current smokers. Because not all participating PanC4 studies had genotype data, we performed a separate analysis between E-DII quintiles and PC risk for studies with genotype data (Mayo, MDACC, UCSF and Yale), followed by stratified analysis by genotype-inferred ABO blood type. The association for these four studies is similar to that observed in the overall PanC4 analysis (OR_{Q5} versus $_{Q1}$=2.29, 95% CI = 1.88–2.80, P_{trend} < 0.001), and the association was evident in both individuals

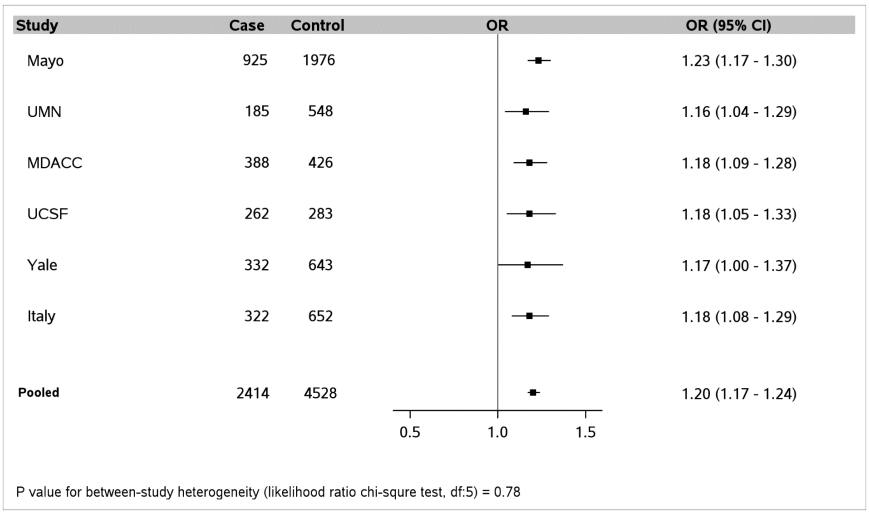

Figure 3. Every 1.87 units (i.e., standard deviation) increase in energy-adjusted dietary inflammatory index (DII) score (continuous variable) is associated with incremental risk of pancreatic cancer in each of the six Pancreatic Cancer Case–Control Consortium (PanC4) studies, in models that adjusted for age (continuous), sex, race (White, other), diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (< 25, 25-29, ≥30 kg/m^2, unknown), pack-years of smoking within smoking category (never, former with <15 pack-years, former with ≥15 pack-years, current with <15 pack-years, current with ≥15 pack-years) and with additional adjustment for study site (Mayo, UMN, MDACC, UCSF, Yale, and Italy) in the pooled estimate. Mayo, Mayo Clinic; MDACC, MD Anderson Cancer Center; UCSF, University of California at San Francisco; UMN, University of Minnesota; Yale, Yale University; Italy, Italian Case control Study.

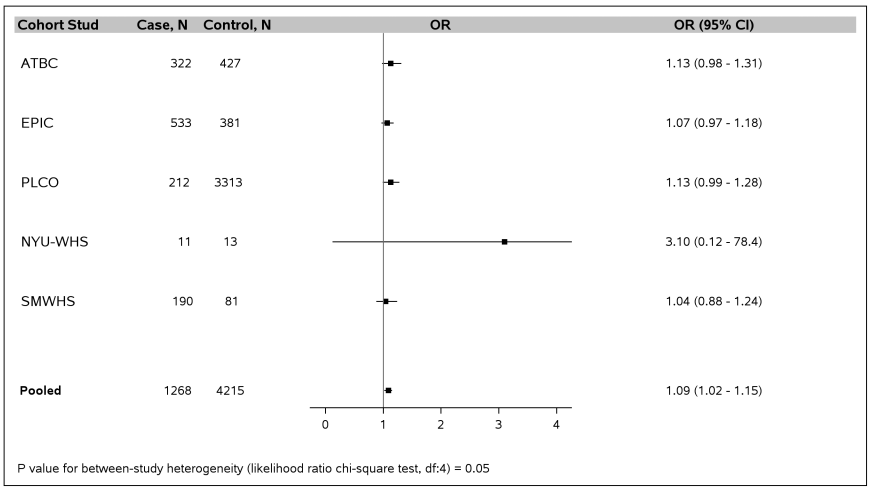

Figure 4. Association between every 1.72 units (i.e. standard deviation) increase in energy-adjusted dietary inflammatory index (DII) score (continuous variable) and pancreatic cancer risk among five Pancreatic Cancer Cohort Consortium (PanScan) studies, in models that adjusted for age (continuous), sex, race (White, other), diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (<25, 25–29, ≥30 kg/m^2, unknown), pack-years of smoking within smoking category (never, former with <15 pack-years, former with ≥15 pack-years, current with <15 pack-years, current with ≥15 pack-years) and with additional adjustment for study (ATBC, EPIC, PLCO, NYU-WHS and SMWHS) in the pooled estimate. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial; EPIC, European Prospective Investigation into Cancer and Nutrition; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SMWHS, Shanghai Men's and Women's Health Study.

with type O blood (OR_{Q5} versus $_{Q1}$=2.04, 95% CI = 1.49–2.81, P_{trend} < 0.001) and those with non-O blood type (OR_{Q5} versus $_{Q1}$ = 2.51, 95% CI = 1.94–3.26, P_{trend} < 0.001); P for interaction by genotype-inferred blood type = 0.10 (Table 3).

For the five PanScan studies, we found a non-significant increased OR for PC risk in the highest, compared with the lowest, E-DII quintile (OR_{Q5} versus $_{Q1}$ = 1.23, 95% CI = 0.92–1.66), with a statistically significant association comparing quintile 4 to quintile 1 (OR_{Q4} versus $_{Q1}$ = 1.47, 95% CI = 1.11–1.95), and a significant linear trend across quintiles (P_{trend} = 0.008) (Table 4). Unlike the PanC4 results, the stratified analysis by smoking status in PanScan did not show homogenous association across strata of never, former and current smokers; a significant association was found only among current smokers (OR_{Q5} versus $_{Q1}$ = 2.20, 95% CI = 1.29–3.74; P_{trend} = 0.003) but no interaction by smoking history was observed ($P_{interaction}$ = 0.62) (Table 4). Analyses restricted to individuals with genotype data in the PanScan studies also showed elevated OR in the highest E-DII quintile (OR_{Q5} versus $_{Q1}$=1.44, 95% CI = 0.99–2.12) with significant linear trend (P_{trend} = 0.02). Again, unlike the PanC4 results, when individuals in the PanScan studies were stratified by blood type, higher E-DII scores were associated with increased PC risk only among individuals with non-O blood type (OR_{Q5} versus $_{Q1}$ = 2.05, 95% CI = 1.26–3.35, P_{trend} = 0.002), but not those with type O blood. Nonetheless, in both PanScan and PanC4, no interaction was observed by genotype-inferred blood type or smoking status (all

Table 3. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for association between quintiles of the dietary inflammatory index (DII)[a] and pancreatic cancer in the six retrospective case–control studies, and stratified by smoking and ABO blood type; the Pancreatic Cancer Case–Control Consortium (PanC4)

	DII Scores						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* trend	*P* interaction[§]
Overall	313: 905	378: 908	468: 904	561: 906	694: 905		
N, case: control							
Age- and study-adjusted	1.00 (ref)	1.21 (1.01–1.45)	1.53 (1.29–1.82)	1.81 (1.53–2.14)	2.40 (2.04–2.84)	<0.0001	
Multivariable-adjusted[b]	1.00 (ref)	1.20 (1.00–1.45)	1.51 (1.27–1.81)	1.71 (1.44–2.04)	2.20 (1.85–2.61)	<0.0001	
Smoking status							
Never							
N, case: control	132: 489	163: 477	200: 489	209: 467	239: 421		
Multivariable-adjusted[b]	1.00 (ref)	1.37 (1.04–1.80)	1.58 (1.22–2.07)	1.66 (1.27–2.17)	2.30 (1.77–3.00)	<0.0001	
Former							
N, case: control	148: 371	172: 353	198: 338	241: 348	272: 339		
Multivariable-adjusted[b,c]	1.00 (ref)	1.21 (0.92–1.60)	1.50 (1.14–1.96)	1.77 (1.35–2.30)	2.12 (1.62–2.77)	<0.0001	
Current							
N, case: control	33: 45	43: 78	70: 77	111: 91	183: 145		
Multivariable-adjusted[b,c]	1.00 (ref)	0.75 (0.41–1.37)	1.26 (0.71–2.23)	1.66 (0.96–2.88)	1.70 (1.00–2.89)	0.001	0.60, 0.92
Among studies with genotype data							
	DII Scores[d]						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Overall	235: 666	308: 667	359: 664	460: 668	545: 663		
N, case: control							
Age- and study-adjusted	1.00 (ref)	1.33 (1.09–1.63)	1.59 (1.30–1.94)	2.02 (1.66–2.45)	2.62 (2.16–3.17)	<0.0001	
Multivariable-adjusted[b]	1.00 (ref)	1.30 (1.06–1.61)	1.52 (1.23–1.86)	1.86 (1.52–2.27)	2.29 (1.88–2.80)	<0.0001	
ABO blood type							
O							
N, case: control	88: 276	127: 271	115: 274	172: 292	198: 296		
Multivariable-adjusted[b]	1.00 (ref)	1.49 (1.07–2.08)	1.29 (0.92–1.80)	1.83 (1.33–2.52)	2.04 (1.49–2.81)	<0.0001	
Non-O							
N, case: control	147: 390	181: 396	244: 390	288: 376	347: 367		
Multivariable-adjusted[b]	1.00 (ref)	1.20 (0.91–1.57)	1.66 (1.28–2.15)	1.88 (1.45–2.44)	2.51 (1.94–3.26)	<0.0001	0.10, 0.12

Mayo, Mayo Clinic; MDACC, MD Anderson Cancer Center; UCSF, University of California at San Francisco; UMN, University of Minnesota; Yale, Yale University; Italy, Italian Case control Study.

[a]The dietary inflammatory index (DII) scores were energy-adjusted per 1000 calories consumed and categorized into quintiles based sex-specific distribution among controls separately in each of the six studies (Mayo, UMN, MDACC, UCSF, Yale, Italy).

[b]Adjusted for age (continuous), sex, race (White, other), diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (<25, 25–29, ≥30 kg/m^2, unknown), pack-years of smoking within smoking category (never, former with <15 pack-years, former with >15 pack-years, current with <15 pack-years, current with ≥15 pack-years), and study site (Mayo, UMN, MDACC, UCSF, Yale, Italy). No adjustment was done for a particular risk factor in the model that was stratified by that risk factor (e.g., no adjustment for cigarette smoking in smoking stratified analyses).

[c]Additional adjustment for pack-years of smoking among former and current smokers.

[d]The energy-adjusted DII variable was categorized into quintiles among controls in the four studies that had genotype data (Mayo, MDACC, UCSF, Yale) and the analysis was restricted to participants in these studies.

[§]The first interaction *P*-value was derived from use of the DII quintile variable (df = 4) and the second was derived from use of a continuous DII variable.

interaction *P*-values >0.05). Results for stratified analyses by age, sex, race, BMI, diabetes and family history of PC did not show interaction by any of these factors, except for personal history of diabetes in PanScan, but not PanC4 (Supplementary Tables 9 and 10, available at *Carcinogenesis* Online).

Discussion

We assessed associations of inflammatory potential of diet (measured by E-DII scores) and ABO blood type in relation to PC risk by pooling individual-level data from six retrospective case–control studies in PanC4, followed by replication using five case–control studies nested within prospective cohorts in PanScan. We found that consumption of a pro-inflammatory diet, reflected by higher E-DII scores, is associated with increased PC risk; the association was stronger for the retrospective PanC4 studies than for the prospective PanScan studies. In secondary analyses, we confirmed that genotype-inferred non-O blood type is associated with increased risk of PC, but did not find evidence of interaction between ABO blood type and

Table 4. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for association between quintiles of the dietary inflammatory index (DII)[a] and pancreatic cancer in the five nested case–control studies, and stratified by risk factors of pancreatic cancer; the Pancreatic Cancer Cohort Consortium (PanScan)

	DII Scores					*P* trend	*P* interaction[§]
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Pooled Overall	239: 844	267: 845	227: 841	303: 843	232: 842		
N, case: control							
Age- and study-adjusted	1.00 (ref)	1.08 (0.82–1.43)	1.09 (0.82–1.44)	1.64 (1.25–2.15)	1.39 (1.05–1.85)	0.001	
Multivariable-adjusted[b]	1.00 (ref)	1.04 (0.78–1.38)	1.03 (0.77–1.38)	1.47 (1.11–1.95)	1.23 (0.92–1.66)	0.008	
Smoking status							
Never							
N, case: control	100: 349	106: 368	80: 301	100: 278	61: 247		
Multivariable-adjusted[b]	1.00 (ref)	0.70 (0.45–1.09)	0.82 (0.51–1.30)	1.31 (0.83–2.07)	0.86 (0.52–1.43)	0.57	
Former							
N, case: control	63: 367	45: 333	44: 388	58: 387	37: 385		
Multivariable-adjusted[b,c]	1.00 (ref)	1.36 (0.73–2.54)	1.01 (0.54–1.87)	1.44 (0.78–2.65)	0.98 (0.49–1.96)	0.86	
Current							
N, case: control	73: 127	114: 144	102: 149	144: 176	129: 210		
Multivariable-adjusted[b,c]	1.00 (ref)	1.68 (0.98–2.89)	1.70 (0.99–2.93)	2.26 (1.33–3.84)	2.20 (1.29–3.74)	0.003	0.62, 0.70
Among individuals with genotype data							
	DII Scores[d]						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Pooled Overall	131: 154	143: 155	132: 154	166: 156	151: 152		
N, case: control							
Age- and study-adjusted	1.00 (ref)	1.09 (0.76–1.58)	1.15 (0.79–1.66)	1.54 (1.08–2.21)	1.58 (1.10–2.28)	0.003	
Multivariable-adjusted[b]	1.00 (ref)	1.01 (0.69–1.47)	1.07 (0.73–1.56)	1.40 (0.96–2.03)	1.44 (0.99–2.12)	0.02	
ABO blood type							
O							
N, case: control	48: 56	46: 61	45: 56	46: 59	36: 63		
Multivariable-adjusted[b]	1.00 (ref)	0.83 (0.45–1.54)	0.94 (0.50–1.74)	1.07 (0.57–1.99)	1.04 (0.39–1.43)	0.64	
Non-O							
N, case: control	83: 98	97: 94	87: 98	120: 97	115: 89		
Multivariable-adjusted[b]	1.00 (ref)	1.14 (0.71–1.85)	1.14 (0.70–1.85)	1.62 (1.01–2.61)	2.05 (1.26–3.35)	0.002	0.13, 0.07

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial; EPIC, European Prospective Investigation into Cancer and Nutrition; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial; SMWHS, Shanghai Men's and Women's Health Study.

[a]The dietary inflammatory index (DII) scores were energy-adjusted per 1000 calories consumed to account for differing levels of energy intake among participants and categorized into quintiles based on sex-specific distribution among controls in each cohort separately.

[b]Adjusted for age (continues), sex, race (White, other), diabetes (yes, no), family history of pancreatic cancer (yes, no), BMI (< 25, 25–29, ≥30 kg/m^2, unknown) and pack-years of smoking within smoking category (never, former with <15pack-years, former with >15 pack-years, current with <15 pack-years, current with ≥15 pack-years) and study site (ATBC, EPIC, PLCO, NYU-WHS, and SMWHS). No adjustment was done for a particular risk factor in the model that was stratified by the respective factor (e.g. no adjustment for cigarette smoking in smoking stratified analyses).

[c]Additional adjustment for pack-years of smoking among former and current smokers.

[d]The DII variable was categorized into quintiles among controls with genotype data and the analyses were restricted to individuals with genotype data.

[§]The first interaction *P*-value was derived from use of the DII quintiles (df = 4) and the second represent use of DII as a continuous variable.

E-DII scores on risk for PC in PanC4 or PanScan. Moreover, no consistent evidence of interaction by other risk factors of PC, including cigarette smoking, was observed. Together, the findings suggest that a pro-inflammatory dietary pattern and genotype-derived non-O blood type are each individually associated with increased PC risk, and that the two exposures do not interact to influence PC risk.

Two previous case–control studies conducted at Mayo Clinic (14) and in Italy (15) by our collaborators found that a higher E-DII score was associated with a 2.5-fold increased odds of PC risk. In this study, we replicated those findings in a large, multicenter retrospective case–control sample that included the two prior studies, followed by replication with prospectively collected dietary data from PanScan. In previous studies, the DII was construct-validated as a predictor of dietary inflammatory potential (12,13). The E-DII has been associated with serum levels of several pro-inflammatory cytokines, including IL-6, high-sensitivity C-reactive protein and TNF-α receptor 2, which reflects activation of the TNF-α system (12,13). A previous version of the DII was adapted by an independent group and was associated with plasma levels of IL-6, TNF-α, C-reactive protein and soluble intercellular adhesion molecule-1 (sICAM-1) (43). The mechanisms for the impact of diet-derived inflammation on PC risk might include increasing systemic levels of pro-inflammatory cytokines, which may reach the pancreas via the bloodstream. Furthermore, some pro-inflammatory food constituents, such as cholesterol and fat, are metabolized in the liver and can form reactive oxygen and nitrogen species, leading to DNA damage, dysregulation of tumor suppressor proteins and ultimately, neoplasia. Related to this, a higher inflammatory potential of diet has been associated with increased risk for hepatocellular carcinoma (44) and greater degree of liver damage (45).

Studies have shown that germline variation in ABO blood type is associated with risk of certain infectious diseases, cardiovascular disorders and cancer susceptibility (19). The observed increased PC risk associated with non-O blood type is consistent with findings from previous studies (18). However, the precise mechanism(s) underlying the association between blood type and PC is not clear, but might be partly explained by data from two non-cancer GWAS suggesting that antigens of the ABO blood type modulate systemic inflammatory processes (20,23). ABO blood type could thus be hypothesized to influence susceptibility to PC through this mechanism (17,19).

However, despite suggestions that ABO blood type may influence PC risk by modulating inflammation (5,17,19,30), we did not observe interaction between inflammatory potential of diet, and ABO blood type or cigarette smoking (a pro-inflammatory substance) in relation to PC risk. The lack of interaction suggests that these exposures may influence PC risk through different pathways, but could also be due to measurement error in the assessment of the exposures, particularly diet and smoking. Moreover, a common constraint for detection of interaction is the requirement of large sample sizes. While we had adequate sample sizes for the overall primary analyses, the sample sizes reduced substantially in the stratified groups. We sought to mitigate this by using a continuous E-DII variable which reduces the number of parameters (i.e. degrees of freedom) required in the statistical models for detection of interaction, but this also did not show significant interaction between inflammatory potential of diet with either ABO blood type or smoking history.

Limitations of this study include the potential for differential recall of dietary intake between cases and controls in the retrospective studies, which is reflected by higher ORs obtained from the retrospective PanC4 studies compared with the prospective PanScan studies. Since up to 30 different dietary components were used in the retrospective case–control studies to calculate the E-DII, variation in recall from study to study could have influenced the results to some extent. Furthermore, the case–control studies' recall-based questionnaire on dietary intake could have reflected dietary changes induced by subclinical disease (i.e. reverse causation). Although the 2-year lag analysis performed among the nested case–control studies in PanScan did not confirm this bias, it is plausible, nevertheless, that it exists in the retrospective case–control studies. Another observation was that some of the results from the stratified analyses were not entirely consistent between the PanC4 and PanScan data. Although trends of association were generally similar, there was more modest magnitude of association in PanScan compared to PanC4; this could be due to the inherent limitation of retrospective studies, including information and selection biases, or the relatively smaller sample sizes of the stratified groups in the prospective PanScan studies. One study (UMN) did not collect information on BMI, and information on diabetes, smoking, BMI, and in many of the participating studies, family history of PC were all based on self-report; thus, residual confounding by these factors is possible. Confounding by unmeasured factors also is a possible limitation. Most of the dietary questionnaires asked about food intake in the 12 months prior to enrollment in the studies. While the questionnaires were generally designed to measure usual diet, the 12-month timeframe may not adequately capture usual dietary patterns in the periods in a person's life that are most relevant to pancreatic tumorigenesis. Major strengths of the study include the use of data from a large, multicenter endeavor through our collaboration in PanC4, followed by replication analysis in PanScan. The large sample sizes made it possible to evaluate interaction by ABO blood type and cigarette smoking and other established risk factors for PC.

In summary, this study confirms and extends previous associations of higher inflammatory potential of diet and increased risk of PC. The results further show that while genotype-inferred non-O blood type is associated with increased PC risk, blood type and dietary inflammatory potential do not interact to influence PC risk. Reducing consumption of pro-inflammatory diet (e.g. high-fat, high-calorie diets) or pro-inflammatory food items may help reduce risk of PC in addition to other health benefits.

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