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Pancreatic cancer: associations of inflammatory potential of diet, cigarette smoking and long-standing diabetes

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Abstract

Epidemiologic studies show strong associations between pancreatic cancer (PC) and inflammatory stimuli or conditions such as cigarette smoking and diabetes, suggesting that inflammation may play a key role in PC. Studies of dietary patterns and cancer outcomes also suggest that diet might influence an individual's risk of PC by modulating inflammation. We therefore examined independent and joint associations between inflammatory potential of diet, cigarette smoking and long-standing (≥5 years) type II diabetes in relation to risk of PC. Analyses included data from 817 cases and 1756 controls. Inflammatory potential of diet was measured using the dietary inflammatory index (DII), calculated from dietary intake assessed via a 144-item food frequency questionnaire, and adjusted for energy intake. Information on smoking and diabetes were obtained via risk factor questionnaires. Associations were examined using multivariable-adjusted logistic regression. Higher DII scores, reflecting a more proinflammatory diet, were associated with increased risk of PC [odds ratio $(OR)_{Quintile\ 5\ versus\ 1}$ = 2.54, 95% confidence interval (CI) = 1.87–3.46, $P_{trend} < 0.0001$]. Excess risk of PC also was observed among former (OR = 1.29, 95% CI = 1.07–1.54) and current (OR = 3.40, 95% CI = 2.28–5.07) smokers compared with never smokers, and among participants with long-standing diabetes (OR = 3.09, 95% CI = 2.02–4.72) compared with nondiabetics. Joint associations were observed for the combined effects of having greater than median DII score, and being a current smoker (OR = 4.79, 95% CI = 3.00–7.65) or having long-standing diabetes (OR = 6.03, 95% CI = 3.41–10.85). These findings suggest that a proinflammatory diet may act as cofactor with cigarette smoking and diabetes to increase risk of PC beyond the risk of any of these factors alone.

Introduction

Pancreatic ductal adenocarcinoma constitutes approximately 90% of pancreatic cancer (PC) cases, and it has dismal 1- and 5-year survival rates of 28 and 7%, respectively (1). Reasons for the dismal survival include a generally very aggressive disease course, the lack of reliable methods to enable early detection and limited understanding of the disease etiology (2–4). Several lines of evidence suggest that inflammation plays a critical role in the pathogenesis of PC (5,6). Nearly one-fourth of all PC cases are attributable to cigarette smoking, which is a potent initiator and promoter of systemic inflammation (7,8). Chronic pancreatitis and type II diabetes mellitus (DM) are inflammatory diseases that have been associated with risk of PC (3,5,6). Body mass index (BMI) tends to correlate positively with chronic inflammation (9–11), and high BMI has been implicated in PC risk (12,13). Diet also is an important, yet poorly characterized, risk factor of PC (14,15). However, there are suggestions that diet might influence PC risk through modulation of inflammation (2,16). Inflammation may thus be a common factor that

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Abbreviations

BMI	body mass index
CI	confidence interval
DII	dietary inflammatory index
DM	type II diabetes mellitus
FFQ	food frequency questionnaire
IL	interleukin
OR	odds ratio
PC	pancreatic cancer
TNF-α	tumor necrosis factor alpha

underlies the roles of cigarette smoking, DM, BMI and potentially diet, in PC risk.

Although several nutrients and individual foods have been examined for their association with PC, results have been inconsistent (reviewed in refs. 2–4,7). However, studies examining dietary patterns have provided some important clues. The Western dietary pattern, which is characterized by high intake of red meat, refined grains and sugar-sweetened beverages, has been associated with increased levels of systemic inflammatory markers (17,18) and increased risk of PC (19). In contrast, the Mediterranean-style diet, which is rich in plant foods, whole grains and fish, has been associated with reduced levels of inflammatory markers (20,21) and reduced risk of PC (22). These observations suggest that assessing the overall quality of diet, instead of specific nutrients or individual foods, may provide better insight on the role of inflammation-modulating diet in PC. It was in this context that the dietary inflammatory index (DII) was developed (23) and construct-validated (23–27) as a predictor of inflammatory potential of diet. The DII is based on extensive review of the literature published between 1950 and 2010 that assessed effects of specific foods or food constituents on six inflammatory biomarkers [interleukin-1 beta (IL-1β), IL-4, IL-6, IL-10, tumor necrosis factor alpha (TNF-α) and C-reactive protein]. The DII was developed to be a summary measure of the inflammatory potential of habitual diet.

The purpose of this study was 2-fold: (i) to examine the association between the inflammatory potential of diet (as measured by the DII) and risk of PC, and (ii) to confirm previously reported associations between cigarette smoking, DM and BMI on risk of PC and to examine joint associations between each of these factors with the DII in relation to PC risk. These analyses sought to provide insight into shared pathway(s) that influence PC risk and to inform effective cancer prevention strategies.

Materials and methods

Study population

Data were obtained from the prospective Biospecimen Resource for Pancreas Research, a patient registry supported by the Mayo Clinic Specialized Program of Research Excellence (SPORE) in Pancreatic Cancer (http://tinyurl.com/MayoClinicPancreasResearch). An ultrarapid case finding process ensures that nearly 86% of PC cases identified at Mayo Clinic campuses are enrolled in the registry within 30 days of diagnosis, with an overall 2-week median time between first contact and enrollment (28,29). This study included cases of incident adenocarcinoma of the exocrine pancreas (World Health Organization histological classification of tumors of the exocrine pancreas codes: 8020/3, 8154/3, 8480/3, 8490/3, 8500/3, 8500/4, 8500/5, 8500/9, 8560/3 and 9997/3) evaluated at Mayo Clinic between 10 October 2000 and 13 January 2015. Cases were eligible if they were 18 years of age or older at the time of diagnosis and had completed all study questionnaires. Participation rate was 67% for cases. Our experience suggests that severe deterioration of health and rapid demise due to the cancer are the major reasons for nonparticipation among cases. The methods used to identify a pool of controls have been described previously (28,29). Briefly, controls were patients with no personal history of cancer except non-malignant skin cancer and were recruited from Mayo Clinic primary care clinics between 27 May 2004 and 20 March 2012. The controls for the current study were selected from this pool and were frequency matched to cases on age (in 5-year age groups), race and sex. A total of 1536 cases and 2180 age-, race- and sex-matched controls were available for analysis. This study was approved by the Mayo Clinic Institutional Review Board. All participants provided written informed consent.

Data collection

Cases and controls completed the same standardized questionnaire that sought information on demographics (age, sex and race/ethnicity), education, smoking history, anthropometry, personal and family health history, and dietary habits. Data on clinical attributes of PC (e.g. tumor subtypes and cancer stage) and information on dates of diagnosis of DM were abstracted from participants' medical records. Participants who reported they had smoked fewer than 100 cigarettes in their lifetime were considered as non-smokers and smoking status was categorized as never (<100 cigarettes) or ever (≥100 cigarette in a lifetime, with subcategories of current and former) smokers. Self-reported height and usual adult weight were used to calculate BMI in kg/m^2.

Diet assessment

Dietary data were ascertained using a scannable 144-item food frequency questionnaire (FFQ) (30,31), described in detail in our previous report (14). The FFQ was adapted from the National Cancer Institute's Diet History Food-Frequency Questionnaire (NCI-DHQ) (31) and was validated in a United States hospital-based population (32,33) and used in the New England Bladder Cancer Study (30). The FFQ was modified to include additional food items primarily related to meat intake and meat cooking/preparation/level of doneness (the latter information was not included in the calculation of the DII). The FFQ asked participants to report their intake of various foods including, frequency and food preparation methods. Portion size was assumed to be medium intake for all food items. A section of the FFQ solicited information on dietary supplement use, which included questions about multivitamins and single nutrient supplements along with usual dose and frequency of use. Responses to the questionnaire were linked to the NCI nutrient database via the Diet*Calc® software to calculate each participant's usual daily nutrient intake.

Calculation of the DII

DII scores were calculated from FFQ-derived nutrient estimates using methods detailed elsewhere (23). In brief, the DII was developed to classify individuals' diet from extremes of pro- to anti-inflammatory and with the ability to adapt to diverse populations worldwide. Hence, in developing the DII, a global food composition database was created based on nutrition surveys conducted in 11 countries around the world. The DII scores up to 45 food parameters including micronutrients and spices such as garlic, ginger, pepper, isoflavones and vitamins as well as macronutrients such as protein, carbohydrates and fat. In calculating the DII, a z-score was derived for each food parameter by subtracting the 'standard global mean' (obtained from the global database) from the amount estimated from the FFQ and dividing this value by the standard deviation. To minimize the effect of 'right skewing' (a common occurrence with dietary data), each z-score was converted to a centered percentile score by doubling the percentile value and subtracting 1. This was then multiplied by the respective food parameter inflammatory effect score (derived from a literature review and scoring of 1943 published articles) to obtain each subject's food parameter-specific DII score. All food parameter-specific DII scores were then summed to create the overall DII score for each subject in the study. Higher DII scores reflect a more proinflammatory diet and lower scores reflect a diet that is more anti-inflammatory. Validation of the DII in relation to biomarkers of inflammation has been published elsewhere (23,24).

The FFQ used in this study provided 28 of the 45 food parameters used in the calculating the DII score. This number of parameters is similar to that used in prior DII calculations based on FFQs (27,34–40). The parameters included in this study were as follows: alcohol; β-carotene; caffeine;

carbohydrates; cholesterol; fiber; iron; isoflavones; magnesium; monounsaturated fatty acids; *n* – 3 and *n* – 6 fatty acids; niacin; protein; energy; polyunsaturated fatty acids; riboflavin; saturated fat; selenium; thiamin; total fat; vitamins A, B_6, B_{12}, C, D and E; and zinc. DII scores were computed for dietary data with and without supplements. Energy intake was not included in calculating the DII; however, DII scores were energy adjusted using the density method (per 1000 calories consumed) to account for differing energy intakes between subjects.

Analytic sample

Data on 3716 cases and frequency-matched controls were considered for analyses. Because the FFQ asked, 'During the last 5 years, how often did you eat….?' to capture usual diet over the previous 5 years, we excluded participants who responded affirmatively to the question, 'Have you recently changed your diet?' and if the diet change occurred within the previous 5 years (cases: *n* = 691; controls: *n* = 369). To further improve the quality of the dietary data, we excluded participants who had 30 or more blank items on the FFQ (cases: *n* = 9; controls: *n* = 15) and those whose responses resulted in implausible values of energy intake (cases: *n* = 11, controls: *n* = 14). Energy intake was considered implausibly low or high among males if <500 or >6000 kcal/day and among females if <600 or >5000 kcal/day. We also excluded participants with missing data on any of the nutrients used for calculating the DII with the exception of dietary supplements (controls: *n* = 1). Participants with type I diabetes (cases: *n* = 6, controls: *n* = 12) and those with missing data on pack-years of cigarette smoking (cases: *n* = 2, controls: *n* = 13) also were excluded from the analyses. These exclusions yielded a final study sample consisting of 2573, with 817 cases and 1756 controls.

Statistical methods

Descriptive analyses were conducted using means and proportions to compare demographic and lifestyle factors between cases and controls. Unconditional logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). The association between inflammatory potential of diet and PC was assessed using quintiles of the DII variable based on the distribution among controls. Prior to evaluating the association between the DII and PC, we examined the distribution of the subject characteristic across DII quintiles among control subjects using analysis of variance and χ^2 tests for continuous and categorical variables, respectively. Analysis of the DII quintiles was performed with adjustment only for age (continuous) and with additional adjustment for sex, race (White, other), BMI (continuous), DM (i.e. yes, no), pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years, current with ≥20 pack-years) and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown). We also performed analyses stratified by sex using sex-specific DII quintiles based on distribution among respective controls and examined whether associations varied by cancer stage at presentation (resectable, locally advanced and metastatic). Linear trends across quintiles of the DII were examined by assigning each quintile its median value and then modeling these variables as continuous.

To maximize sample size for evaluation of joint associations, the DII variable was categorized into two levels (less than or equal to median and greater than median). Each main exposure variable (dichotomous DII, smoking, DM and BMI) was first examined independently in relation to PC risk. Joint association of the DII and cigarette smoking was measured in three ways: smoking status (never, former and current), pack-years of smoking (0, >0–9, 10–19 and ≥20 years) and pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years and current with ≥20 pack-years). ORs were computed for a composite variable that combines the DII with smoking status (2×3 variable), pack-years of smoking (2×4 variable) or pack-years of smoking within smoking categories (2×7 variable) using never smokers with less than or equal to median DII score as the referent group. Similar composite variables were created for evaluation of joint association between the DII with overall diagnosis of DM (no DM and DM) and with duration (no DM, 1–4 years, ≥5 years) using a common referent group (participants with less than or equal to median DII score and no history of DM). BMI was categorized into normal (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) and examined jointly with the DII using participants with less than or equal to median DII score and normal BMI as the referent group. A statistical test for multiplicative interaction also was performed between the dichotomous DII variable, and each main effect variable using likelihood ratio tests with appropriate degrees of freedom (41). A common constraint of statistical tests for interaction is that sample size requirements increase as the number of parameters (i.e. degrees of freedom) increase. Therefore, in order not to obscure potentially relevant interactions, we also examined quantitative additive and multiplicative interactions (42,43). This was done by calculating the expected OR for joint effect and comparing this value with the observed OR for joint association, under the null hypothesis that the observed OR is less than or equal to the expected OR. Expected ORs under the multiplicative model were calculated as the product of the main effects; expected ORs under the additive model were calculated as the sum of the main effects minus one (42–44). All statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC). Statistical tests were two sided, and *P* values <0.05 were considered statistically significant.

Results

Characteristics of the 817 PC cases and 1756 controls are shown in Table 1. On average, cases were about a year older than controls (66.7 versus 65.4 years). However, by design, the proportion of cases in each age, race and sex category was similar to that of controls. Compared with controls, cases were significantly more likely to be current or former smokers, were less educated and more likely to have a history of DM. Additionally, cases had a slightly higher BMI than controls.

Subject characteristics across DII quintiles

DII scores in this study overall ranged from a maximally anti-inflammatory score of –5.33 to a maximally proinflammatory score of +4.47, with a mean of –1.29 and a standard deviation (±SD) of 1.77. Mean DII score among cases and controls were –0.82 (±1.80) and –1.51 (±1.72), respectively. Table 2 presents the distribution of subject characteristics across quintiles of the DII among control subjects only. Higher DII quintiles indicate a more proinflammatory diet, whereas lower quintiles indicate a more anti-inflammatory diet. An inverse relationship was observed between age and the DII quintiles such that older subjects tended to have a more anti-inflammatory diet whereas younger subjects tended to have a more proinflammatory diet. No differences were observed by race or diabetes status. However, we observed that female subjects had a tendency toward a more anti-inflammatory diet whereas male subjects tended to have a more proinflammatory diet. There were higher proportions of never smokers and college-educated subjects in the more anti-inflammatory diet categories than in the more proinflammatory categories. We also observed a linear pattern of increasing BMI across quintiles of the DII. These findings are identical to those observed among cases only, and there was no difference by tumor stage at presentation across quintiles defined by distribution among controls of the DII (Supplementary Table 1).

Association between DII and PC

Age-adjusted analysis of the DII revealed more than a 3-fold increased risk of PC in the highest compared with lowest quintile (OR = 3.14, 95% CI = 2.37–4.17), with a dose-dependent gradient across quintiles (P_{trend} < 0.0001) (Table 3). The association persisted after additional adjustment for sex, race, DM, BMI, pack-years of smoking within smoking categories and education ($OR_{Q5\ versus\ Q1}$ = 2.54, 95% CI = 1.87–3.46; P_{trend} < 0.0001). In stratified analysis by sex, we observed positive associations among males ($OR_{Q5\ versus}$

Table 1. Demographic and risk factor characteristics of PC by case and control status; Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015

	Cases, *n* = 817	Controls, *n* = 1756
Age, years[a]		
<50	45 (6%)	117 (7%)
50–54	48 (6%)	126 (7%)
55–59	98 (12%)	239 (14%)
60–64	144 (18%)	288 (16%)
65–69	147 (18%)	327 (19%)
70–74	132 (16%)	310 (17%)
75–79	116 (14%)	223 (13%)
80–84	67 (8%)	100 (6%)
≥85	20 (2%)	26 (1%)
Mean (SD)	66.7 (10.3)	65.4 (10.3)
Race		
White	799 (98%)	1,734 (99%)
Other	18 (2%)	22 (1%)
Sex		
Female	356 (44%)	801 (46%)
Male	461 (56%)	955 (54%)
DM[b]		
No	606 (74%)	1605 (91%)
Yes	211 (26%)	151 (9%)
Smoking status		
Never	375 (46%)	1003 (57%)
Former	375 (46%)	702 (40%)
Current	67 (8%)	51 (3%)
Pack-years of smoking		
0	375 (46%)	1003 (57%)
>0–9	121 (15%)	273 (15%)
10–19	90 (11%)	169 (10%)
≥20	231 (28%)	311 (18%)
Education level		
Less than high-school education	36 (4%)	39 (2%)
High-school graduate/some college	439 (54%)	834 (47%)
College graduate	183 (22%)	406 (23%)
Postgraduate education	157 (19%)	475 (27%)
Unknown	2 (<1%)	2 (<1%)
BMI, kg/m^2		
Mean (SD)	27.7 (5.1)	26.9 (4.6)

SD, standard deviation.

[a]Age at diagnosis (cases) or at the time of consent/recruitment (controls).

[b]Diagnosis of diabetes was categorized as ever (yes) or never (no).

$_{Q1}$ = 2.72, 95% CI = 1.77–4.17) and females ($OR_{Q5\ versus\ Q1}$ = 2.23, 95% CI = 1.43–3.48; *P* value for interaction by sex = 0.22). Similar patterns of association were observed when analyses were carried out with DII from diet plus supplements (Supplementary Table 2). To examine whether associations vary by disease severity, we performed separate analysis among cases with resectable, locally advanced and metastatic disease, with each group being compared with the same control population (Table 4). This analysis also showed significant association between having a higher DII score and presenting with resectable ($OR_{Q5\ versus\ Q1}$ = 2.36, 95% CI = 1.48–3.75), locally advanced ($OR_{Q5\ versus\ Q1}$ = 2.21, 95% CI = 1.41–3.46) or metastatic ($OR_{Q5\ versus\ Q1}$ = 3.13, 95% CI = 1.85–5.29) tumor (*P* value for interaction by tumor stage = 1.00) (Table 4). We also performed stratified analyses by smoking status for the overall association between the DII and PC and associations of the DII and PC by cancer stage at presentation, but none differed by smoking status (Supplementary Tables 3 and 4).

Joint association of DII and cigarette smoking on risk of PC

For the joint association analyses, the DII variable was dichotomized by the median value among controls (Table 5). Subjects with greater median DII score had higher risk of PC compared with those with less than or equal to median DII score (OR = 1.68, 95% CI = 1.39–2.02). Former (OR = 1.29, 95% CI = 1.07–1.54) and current (OR = 3.40, 95% CI = 2.28–5.07) smokers also had higher risks of PC compared with never smokers. The observed joint association for combined effect of current smoking and having greater than median DII score (OR = 4.79, 95% CI: 3.00–7.65), as compared with never smoking and having less than or equal to median DII score, was larger than expected under additive (OR = 2.91 + 1.49 – 1 = 3.40) and multiplicative (OR = 2.91 × 1.49 = 4.33) models. However, the statistical test for multiplicative interaction was nonsignificant (*P* = 0.27). Interestingly, when compared with never smokers with less than or equal to median DII scores, former smokers with greater than median DII score had increased risk of PC (OR = 2.14, 95% CI = 1.66–2.77), whereas a null association was observed among former smokers with less than or equal to median DII scores (OR = 1.06, 95% CI = 0.80–1.41). Pack-years of smoking also was associated with an increased risk of PC ($OR_{\geq 20\ versus\ 0\ pack\text{-}years}$ = 1.77, 95% CI = 1.42–2.21). The observed joint association for pack-years of smoking and higher DII scores ($OR_{\geq 20\ pack\text{-}years\ +\ >\ median\ DII\ score\ versus\ 0\ pack\text{-}years\ +\ \leq\ median\ DII\ score}$ = 2.79, 95% CI = 2.09–3.72) was also larger than expected under additive (OR = 1.80) and multiplicative (OR = 1.95) models, although the test for statistical interaction was nonsignificant (*P* = 0.31). Evaluation of pack-years of smoking within smoking categories also showed significantly increased risk of PC among former smokers (OR = 1.48, 95% CI = 1.17–1.88) and current smokers (OR = 4.38, 95% CI = 2.73–7.04) with ≥20 pack-years of smoking when compared with never smokers. We also observed a joint association OR of 5.94 (95% CI = 3.49–10.12) for current smokers with ≥20 pack-years of smoking and had greater than median DII score as compared with never smokers with less than or equal to median DII score; however, there was no evidence of multiplicative interaction (*P* = 0.78). The OR for the joint effect was larger than expected under additive (OR = 4.48), but not multiplicative (OR = 5.94), model, suggesting that higher DII score and current smoking with ≥20 pack-years of smoking history may act as contributory factors, rather than act via direct synergistic interaction, to increase risk of PC.

Joint association of DII and DM on risk of PC

Subjects with a history of DM had a markedly higher risk of PC compared with those with no history of DM (OR = 3.27, 95% CI = 2.58–4.17) (Table 6). Long-standing duration of DM (≥5 years) also was associated with increased risk of PC ($OR_{\geq 5\ years\ with\ DM\ versus\ no\ DM}$ = 3.09, 95% CI = 2.02–4.72). Risk of PC was over 5-fold higher among subjects with greater than median DII score and had history of DM (OR = 5.80, 95% CI = 4.17–8.07), and 6-fold higher among those with long-standing DM and had greater than median DII score (OR = 6.03, 95% CI = 3.41–10.65) compared with subjects with no history of DM and had less than or equal to median DII score. The magnitude of the observed joint associations was larger than expected in the additive model (DM: OR = 3.35; long-standing DM: OR = 2.97) and the multiplicative model (DM: OR = 4.40; long-standing DM: OR = 3.79), although tests of multiplicative interaction were not statistically

Table 2. Characteristics of control subjects across quintiles of energy-adjusted DII[a], *n* = 1756; Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015

Quintile	1	2	3	4	5	
DII cut-points	−5.33, −3.07	> −3.07, −2.15	> −2.15, −1.17	> −1.17, −0.03	> −0.03, 4.47	
n	351	351	351	351	352	*P* value*
Age, years[b]						
Mean	66.6	66.6	66.0	64.7	62.8	<0.0001
SD	10.0	9.2	10.0	10.6	11.2	
Race						
White	345 (98%)	347 (99%)	349 (99%)	344 (98%)	349 (99%)	0.41
Other	6 (2%)	4 (1%)	2 (1%)	7 (2%)	3 (1%)	
Sex						
Female	204 (58%)	188 (54%)	163 (46%)	142 (40%)	104 (30%)	<0.0001
Male	147 (42%)	163 (46%)	188 (54%)	209 (60%)	248 (70%)	
DM[c]						
No	331 (94%)	316 (90%)	320 (91%)	321 (91%)	317 (90%)	0.24
Yes	20 (6%)	35 (10%)	31 (9%)	30 (9%)	35 (10%)	
Smoking status						
Never	210 (60%)	214 (61%)	202 (57%)	201 (57%)	176 (50%)	<0.0001
Former	137 (39%)	130 (37%)	146 (42%)	139 (40%)	150 (43%)	
Current	4 (1%)	7 (2%)	3 (1%)	11 (3%)	26 (7%)	
Pack-years of smoking						
0	210 (60%)	214 (61%)	202 (58%)	201 (57%)	176 (50%)	<0.0001
>0–9	66 (19%)	63 (18%)	54 (15%)	48 (14%)	42 (12%)	
10–19	33 (9%)	26 (7%)	39 (11%)	36 (10%)	35 (10%)	
≥20	42 (12%)	48 (14%)	56 (16%)	66 (19%)	99 (28%)	
Pack-years of smoking within smoking categories						
Never	210 (60%)	214 (61%)	202 (58%)	201 (57%)	176 (50%)	<0.0001
Former						
>0–9	64 (18%)	61 (17%)	53 (15%)	47 (13%)	40 (11%)	
10–19	32 (9%)	24 (7%)	38 (11%)	31 (9%)	32 (9%)	
≥20	41 (12%)	45 (13%)	55 (16%)	61 (17%)	78 (22%)	
Current						
>0–9	2 (1%)	2 (<1%)	1 (<1%)	1 (<1%)	2 (1%)	
10–19	1 (<1%)	2 (<1%)	1 (<1%)	5 (1%)	3 (1%)	
≥20	1 (<1%)	3 (1%)	1 (<1%)	5 (1%)	21 (6%)	
Education level						
Less than high-school education	3 (1%)	11 (3%)	9 (3%)	9 (3%)	7 (2%)	<0.0001
High-school graduate/some college	142 (40%)	146 (42%)	151 (43%)	186 (53%)	209 (59%)	
College graduate	90 (26%)	87 (25%)	77 (22%)	75 (21%)	77 (22%)	
Postgraduate education	116 (33%)	107 (30%)	112 (32%)	81 (23%)	59 (17%)	
Unknown	0 (0%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	
BMI, kg/m^2						
Mean	25.7	26.6	27.0	27.4	27.9	<0.0001
SD	4.3	4.1	4.3	4.6	5.3	

[a]DII was calculated per 1000 calories consumed to account for differences in energy intake between subjects.
[b]Age at diagnosis (cases) or at the time of consent/recruitment (controls).
[c]Diagnosis of DM categorized as ever (yes) or never (no).
*Analysis of variance and Fisher's exact test for continuous and categorical variables, respectively.

significant (*P* values of 0.24 and 0.11 for diagnosis of DM and long-standing DM, respectively).

Joint association of DII and BMI on risk of PC

No association was observed between usual adult BMI and PC (Supplementary Table 5). Joint association between the highest BMI category and higher DII scores yielded an OR of 1.72 (95% CI = 1.23–2.39; $_{\geq 30\,kg/m2\,+\,>\,median\,DII\,score\,versus\,\leq 24.9\,kg/m2\,+\,\leq\,median\,DII\,score}$; *P* value for interaction = 0.86). This OR is nearly identical to the main effect of the dichotomous DII variable, implying that the joint association was primarily driven by the DII. The observed joint association also was similar to that expected under additive (OR = 1.69) and multiplicative (OR = 1.73) models, indicating no evidence of interaction between BMI and DII.

Discussion

In this clinic-based case–control study, a more proinflammatory diet, as measured by higher DII scores, was associated with an increased risk of PC. Results were similar for males and females. The study also shows that cigarette smoking, DM and, more

Table 3. Association between DII[a] and PC among the entire study population (817 cases and 1756 controls) and by sex; Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015.

Quintile DII categories		Cases	Controls	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[b]
1	–5.33, –3.07	92	351	1.00 (ref.)	1.00 (ref.)
2	> –3.07, –2.15	119	351	1.31 (0.96–1.79)	1.24 (0.90–1.70)
3	> –2.15, –1.17	150	351	1.66 (1.23–2.24)	1.60 (1.17–2.18)
4	> –1.17, –0.03	191	351	2.15 (1.61–2.87)	1.94 (1.43–2.63)
5	> –0.03, 4.47	265	352	3.14 (2.37–4.17)	2.54 (1.87–3.46)
P trend				<0.0001	<0.0001
Females (*N* = 1157)					
Quintile DII categories		Cases	Controls	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[c]
1	–4.88, –3.33	45	160	1.00 (ref.)	1.00 (ref.)
2	> –3.33, –2.59	60	160	1.41 (0.90–2.21)	1.32 (0.83–2.09)
3	> –2.59, –1.61	57	160	1.31 (0.83–2.05)	1.24 (0.78–1.98)
4	> –1.61, –0.52	77	160	1.77 (1.15–2.73)	1.50 (0.96–2.36)
5	> –0.52, 4.47	117	161	2.94 (1.94–4.46)	2.23 (1.43–3.48)
P trend				<0.0001	0.0005
Males (*N* = 1416)					
Quintile DII categories		Cases	Controls	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[c]
1	–5.33, –2.74	46	191	1.00 (ref.)	1.00 (ref.)
2	> –2.74, –1.80	69	191	1.52 (0.99–2.32)	1.47 (0.95–2.29)
3	> –1.80, –0.77	99	191	2.17 (1.45–3.25)	2.18 (1.43–3.32)
4	> –0.77, 0.42	112	191	2.52 (1.69–3.76)	2.43 (1.59–3.70)
5	>0.42, 4.36	135	191	3.19 (2.15–4.73)	2.72 (1.77–4.17)
P trend				<0.0001	<0.0001
P interaction by sex				0.35	0.22

[a]DII was calculated per 1000 calories consumed to account for differing energy intake among subjects. Quintile cut-points were based on distribution among controls.
[b]Adjusted for age (continues), sex, race (White, other), diabetes (yes, no), BMI (continues), pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years and current with ≥20 pack-years), and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown).
[c]Adjusted for the above list of variables except sex.

specifically, long-standing DM (≥5 years) are associated with increased risk of PC. Combinations of a more proinflammatory diet with cigarette smoking, DM or long-standing DM also were strongly associated with risk of PC. A particularly interesting finding was a regression of the observed increased risk of PC associated with former smoking toward a null association among former smokers who had a more anti-inflammatory diet. However, no association was observed between self-reported BMI and PC in this study, and there was no evidence of a joint association between BMI and a more proinflammatory diet on risk of PC.

The present study found an association between higher DII scores and increased risk of PC ($OR_{Q5\ versus\ Q1}$ = 2.54, 95% CI: 1.87–3.46, P_{trend} < 0.0001), confirming a previous association reported in an Italian population between higher DII scores and PC risk ($OR_{Q5\ versus\ Q1}$ = 2.48, 95% CI = 1.50–4.10, P_{trend} = 0.0015) (16). Higher DII scores also have been associated with increased risk of colorectal (34–37), esophageal (38) and prostate (39) cancers, as well as increased risk of cardiovascular disease (40) and metabolic syndrome (27). Null associations have been reported between DII scores and overall risk of postmenopausal breast cancer (45,46), although one study reported an increased risk of HER2+ breast cancer among postmenopausal women with higher DII scores (46). At present, the DII has been used to successfully predict blood levels of several inflammatory biomarkers, including high-sensitive C-reactive protein level in the Seasonal Variation of Blood Cholesterol Study (25), IL-6 and TNF-α2 in the Women's Health Initiative (24) and serum IL-6 levels in a case–control study in Australia (26). An earlier version of the DII was adapted by investigators from the Netherlands and was successfully used to predict blood levels of several inflammatory markers, including C-reactive protein, IL-6, IL-8, TNF-α and serum amyloid A (47). The exact mechanism by which diet-associated inflammation may increase the risk of PC is not entirely clear. However, it is well-recognized that PC tends to be fostered in a proinflammatory milieu (6). Inflammatory potential of diet may contribute to tumorigenesis of the pancreas by increasing blood levels of inflammatory cytokines (e.g. IL-6, IL-8, TNF-α and interferon γ), which can lead to excessive generation of reactive oxygen species as a normal immune response to cytotoxicity (5). In turn, this may result in damage to DNA, mutagenesis and, ultimately, tumorigenesis (5,6).

This is the first study to examine joint associations between the DII and cigarette smoking, DM or BMI in relation to risk of cancer. Cigarette smoking is the most well-established environmental risk factor for PC and is estimated to account for ~25% of all PC cases (7). Tobacco smoke is a highly proinflammatory substance, and inflammation is thought to be a primary mechanism underlying the role of smoking in PC (5,6). The potentially shared biologic pathway between cigarette smoking and proinflammatory diet is supported in this study by the strong joint association between smoking and higher DII score on risk of PC. The magnitude of the combined effect was substantially larger than was observed for each of these factors alone, suggesting that cancer prevention strategies to eliminate smoking should be advanced in parallel with the promotion of a healthy, anti-inflammatory dietary pattern.

The relationship between DM and PC is complex. DM has been implicated both as a risk factor for PC and a marker of early manifestation of PC (48,49). To delineate the role of DM in the incidence

Table 4. Association between DII (diet alone)[a] and PC by cases' cancer stage[b]; Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015

Quintile DII categories		Cases	Controls	Age-adjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[c]
Resectable (cases: *n* = 271; controls: *n* = 1756)					
1	−5.33, −3.07	34	351	1.00 (ref.)	1.00 (ref.)
2	> −3.07, −2.15	48	351	1.42 (0.89–2.27)	1.35 (0.84–2.17)
3	> −2.15, −1.17	49	351	1.47 (0.93–2.34)	1.44 (0.89–2.32)
4	> −1.17, −0.03	62	351	1.91 (1.22–2.98)	1.80 (1.14–2.86)
5	> −0.03, 4.47	78	352	2.54 (1.64–3.92)	2.36 (1.48–3.75)
P trend				<0.0001	0.0002
Locally advanced (cases: *n* = 285; controls: *n* = 1756)					
1	−5.33, −3.07	37	351	1.00 (ref.)	1.00 (ref.)
2	> −3.07, −2.15	34	351	0.93 (0.56–1.51)	0.84 (0.51–1.39)
3	> −2.15, −1.17	51	351	1.40 (0.89–2.20)	1.34 (0.84–2.14)
4	> −1.17, −0.03	70	351	1.96 (1.28–3.01)	1.83 (1.17–2.86)
5	> −0.03, 4.47	93	352	2.77 (1.83–4.19)	2.21 (1.41–3.46)
P trend				<0.0001	<0.0001
Metastatic (cases: *n* = 257; controls: *n* = 1756)					
1	−5.33, −3.07	21	351	1.00 (ref.)	1.00 (ref.)
2	> −3.07, −2.15	36	351	1.72 (0.98–3.00)	1.53 (0.87–2.69)
3	> −2.15, −1.17	50	351	2.39 (1.40–4.06)	2.14 (1.25–3.67)
4	> −1.17, −0.03	57	351	2.74 (1.62–4.62)	2.23 (1.30–3.80)
5	> −0.03, 4.47	93	352	4.50 (2.73–7.41)	3.13 (1.85–5.29)
P trend				<0.0001	<0.0001
P interaction by stage				0.99	1.00

[a]DII was calculated per 1000 calories consumed to account for differing energy intake among subjects. Quintile cut-points were based on distribution among controls.
[b]Four subjects with missing data on tumor stage were excluded from this analysis.
[c]Adjusted for age (continues), sex, race (White, other), diabetes (yes, no), BMI (continues), pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years and current with ≥20 pack-years) and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown).

of PC, we categorized DM participants by duration: new-onset, pre-existing DM (1–4 years) or long-standing DM (≥5 years). This report focuses on long-standing DM because it is least prone to confounding by reverse causation. The very strong joint association between a proinflammatory diet and long-standing DM on risk of PC further support the need for a comprehensive intervention strategy that integrates the promotion of an anti-inflammatory dietary pattern.

Although high BMI has been associated with an increased risk of PC in many studies (summarized in refs. 12,13,50), we found no association between BMI based on self-reported height and weight and PC risk. Besides the use of self-reported usual adult weight and height to calculate BMI, another limitation is that although we had adequate sample size to detect main effects, the study had insufficient power to detect significant multiplicative interaction, a constraint commonly affecting statistical modeling of multiple parameters (41,42,44). However, there was sufficient evidence of additive interaction for the observed associations, suggesting that a proinflammatory diet may act as a cofactor, rather than act synergistically, with cigarette smoking and diabetes to increase the risk of PC beyond the magnitude of risk associated with each of these factors when examined in isolation. It should be noted that such additive interaction is of significant value in public health as it helps discern the relative contribution of each risk factor to inform intervention strategies (42,43).

As with all case–control studies, the potential for recall bias and selection bias need to be considered. Although we cannot rule out the possibility of differential recall between the cases and controls, it is worth noting that the study participants were recruited from sectors of the same health system with similar referral patterns (29). Because the control subjects were patients without PC and they were unaware of the outcome of interest, recall bias is likely to be nondifferentially related to PC status; and thus, may have attenuated ORs toward the null value (42). Selection bias, particularly among controls, is another potential limitation of the study, as is confounding by unmeasured factors such as genetic variability in procarcinogen metabolism. Although we carefully adjusted for several risk factors of PC, residual confounding (e.g. from BMI) may still exist. The observational nature of the study also implies that noncausal explanations should be considered when interpreting results. Moreover, self-report of diet can be problematic, especially when asking people to report intake from the 5 years prior to completing the questionnaire. This should also be considered in the interpretation of findings. In this study, data were available on 28 of the food parameters. Missing information on the remaining 17 food parameters could be a possible limitation. However, previous work in United States populations indicates no drop off in predictive ability when reducing the number of food parameters to as few as 25 (26).

Major strengths of the study include the use of a comprehensive FFQ that allowed for assessment of major sources of nutrients in the American diet (30). In addition to adjusting for an array of known or putative risk factors of PC, we also performed detailed evaluation of diabetes and cigarette smoking, which adds to the strengths of the study. Furthermore, the strength of associations, the dose–response patterns and the consistency of findings across subgroups of the study population, as well as consistency with a previous study obviates the possibility that these findings may be due to chance alone. Evaluation of joint association between inflammatory potential of diet and known risk factors of PC also provides a novel insight into factors that seem to play major roles in the etiology of the disease.

In summary, we found that higher DII scores, indicating a greater inflammatory potential of diet, are associated with an

Table 5. Independent and joint association between DII[a] and cigarette smoking on PC risk (n = 2573); Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015

Main effect associations					
	Case/control	OR (95% CI)			
DII					
< median (–5.33, –1.66)	287/878	1.00 (ref.)[b]			
≥ median (> –1.66, 4.47)	530/878	1.68 (1.39–2.02)			
Smoking status					
Never	375/1003	1.00 (ref.)[c]			
Former	375/702	1.29 (1.07–1.54)			
Current	67/51	3.40 (2.28–5.07)			
Pack-years of smoking					
0	375/1003	1.00 (ref.)[c]			
>0–9	121/273	1.12 (0.87–1.44)			
10–19	90/169	1.33 (0.99–1.79)			
≥ 20	231/311	1.77 (1.42–2.21)			
Joint association					
	DII category				
	≤ median (–5.33, –1.66)		> median (> –1.66, 4.47)		P*
	Case/control	OR (95% CI)[c]	Case/control	OR (95% CI)[c]	
Smoking status					
Never	159/528	1.00 (ref.)	216/475	1.49 (1.16–1.92)	
Former	118/338	1.06 (0.80–1.41)	257/364	2.14 (1.66–2.77)	
Current	10/12	2.91 (1.21–7.03)	57/39	4.79 (3.00–7.65)	0.27
Pack-years of smoking					
0	159/528	1.00 (ref.)	216/475	1.49 (1.16–1.92)	
>0–9	48/160	0.93 (0.64–1.36)	73/113	2.05 (1.43–2.93)	
10–19	30/79	1.28 (0.80–2.05)	60/90	2.03 (1.36–3.00)	
≥20	50/111	1.31 (0.88–1.94)	181/200	2.79 (2.09–3.72)	0.31
Main effect associations					
	Case/control	OR (95% CI)[c]			
Pack-years of smoking within smoking categories[c]					
Never	375/1003	1.00 (ref.)			
Former					
>0–9	116/265	1.11 (0.86–1.44)			
10–19	81/157	1.30 (0.96–1.76)			
≥20	178/280	1.48 (1.17–1.88)			
Current					
>0–9	5/8	1.70 (0.52–5.54)			
10–19	9/12	1.94 (0.78–4.84)			
≥20	53/31	4.38 (2.73–7.04)			
Joint association					
	DII category				
	≤ median (–5.33, –1.66)		> median (> –1.66, 4.47)		P*
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	
Pack-years of smoking within smoking categories[c]					
Never	159/528	1.00 (ref.)	216/475	1.49 (1.16–1.92)	
Former					
>0–9	46/156	0.91 (0.62–1.34)	70/109	2.03 (1.41–2.92)	
10–19	28/76	1.23 (0.76–1.99)	53/81	1.98 (1.31–2.99)	
≥20	44/106	1.17 (0.78–1.77)	134/174	2.31 (1.70–3.15)	

Table 5. *Continued*

Joint association					
	Case/control	OR (95% CI)			
Current					
>0–9	2/4	1.63 (0.26–10.31)	3/4	2.58 (0.54–12.33)	
10–19	2/3	2.55 (0.42–15.57)	7/9	2.35 (0.81–6.86)	
≥20	6/5	3.99 (1.18–13.51)	47/26	5.94 (3.49–10.12)	0.78

[a]DII was calculated per 1000 calories consumed to account for differences in energy intake between subjects.
[b]Adjusted for age (continues), sex, race (White, other), diabetes (yes, no), BMI (continues), pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years and current with ≥20 pack-years) and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown).
[c]Adjusted for age (continues), sex, race (White, other), diabetes (yes, no), BMI (continues) and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown).
*Interaction *P* value from likelihood ratio test. Degrees of freedom for models with and without interaction term were 16 and 14, respectively, for smoking status, 16 and 13 for pack-years of smoking, and 22 and 16 for pack-years of smoking within smoking categories.

Table 6. Independent and joint association between type II DM and DII[a] with PC risk; Mayo Clinic Biospecimen Resource for Pancreas Research, 2000–2015

Main effect associations					
	Case/control	Multivariable-adjusted OR (95% CI)[b]			
Type II DM[c]					
No	606/1605	1.00 (ref.)			
Yes	208/151	3.27 (2.58–4.17)			
Duration of type II DM[d]					
No	606/1605	1.00 (ref.)			
Yes, 1–4 years	30/27	2.63 (1.52–4.53)			
Yes, ≥5 years	56/43	3.09 (2.02–4.72)			
Joint association					
	DII category				
	≤ median (–5.33, –1.66)		> median (> –1.66, 4.47)		*P**
	Case/control	OR (95% CI)[b]	Case/control	OR (95% CI)[b]	
Type II DM[c]					
No	227/807	1.00 (ref.)	379/798	1.60 (1.31–1.96)	
Yes	58/71	2.75 (1.87–4.04)	150/80	5.80 (4.17–8.07)	0.24
Duration of type II DM[d]					
No DM	227/807	1.00 (ref.)	379/798	1.60 (1.31–1.96)	
Yes, 1–4 years	8/17	1.55 (0.65–3.66)	22/10	6.94 (3.16–15.25)	
Yes, ≥5 years	16/22	2.37 (1.20–4.67)	40/21	6.03 (3.41–10.65)	0.11

[a]DII was calculated per 1000 calories consumed to account for differences in energy intake between subjects.
[b]Adjusted for age (continues), sex, race (White, other), BMI (continues), pack-years of smoking within smoking categories (never, former with <10 pack-years, former with 10–19 pack-years, former with ≥20 pack-years, current with <10 pack-years, current with 10–19 pack-years and current with ≥20 pack-years) and education (less than high school, high-school graduate/some college, college graduate, postgraduate and unknown).
[c]Excluded subjects diagnosed with diabetes after the diagnosis of PC ($n = 3$).
[d]Subjects with missing data on date of diabetes diagnosis ($n = 142$; case: $n = 67$, controls: $n = 75$), those diagnosed with diabetes after the diagnosis of PC ($n = 3$), those with concomitant diagnosis of diabetes and PC ($n = 7$), and those diagnosed with diabetes <12 months before diagnosis of PC ($n = 48$) or <12 months before enrollment in the study ($n = 6$) were excluded (total $n = 206$; cases: $n = 125$, controls: $n = 81$).
*Interaction *P* value from likelihood ratio test. Degrees of freedom for models with and without interaction term were 17 and 16, respectively, for type II DM, and 19 and 17 for duration of type II DM.

increased risk of PC. Our study demonstrates, for the first time, that diet-associated inflammation may act as a cofactor with cigarette smoking and diabetes to increase the risk of PC beyond the risk of any of these factors alone. Cancer prevention strategies should therefore consider incorporating promotion of an anti-inflammatory dietary pattern to maximize impact of interventions.

Supplementary material

Supplementary Tables 1–5 can be found at http://carcin.oxfordjournals.org/

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