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Dietary inflammatory index and risk of pancreatic cancer in an Italian case–control study

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Abstract

Previous studies have shown that various dietary components may be implicated in the aetiology of pancreatic cancer. However, the possible relationship between diet-related inflammation and the risk of pancreatic cancer has not yet been investigated. We examined the ability of a newly developed literature-derived dietary inflammatory index (DII) to predict the risk of pancreatic cancer in a case–control study conducted in Italy between 1991 and 2008. This included 326 incident cases and 652 controls admitted to the major teaching and general hospitals for non-neoplastic diseases, frequency-matched to cases by study centre, sex and age. The DII was computed based on dietary intake assessed using a validated and reproducible seventy-eight-item FFQ. Logistic regression models were used to estimate multivariable OR adjusted for age, sex, study centre, education, BMI, smoking status, alcohol drinking and history of diabetes. Energy adjustment was performed using the residual method. Subjects with higher DII scores (i.e. representing a more pro-inflammatory diet) had a higher risk of pancreatic cancer, with the DII being used as both a continuous variable ($OR_{continuous}$ 1·24, 95 % CI 1·11, 1·38) and a categorical variable (i.e. compared with the subjects in the lowest quintile of the DII, those in the second, third, fourth and fifth quintiles had, respectively, $OR_{quintile2\,v.\,1}$ 1·70, 95 % CI 1·02, 2·80; $OR_{quintile3\,v.\,1}$ 1·91, 95 % CI 1·16, 3·16; $OR_{quintile4\,v.\,1}$ 1·98, 95 % CI 1·20, 3·27; $OR_{quintile5\,v.\,1}$ 2·48, 95 % CI 1·50, 4·10; $P_{trend} = 0·0015$). These data suggest that a pro-inflammatory diet increases the risk of pancreatic cancer.

Key words: Diet: Inflammation: Pancreatic cancer: Case–control studies: Italy: Risk

Pancreatic cancer is the most fatal of all gastrointestinal cancers, with a survival rate of only 6 % at 5 years[1]. This cancer is characterised by a high mortality rate, rapid progression, and resistance to chemotherapy and radiation[2]. There is growing evidence on the role of chronic inflammation in pancreatic cancer[3,4], as in other neoplasms[5,6]. While inflammation typically occurs as part of the body's response to tissue insult/injury[6,7], chronic inflammation is a persistent condition in which tissue destruction and repair occur simultaneously[8,9].

Results from human studies on the association between the risk of pancreatic cancer and inflammation have been mixed so far. A case–control study has shown that the levels of C-reactive protein and IL-6 were higher among pancreatic cancer patients than among those without cancer[10] and, in another case–control study, pancreatic adenocarcinoma patients have been shown to have higher levels of TNF-α and interferon-γ than those with chronic pancreatitis and healthy volunteers[11]. Combined results from three cohort studies conducted in the USA have also shown that inflammation is associated with pancreatic cancer over a long follow-up period (>10 years)[12]. However, in a nested case–control study from the European Prospective Investigative Cohort, no associations were observed between C-reactive protein and IL-6 and the risk of pancreatic cancer, although there was a positive association with soluble TNF receptor 1 among women[13]. A combined analysis of

Abbreviation: DII, dietary inflammatory index.

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five cohort studies has shown no association between inflammatory markers and the risk of pancreatic cancer[14]. Pancreatic cancer has been positively associated with chronic pancreatitis[15] but inversely with allergy, a condition known to be related to inflammation[16–19].

Diet represents a complicated set of exposures that often interact and whose cumulative effect modifies both inflammatory responses and health outcomes. According to the latest report from the World Cancer Research Fund. American Institute for Cancer Research, which was based on the systematic reviews of cohort and case–control studies, both decaffeinated and caffeinated coffee have not been found to be associated with the risk of pancreatic cancer, while results for other food items, such as red and processed meat, or nutrients such as total fat and saturated fat, are still unclear[20]. Although several studies have been conducted, the relationship between diet and the risk of pancreatic cancer is still unclear[21–24]. In a case–control study conducted in the USA, nutrients from fruits and vegetables have been found to reduce the risk of pancreatic cancer[24]. Similarly, consumption of dietary antioxidants has been found to be protective against developing pancreatic cancer in the European Prospective Investigative Cohort-Norfolk study[25]. In a pooled analysis carried out using data from fourteen cohort studies, consumption of dairy foods, Ca or vitamin D during adulthood was not associated with the risk of pancreatic cancer[26], and no association has been observed between intake of vegetables, fruits, carotenoids and vitamins C and E and the risk of pancreatic cancer in The Netherlands Cohort Study[23]. In the National Institute of Health–American Association of Retired Professionals cohort study conducted in the USA, a high-quality diet, as indicated by increasing Healthy Eating Index 2005 scores, has been found to be protective against pancreatic cancer[27], and in a case–control study conducted in Italy, the Mediterranean diet score has been inversely associated with pancreatic cancer[28]. These results further stress the importance of studying diet in its entirety rather than studying individual dietary components. In a case–control study conducted in California, a positive association was observed between the risk of pancreatic cancer and a Western dietary pattern, characterised by a higher intake of red and processed meat, salty high-fat snacks, sugary beverages, sweets, high-fat dairy products, eggs and refined grains[22]. In an Italian case–control study, a starch-rich dietary pattern has been associated with the increased risk of pancreatic cancer, while inverse associations have been reported for diets rich in vegetables, fruits and vitamins[29]. However, the evidence is still inconsistent in two cohort studies[23,24]. The possible relationship between diet-related inflammation and the risk of pancreatic cancer has not yet been investigated.

The paucity of research related to diet and inflammation is probably due to logistical issues resulting from methodological complexity involved in linking diet, inflammation and cancer risk in the same study. In an effort to fill obvious methodological gap, researchers at the University of South Carolina's Cancer Prevention and Control Program developed a dietary inflammatory index (DII), which can be used in diverse populations in order to predict the levels of inflammatory markers associated with diet and related health outcomes[30,31]. Developing the DII involved careful review and scoring of the scientific literature on diet and inflammation, and obtaining datasets from around the world with which individuals' dietary intakes could be compared[30].

The purpose of the present study was to examine the association between the DII and the risk of pancreatic cancer in a case–control study conducted in Italy. We hypothesised that subjects consuming a pro-inflammatory diet, as represented by a higher DII score, will exhibit an increase in the levels of circulating inflammatory cytokines, resulting in a higher risk of developing pancreatic cancer.

Methods

Full details of the case–control study have been given elsewhere[32]. Briefly, the study was conducted between 1991 and 2008 in the province of Pordenone and in the greater Milan area, northern Italy. Cases were 326 patients (174 men, 152 women; median age 63 years) admitted to the major teaching and general hospitals in the areas under study with incident pancreatic carcinoma. Controls were 652 patients (348 men, 304 women; median age 62 years) admitted to the same hospitals as cases for a wide spectrum of acute conditions other than neoplastic or digestive tract diseases related neither to known risk factors for pancreatic cancer nor to long-term dietary modifications. Controls were frequency-matched to cases by study centre, sex and age (±5 years), with a control: case ratio of 2:1. More than 95% of cases and controls who were approached agreed to participate in the study.

Information on sociodemographic characteristics, anthropometric measures, lifestyle habits, including smoking and alcohol drinking, personal medical history, and family history of cancer in first-degree relatives was assessed during the hospital stay of the subjects using a standard questionnaire administered by trained interviewers. To determine the usual diets of the subjects during the 2 years before cancer diagnosis or hospital admission (for controls), an interviewer-administered FFQ was used, which included seventy-eight foods and beverages, as well as a range of the most common Italian recipes. The subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes less than once per week, but at least once per month, were coded as 0·5 per week. Nutrient and total energy intakes were determined using an Italian food composition database[33]. The FFQ showed satisfactory validity[34] and reproducibility[35,36], with Spearman's correlation coefficients ranging between 0·60 and 0·80 for most food items and nutrients.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all eligible patients agreed to participate in the study by signing an informed consent approved by the internal review boards of the study hospitals.

The FFQ-derived dietary information was used to calculate the DII scores for all of the subjects, using a procedure described in detail elsewhere[30]. Briefly, to compute the DII, dietary

data for each study subject were first linked to a global database derived from surveys conducted in eleven countries worldwide that included data on the consumption of forty-five food/nutrient parameters used in the computation of the DII (i.e. foods such as garlic and onions, nutrients such as saturated fat and vitamin C, and other food components such as flavonoids)[30]. For each subject and each food parameter, a z score was derived by subtracting the 'standard global mean' from the amount reported and dividing this value by the standard deviation. To minimise the effect of 'right skewing' (a common occurrence with dietary data), this value was then converted to a centred percentile score, which was then multiplied by the respective food parameter effect score (derived from a literature review and scoring of 1943 articles) to obtain the food parameter-specific DII score of the subjects. All food parameter-specific DII scores were then summed to create the overall DII score for each subject in the study. The higher DII scores reflected a greater pro-inflammatory potential of the diet. The study had data on thirty-one of the forty-five food parameters studied for the development of the DII: carbohydrate; protein; fat; alcohol; fibre; cholesterol; SFA; MUFA; PUFA; *n*-3; *n*-6; niacin; thiamin; riboflavin; vitamin B_6; Fe; Zn; vitamin A; vitamin C; vitamin D; vitamin E; folic acid; β-carotene; anthocyanidins; flavan-3-ol; flavonol; flavonones; flavones; isoflavones; caffeine; tea. A more detailed description of the validation of the DII score, based on both dietary recalls and a structured questionnaire similar to a FFQ, is available elsewhere[31]. BMI was calculated as weight (in kg) divided by height (in m) squared, and was categorised into normal weight (BMI $< 25{\cdot}0\,kg/m^2$), overweight ($25{\cdot}0\,kg/m^2 \leq$ BMI $< 30{\cdot}0\,kg/m^2$) and obese (BMI $\geq 30{\cdot}0\,kg/m^2$).

The DII was analysed both as a continuous variable (i.e. a one-unit increment in the DII corresponds to approximately 7 % of its global range) and by quintiles of exposure. The DII also was examined across the strata of factors such as age, education, BMI, smoking status, alcohol drinking and history of diabetes using the ANOVA test for continuous variables or the χ^2 test for categorical variables. OR and the corresponding 95 % CI were estimated using logistic regression models, adjusting only for age, and then additionally for sex, study centre, year of interview (continuous), education, (<7, 7–11 and ≥12 years) and major recognised risk factors for pancreatic cancer, i.e. BMI ($<25{\cdot}0\,kg/m^2$, $25{\cdot}0–29{\cdot}9\,kg/m^2$ and $\geq 30{\cdot}0\,kg/m^2$), smoking status (never smoker, ex-smoker and current smoker), alcohol drinking (0, <21 and ≥21 drinks/week) and history of diabetes (yes/no). Energy adjustment was performed by using the residual method[37]. Linear tests for trend were performed using the median value within each quintile as an ordinal variable. Stratified analyses were carried out across the strata of the following factors: sex; BMI; smoking status. Statistical tests were performed using SAS® 9.3 (SAS Institute, Inc.). All P values were two-sided.

Results

Table 1 shows the distribution of 326 cases of pancreatic cancer and 652 controls according to study centre, sex, age and other selected covariates. By design, cases and controls had similar distribution by study centre, sex and age. Compared with the controls, the cases had a higher level of education, were more frequently heavy drinkers and smokers, had normal BMI and reported more frequently a history of diabetes.

The mean DII value among the cases was 0·26 (SD 1·44) and among the controls was −0·13 (SD 1·40), indicating a more pro-inflammatory diet for cases. The characteristics of the subjects across the quintiles of the DII are presented in Table 2. There were small differences in sociodemographic, anthropometric and lifestyle habits across the quintiles of the DII. There were a higher percentage of current smokers in the higher quintiles of the DII than that in the first quintile.

The OR of pancreatic cancer according to quintiles and continuous DII are shown in Table 3. In age-adjusted models, positive associations were observed between the DII and pancreatic cancer ($OR_{continuous}$ 1·22, 95 % CI 1·11, 1·34 and $OR_{quintile5\,v.\,1}$ 2·10, 95 % CI 1·35, 3·24; $P_{trend} = 0{\cdot}004$). Significant positive associations were found in multivariate analysis, with an $OR_{continuous}$ of 1·24 (95 % CI 1·11, 1·38). Similarly, when the analysis was carried out with the DII expressed as quintiles, subjects in the second, third,

Table 1. Distribution of 326 patients with pancreatic cancer and 652 controls according to study centre, sex, age, education, and other selected variables in a case–control study conducted in Italy between 1991 and 2008

(Number of subjects and percentages)

	Cases		Controls	
	n	%	*n*	%
Study centre				
Milan	151	46·3	302	46·3
Aviano (Pordenone)	175	53·7	350	53·7
Sex				
Men	174	53·4	348	53·4
Women	152	46·6	304	46·6
Age (years)				
<50	32	9·8	64	9·8
50–59	89	27·3	178	27·3
60–69	122	37·4	244	37·4
≥70	83	25·5	166	25·5
Education (years)*				
<7	166	51·2	350	53·9
7–11	86	26·5	192	29·5
≥12	72	22·2	108	16·6
BMI (kg/m^2)				
<25	141	43·2	266	40·8
25–29·9	135	41·4	293	44·9
≥30·0	50	15·3	93	14·3
Alcohol drinking				
No	44	13·5	101	15·5
<21 drinks/week	155	47·5	343	52·6
≥21 drinks/week	127	39·0	208	31·9
Smoking status*				
Never smoker	137	42·2	328	50·5
Ex-smoker	88	27·2	195	30·0
Current smoker	98	30·3	126	19·4
History of diabetes				
No	269	82·5	615	94·3
Yes	57	17·5	37	5·7

*The sum does not add up to the total because of some missing values.

Table 2. Characteristics of 652 controls across the quintiles of the energy-adjusted dietary inflammatory index (DII), in a case–control study conducted in Italy between 1991 and 2008

(Mean values and standard deviations; number of subjects and percentages)

	DII quintiles										
	< −1·28		−1·28, −0·39		−0·38, +0·38		+0·38, +1·26		≥ +1·27		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P**
Age (years)											0·19
Mean	61·7		63·5		60·9		62·5		61·7		
SD	8·7		9·8		9·4		9·5		8·7		
Education (years)											0·01
<7	74	52·5	77	54·2	72	56·3	71	55·5	56	49·6	
7–11	37	26·2	43	30·3	41	32·0	26	20·3	45	39·8	
>11	30	21·3	22	15·5	15	11·7	31	24·2	12	10·6	
BMI (kg/m^2)											0·64
<25	65	46·1	47	33·1	54	42·2	51	39·8	49	43·4	
25–29·9	58	41·1	74	52·1	56	43·7	58	45·3	47	41·6	
≥30·0	18	12·8	21	14·8	18	14·1	19	14·8	17	15·0	
Alcohol drinking											0·47
No	32	17·0	30	14·4	28	14·4	21	10·7	34	17·8	
<21 drinks/week	103	54·8	110	52·9	99	51·0	100	50·8	86	45·0	
≥21 drinks/week	53	28·2	68	32·7	67	34·5	76	38·6	71	37·2	
Smoking status											0·01
Never smoker	83	58·8	76	53·9	65	50·8	54	42·2	50	44·6	
Ex-smoker	38	26·9	44	31·2	36	28·1	47	36·7	30	26·8	
Current smoker	20	14·2	21	14·9	27	21·1	27	21·1	32	28·5	
History of diabetes											0·91
No	134	95·0	133	93·7	122	95·3	119	93·0	107	94·7	
Yes	7	5·0	9	6·3	6	4·7	9	7·0	6	5·3	

* ANOVA and χ^2 tests were used for continuous and categorical variables, respectively.

fourth and fifth quintiles of the DII had increased OR for pancreatic cancer ($OR_{quintile2\,v.\,1}$ 1·70, 95% CI 1·02, 2·80; $OR_{quintile3\,v.\,1}$ 1·91, 95% CI 1·16, 3·16; $OR_{quintile4\,v.\,1}$ 1·98, 95% CI 1·20, 3·27; $OR_{quintile5\,v.\,1}$ 2·48, 95% CI 1·50, 4·10) compared with those in the lowest quintile of the DII ($P_{trend} = 0·0015$).

When stratified by sex, a significant association between the DII and the risk of pancreatic cancer was observed for women ($OR_{quintile5\,v.\,1}$ 3·71, 95% CI 1·73, 7·94; $P_{trend} = 0·001$; Table 4). When stratified by BMI, a significant association between the DII and the risk of pancreatic cancer was observed for normal-weight subjects (BMI < 25 kg/m^2: $OR_{quintile5\,v.\,1}$ 2·24, 95% CI 1·03, 4·86; $P_{trend} = 0·16$) and overweight subjects (BMI 25·0–29·9 kg/m^2: $OR_{quintile5\,v.\,1}$ 2·32, 95% CI 1·03, 5·21; $P_{trend} = 0·005$). When stratified by smoking status, a significant association between the DII and the risk of pancreatic cancer was observed for never smokers ($OR_{quintile5\,v.\,1}$ 2·32, 95% CI 1·08, 4·99; $P_{trend} = 0·01$) and ex-smokers ($OR_{quintile5\,v.\,1}$ 3·37, 95% CI 1·22, 9·35; $P_{trend} = 0·07$).

Discussion

The present study demonstrated a positive association between the DII and the risk of pancreatic cancer, with risk estimates being statistically significant for the DII expressed both as a continuous variable and by quintiles. This result supports the hypothesis that people eating a pro-inflammatory diet are at a higher risk of developing pancreatic cancer.

Some dietary factors have been shown to increase the risk of developing pancreatic cancer, including animal protein and (red) meat[26,38,39]. Other dietary factors, such as vegetables

Table 3. Odds ratios of pancreatic cancer for the energy-adjusted dietary inflammatory index (DII) among 326 cases and 652 controls, in a case–control study conducted in Italy between 1991 and 2008

(Odds ratios and 95% confidence intervals)

	DII quintiles							
	< −1·28	−1·28, −0·39	−0·38, +0·37	+0·38, +1·26	≥ +1·27	P_{trend}	OR*	95% CI
Cases (*n*)	47	66	66	69	78			
Controls (*n*)	141	142	128	128	113			
Age-adjusted OR	1†	1·38	1·55	1·62	2·10	0·004	1·22	1·11, 1·34
95% CI		0·89, 2·15	0·99, 2·41	1·04, 2·52	1·35, 3·24			
Multivariable OR‡	1†	1·70	1·91	1·98	2·48	0·0015	1·24	1·11, 1·38
95% CI		1·02, 2·80	1·16, 3·16	1·20, 3·27	1·50, 4·10			

* Continuous OR for a one-unit increment of the DII, corresponding to approximately 7% of its global range.
† Reference category.
‡ Adjusted for age, sex, study centre, year of interview, education, BMI, smoking status, alcohol drinking, and history of diabetes.

Table 4. Odds ratios* of pancreatic cancer for the energy-adjusted dietary inflammatory index (DII), stratified by sex, BMI and smoking status, among 326 cases and 652 controls in a case–control study conducted in Italy between 1991 and 2008
(Odds ratios and 95 % confidence intervals)

	DII quintiles											
	< −1·28	−1·28, −0·39		−0·38, +0·37		+0·38, +1·26		≥ +1·27				
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	OR†	95 % CI
Sex												
Men	1‡	1·28	0·61, 2·68	1·77	0·87, 3·60	1·47	0·73, 3·00	1·85	0·91, 3·76	0·10	1·17	1·00, 1·36
Women	1‡	2·20	1·09, 4·46	1·98	0·93, 4·21	2·57	1·20, 5·49	3·71	1·73, 7·94	0·001	1·33	1·12, 1·57
BMI (kg/m^2)												
<25·0	1‡	2·42	1·09, 5·35	1·71	0·77, 3·77	1·58	0·72, 3·51	2·24	1·03, 4·86	0·16	1·16	0·98, 1·38
25·0–29·9	1‡	1·13	0·52, 2·47	1·80	0·83, 3·93	2·59	1·21, 5·53	2·32	1·03, 5·21	0·005	1·29	1·08, 1·54
≥30·0	1‡	1·72	0·39, 7·62	1·59	0·32, 8·03	0·57	0·10, 3·29	2·24	0·46, 10·84	0·61	1·17	0·85, 1·62
Smoking status												
Never smoker	1‡	1·39	0·67, 2·90	1·70	0·81, 3·59	2·18	1·03, 4·61	2·32	1·08, 4·99	0·01	1·25	1·06, 1·48
Ex-smoker	1‡	2·84	1·08, 7·47	3·48	1·33, 9·10	2·24	0·84, 5·94	3·37	1·22, 9·35	0·07	1·20	0·98, 1·48
Current smoker	1‡	1·45	0·50, 4·19	0·96	0·33, 2·79	1·35	0·46, 3·97	1·80	0·66, 4·89	0·26	1·21	0·97, 1·51

* Adjusted for age, sex, study centre, year of interview, education, BMI, smoking status, alcohol drinking, and history of diabetes.
† Continuous OR for a one-unit increment of the DII, corresponding to approximately 7 % of its global range.
‡ Reference category.

and fruits, have been shown to reduce the risk[25,24,38]. In particular, previous research conducted in this case–control study database has revealed a strong positive association between the risk of pancreatic cancer and increased intake of (red) meat, other animal products, (refined) cereals and sugars[32], and for a Western dietary pattern[29]; however, fruit and vegetable intake[32] and increasing adherence to a Mediterranean diet[28] appeared to exert a protective effect[29]. A normal human diet consists of both pro-inflammatory and anti-inflammatory foods/nutrients. The DII score is designed to take this into account. Thus, it more accurately reflects the potential inflammatory effect of diet as a whole. Thus far, the DII has been successful in predicting C-reactive protein in the Seasonal Variation of Blood Cholesterol Study[31] and IL-6 in a case–control study conducted in Australia[40]. An older version of this index has been used by a group in The Netherlands to predict inflammatory biomarkers (i.e. C-reactive protein, IL-6, IL-8, TNF-α and serum amyloid A) and soluble intercellular adhesion molecule-1[41,42]. Using the data from the National Health and Nutrition Examination Survey, the new version of DII also has been used to compare the inflammatory potential of diet among workers assigned to different shifts[43]. Additionally, the DII has been shown to predict prostate cancer among Italian men[44] and colorectal cancer among women in the Iowa Women's Health Study[45].

One of the possible mechanisms responsible for the association between a high-inflammatory diet and the risk of pancreatic cancer is increased production of cytokines in cellular organelles, which can lead to the release of proteolytic enzymes and reactive oxygen species. These, in turn, can produce genotoxic effects such as DNA strand breaks, sister chromatid exchanges, mutations, and formation of adducts with DNA[3]. Another mechanism is through the effect of growth factors: chronic inflammation in the pancreas leads to an increased release of growth factors such as platelet-derived growth factor and transforming growth factor-α, which leads to increased proliferation of pancreatic cells[46].

The influence of diet on cancer is difficult to estimate, and challenges in assessing dietary exposures are greatest in case–control studies. Potential selection and recall bias of hospital-based case–control studies also should be considered. Dietary habits of hospital controls may be different from those of the general population; however, we were careful to exclude from the control group all diagnoses that could be associated with long-term dietary modifications. A recent diagnosis of cancer may have influenced recall of diet for the cases, although we asked for dietary habits 2 years before cancer diagnosis, and the role of diet in pancreatic cancer was unknown in the general Italian population at the time of the study. The use of a similar interview setting for both cases and controls would reduce potential information bias. Some of the associations observed in the present study, in particular the inverse ones with vegetables, and the direct ones with (red) meat, are apparently stronger than those reported in most cohort investigations. However, inverse relationships with folate and flavonoids in vegetables have been reported in cohort studies as well[47,48]. Some have reported positive associations with the consumption of meat and total sugar[49,50].

One of the strengths of the present study is the use of a validated[34] and reproducible[35,36] FFQ, which allowed for a comprehensive assessment of major nutrient sources in the Italian diet, although some measurement error inherent in the FFQ may be present. Moreover, we had detailed information on major recognised risk factors for pancreatic cancer. Notwithstanding the limitations of case–control studies in general, we believe that our findings on a positive association between the DII and the risk of pancreatic cancer are plausible and could be related to immune and hormonal factors[2–4,10,11]. Also, the association is too strong to be accounted for by bias or confounding only, with an OR of 2·48 in the highest quintile.

In conclusion, the present study on the risk of pancreatic cancer and the DII in a Southern European population

indicates a possible role of diet in the risk of developing pancreatic cancer, which we hypothesised would be through the process of inflammation. However, further confirmatory results from other studies conducted in different populations with different study designs (e.g. cohort studies) are required to establish this association.

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The author's contributions are as follows: N. S. was involved in the calculation of the DII, performed all the analyses, and drafted the first version of the manuscript; C. B. and C. L. V. helped with the analyses, data acquisition interpretation of the data, and critical revision of the manuscript; A. Z. and D. S. contributed in data acquisition and to the interpretation of the data and drafting of the manuscript; J. R. H. provided expertise and oversight throughout the process. All authors revised and approved the final version of the manuscript.

The authors declare that there are no conflicts of interest.

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