



Allergies, variants in *IL-4* and *IL-4Rα* genes, and risk of pancreatic cancer[☆]

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Abstract

Background: Several studies in epidemiology indicate that risk of pancreatic cancer is reduced in individuals with allergies. Although genes have been identified that are critical in allergic response, polymorphisms in these genes have not been studied in relation to risk of pancreatic cancer. We hypothesized that variants in these genes are related to risk. **Methods:** We investigated the association of allergies and pancreatic cancer in a hospital-based case–control study with 405 cases and 212 controls. In a subgroup of 149 cases and 135 controls, we studied the association of variants in *IL-4* (C-589T, G3017T) and *IL-4Rα* (Gln576Arg) with allergies and with risk of pancreatic cancer. **Results:** We found reduced risk of pancreatic cancer associated with allergies, with adjusted odds ratios of 0.58 (95% CI 0.40–0.84) for any allergies, 0.45 (95% CI 0.29–0.70) for hay fever, and 0.43 (95% CI 0.23–0.80) for animals. The minor allele at each locus studied was associated with reduced risk of allergies in controls, leading us to hypothesize that they would be associated with increased risk of pancreatic cancer. Overall, there was no association between the genotypes studied and risk of pancreatic cancer. In analyses within strata defined by presence or absence of allergies, there were differences in risk associated with genotype for *IL-4* G3017T: there was slightly increased risk among those with allergies and reduced risk among those without allergies. **Conclusions:** The consistent association of allergies with risk of pancreatic cancer and these results suggest that associations between variants in genes related to allergic response and pancreatic cancer warrant further study.

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Keywords: Epidemiology; Genotypes; Polymorphisms; Case–control study; Hay fever

1. Introduction

Cancer of the pancreas is the fourth leading cause of cancer mortality in the United States [1]. In addition to known risk factors including cigarette smoking, family history, and obesity, epidemiologic studies have consistently found that the presence of allergies is a protective factor. This was confirmed in recent reviews [2,3] and a meta-

analysis [4]. While the mechanism for possible reduction in risk is not clear, it is thought that the activated immune surveillance in individuals with allergies may serve to protect against pancreatic cancer.

Individuals with atopy (allergies to environmental allergens) are characterized by high levels of IgE, both total serum IgE and IgE to specific allergens. *IL-4* is an important cytokine of adaptive immunity and, along with *IL-13*, the only cytokine that leads to IgE synthesis [5]. Individuals with allergies have been found to have higher circulating levels of *IL-4* [6]. In individuals who develop allergies, exposure to an allergen stimulates CD4 + T cells to become TH2 effector cells; these cells produce *IL-4*. *IL-4* binds to its receptor, *IL-4Rα*, on B cells and stimulates B

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cells to produce IgE, which in turn binds to receptors on basophils and mast cells. When the allergen is reintroduced, it binds to the IgE on the resting mast cells, and subsequent cross-linking of allergens and IgE leads to the release of mediators and cytokines that cause symptoms. Individuals without allergies produce mainly IgM and IgG, and only small amounts of IgE [7–11].

In a hospital-based case–control study at Memorial Sloan-Kettering Cancer Center (MSKCC), we investigated the association of allergies with pancreatic cancer. In addition, we undertook a pilot study in a subgroup of these cases and controls in order to evaluate whether polymorphisms in IL-4 and IL-4R α are associated with risk of pancreatic cancer. We studied two variants in IL-4 (chromosome 5q31–33), C-589T (rs2243250) in the promoter region and G3017T (rs2227284) in intron 2, and one variant in IL-4R α (chromosome 16p11–12), Gln576Arg in exon 11 (rs1801275) (also called Gln551 Arg). We investigated the association of these polymorphisms with presence of allergies in the controls, hypothesizing that genotypes associated with reduced risk of allergies would be associated with increased risk of pancreatic cancer and vice versa.

2. Materials and methods

2.1. Study population

Cases ($n = 405$) at MSKCC are eligible if they have pathologically or cytologically confirmed pancreatic adenocarcinoma and speak English. They are identified when they are seen by clinicians for initial consultation and diagnosis, follow-up after surgery, or chemotherapy. Controls ($n = 212$) are eligible if they speak English and have no personal history of cancer other than non-melanoma skin cancer. They are either spouses of patients with pancreatic cancer ($n = 99$) or individuals who are accompanying patients to our endoscopy clinics ($n = 113$). Cases and controls who agree to take part and sign Informed Consent are personally interviewed to determine environmental and lifestyle risk factors for pancreatic cancer. We ask if respondents ever had hay fever or allergies to foods, animals, pollen, plants such as poison ivy, bee stings, molds, medicine or vaccines. If they answer affirmatively, they are further questioned as to what they are or have been allergic to. Respondents also complete a detailed family history questionnaire and provide a buccal or blood specimen for DNA. For this pilot study of polymorphisms in IL-4 and IL-4R α , we randomly selected 150 cases from those enrolled; one was eliminated because he was found not to have adenocarcinoma. At the time we undertook the pilot study, there were 136 controls; one was eliminated because of inadequate DNA for genotyping. Cases and controls in this analysis were interviewed between April 2003 and February 2007. Among cases approached, 13% were ineligible

(primarily because they did not speak English); of those eligible, 79% took part. Among controls approached, 15% were ineligible (primarily because of history of cancer); of those eligible, 59% took part. The study was approved by the Institutional Review Board at MSKCC.

2.2. Genotyping and quality control

DNA was obtained from buccal cells collected with mouthwashes using the Puregene DNA isolation kit (Gentra Systems Inc., Minneapolis, MN) in 286 individuals and from blood with the QIAamp DNA Blood kit (QIAGEN Inc., Valencia, USA) in one individual. DNA concentration was measured by spectrophotometry at 260 nm in a Spectramax Plus 384 (Molecular Devices, Sunnyvale, USA). The DNA quality was determined by the ratio A260/A280.

Genotyping was done with PCR-based methods and included the melting temperature analysis [12] coupled to the LightTyper instrument (Roche Applied Science, Indianapolis, USA) and pyrosequencing [13] with the PSQTM HS 96A instruments (Biotage AB, Uppsala, Sweden). The PCR primers and PCR annealing temperatures are available on request. PCR fragments were amplified in a reaction containing 0.4 μ M each of the specific forward and reverse primers, 1.5–2.0 mM MgCl₂, 200 μ M dNTP, 0.025 U/ μ l Taq Polymerase (Applied Biosystems, Foster City, CA) for IL-4 single nucleotide polymorphisms (SNPs) and FastStart Taq DNA polymerase (Roche Diagnostics Corporation, Indianapolis, IN) for the IL-4R α SNP, 1 M betaine, and PCR buffer 1 $\times$. For the analysis of SNPs using melting temperature profiles, the cycling consisted of a denaturation at 95 °C for 5–10 min followed by 40 cycles of 95 °C for 60 s, 55 °C for 60 s, 72 °C for 60 s, with a final extension at 72 °C for 7 min. For the analysis by pyrosequencing, the cycling time at each temperature was reduced to 30 s. Products were immobilized and denatured at 80 °C for 2 min. For the pyrosequencing reaction, the corresponding sequencing primer was added to the single stranded DNA and nucleotides dispensed automatically by the PSQTM HS 96A instrument and software (Uppsala, Sweden). To distinguish genotypes using melting temperature profiling, DNA was amplified in presence of a fluorescent probe and products were then heated and scanned between 40 and 80 °C in the LightTyper.

For quality control, all genotyping included known internal controls (homozygous wild type, homozygous variant, and heterozygous) and blanks (water) and pyrograms were read twice. Laboratory personnel were blinded to case–control status. The control and water samples tested showed the expected signal and there was 100% agreement in the genotyping calls between two independent laboratory members. We randomly selected 10% of the samples for second assays and found 100% agreement between the two independent assays.

2.3. Statistical analysis

We used χ^2 tests to evaluate whether genotypes were in Hardy–Weinberg equilibrium (HWE). Logistic regression was used to determine crude and adjusted odds ratios. Potential confounding variables that we considered were gender, age (continuous), race (Caucasian vs. other), education (high school or less, college, graduate school), smoking (never, former, current and >15 pack years vs. all others), marital status (married, widowed/separated/divorced, single) body mass index (<25, 25 to <30, >30, based on usual adult weight), and area of residence (New York City, other New York State, New Jersey, and other areas). We investigated the association of genotype and pancreatic cancer in strata defined by presence or absence of allergies.

3. Results

3.1. Characteristics of cases and controls

Table 1 shows the characteristics of cases and controls. Cases were more likely to be male and were older than controls. For other characteristics, odds ratios adjusted for gender and age are shown. Cases were more likely to be unmarried, reflecting the use of spouse controls. Current smoking was associated with increased risk, as were higher pack years of smoking. Cases were more likely to be overweight or obese at their usual adult weight and were more likely to have a first degree relative with pancreatic cancer. History of pancreatitis was associated with increased risk while history of diabetes was not. Cases and controls were similar in area of residence.

3.2. Allergies and risk of pancreatic cancer

As shown in Table 2, allergies were more often reported by controls (69%) than by cases (55%). Allergies were more common in younger respondents, women, those with graduate education, and those who had never smoked (data not shown). Adjusting for these variables resulted in an OR of 0.58 (95% CI 0.40–0.84). Hay fever was the most commonly reported allergy and was associated with reduced risk (OR = 0.45, 95% CI 0.29–0.70), compared to those with no allergies. Allergies to animals were also strongly associated with risk (OR = 0.43, 95% CI 0.23–0.80); this was attributable to allergies to cats and other animals (e.g., horses, birds) but not to dogs. Reduced risk was also noted for allergies to medications, foods, dust, and mold, but these were not statistically significant. There was no evidence of further decreased risk among those reporting two or more allergies.

3.3. Genotypes and risk of allergies

Among controls, genotypes were in HWE for IL-4 G3017T and IL-4R α Gln576Arg. For IL-4 C-589T, the

genotypes were not in HWE among all controls, but were in HWE among Caucasians alone. The distribution of genotypes varied widely by race (Supplementary table I).¹ The minor alleles of the two SNPs in IL-4 were likely to be inherited together (Supplementary table II).² We determined the relationship between the presence of allergies and genotypes in controls, with the expectation that genotypes that were related to decreased risk of allergies would be associated with increased risk of pancreatic cancer, and vice versa. For IL-4, controls with the variant T allele at either –589 or 3017 were at decreased risk of allergies (OR = 0.48, 95% CI 0.22–1.05, and 0.38, 95% CI 0.18–0.83, respectively). For IL-4R α , there was a tendency toward lower risk for allergies in the controls with the variant Arg (OR = 0.69, 95% CI 0.32–1.49). Results were unchanged when restricted to Caucasians only (Supplementary table III).³

3.4. Genotypes and risk of pancreatic cancer

None of the genotypes studied were related to risk of pancreatic cancer overall (Table 3). Adding potential confounding variables to the models did not change these results, nor did restricting the analysis to Caucasians (Supplementary table IV).⁴ The hypothesis that variants related to decreased risk of allergies (i.e., the T allele in either IL-4 locus and the Arg variant in IL-4R α) would increase risk of pancreatic cancer was not supported.

We further investigated the association of genotypes with risk of pancreatic cancer within subgroups defined by presence or absence of allergies (Table 4). For both variants of IL-4, there was evidence of slightly increased risk among those with any variant T allele who had allergies, while among those with no allergies, the variant T alleles were associated with reduced risk. For the G3017T change, the interaction term in logistic regression was statistically significant ($p = 0.02$). For IL-4R α , results were similar in the two subgroups.

4. Discussion

Results of this study are consistent with those from other studies in showing reduced risk of pancreatic cancer associated with allergies [14–26], particularly for hay fever [14–19]. The proportion of controls with any allergy in our study (69%) is higher than in earlier studies. There has been an increase in this proportion from the 1970s and 1980s [14,18,21,23] to more recent studies [19], reflecting

¹ Supplementary tables I–IV are accessible from the online version of this article: S-1: Distribution of genotypes in IL-4 and IL-4R α according to race (cases and controls combined).

² S-2: Observed and expected distribution of genotypes in IL4.

³ S-3: Risk of allergies in controls according to genotypes, all controls and Caucasians only.

⁴ S-4: Association of genotypes in IL-4 and IL-4R α with pancreatic cancer, all participants and Caucasians only.

Table 1
Characteristics of cases and controls

	Cases		Controls		Adjusted ^a OR (95% CI)
	n = 405	%	n = 212	%	
Age					
<50	55	14	57	27	
50–59	94	23	63	30	
60–69	139	34	63	30	
≥70	118	29	29	14	
Gender					
Male	205	51	88	42	
Female	200	49	124	58	
Education					
High school	104	26	40	19	1
College	164	40	90	42	0.83 (0.52–1.33)
Graduate school	137	34	82	39	0.67 (0.42–1.09)
Race					
Caucasian	367	91	189	89	1
Black/Asian/other	38	9	23	11	1.1 (0.65–2.06)
Marital status					
Married	289	71	182	86	1
Widowed, separated, divorced	84	21	19	9	2.40 (1.38–4.17)
Never married	32	8	11	5	2.91 (1.36–6.20)
Smoking					
Never	183	45	111	52	1
Past	195	48	88	42	1.01 (0.70–1.47)
Current	27	7	13	6	2.37 (1.23–4.55)
Pack years ≥15 ^b	127	31	39	18	1.77 (1.17–2.69)
Usual adult body mass index (BMI)					
Normal	151	37	117	55	1
Overweight	165	41	70	33	1.56 (1.06–2.28)
Obese	87	22	25	12	2.16 (1.21–3.85)
Family history of pancreatic cancer					
None	337	84	190	90	1
1° relative	38	9	9	4	2.18 (1.01–4.73)
2° or other relative	27	7	13	6	1.32 (0.65–2.69)
Pancreatitis (≥1 year before diagnosis in cases) ^c					
No	386	95	210	99	1
Yes	19	5	2	1	5.51 (1.25–24)
Diabetes (≥3 years before diagnosis in cases)					
No	368	91	197	93	1
Yes	37	9	15	7	0.94 (0.64–1.40)
Residence					
NYS outside NYC ^d	153	38	85	40	1
New York City	86	21	40	19	1.08 (0.67–1.74)
New Jersey	82	20	46	22	0.93 (0.58–1.47)
Other	84	21	41	19	1.15 (0.71–1.84)

^a Adjusted for age (continuous) and gender.

^b Reference category is non-smokers and those with <15 pack years.

^c Eleven cases were not asked time of diagnosis of pancreatitis.

^d NYS: New York State and NYC: New York City.

a reported increase in allergies in general (reviewed in Howarth 1998) [27]. Our odds ratios for the associations of allergies and hay fever were similar to those for other studies.

To our knowledge, this is the first study of the associations of genotypes in genes related to the allergic response

and pancreatic cancer. For the three genotypes that we studied, IL-4 C-589T, IL-4 G3017T, and IL-4Rα Gln576Arg, there was evidence of association of genotypes with allergies but no overall association with risk of pancreatic cancer. For IL-4, we noted an interaction effect for the IL-4 G3017T genotype, with slightly increased risk

Table 2
Association of allergies with pancreatic cancer

	Cases		Controls		Adjusted ^a OR (95% CI)
	n = 405	%	n = 212	%	
Allergies					
No allergies	183	45	65	31	1 (ref)
Any allergies	222	55	147	69	0.58 (0.40–0.84)
Specific allergies					
Hay fever, pollen, grass, seasonal	90	22	77	36	0.45 (0.29–0.70)
Any medications	90	22	51	24	0.75 (0.46–1.19)
Antibiotics	53	13	32	15	0.70 (0.39–1.23)
Pain relievers	22	5	13	6	0.71 (0.32–1.58)
Other medications	24	6	12	6	0.91 (0.40–2.07)
Any animals	29	7	29	14	0.43 (0.23–0.80)
Cats	20	5	14	7	0.60 (0.27–1.32)
Dogs	12	3	5	2	0.97 (0.32–2.99)
Other animals	7	2	13	6	0.24 (0.09–0.66)
Any food	40	10	21	10	0.74 (0.39–1.40)
Dust	28	7	19	9	0.57 (0.29–1.12)
Mold	18	4	11	5	0.71 (0.31–1.65)
Number of allergies					
One	134	33	84	40	0.57 (0.38–0.86)
Two	45	11	35	17	0.59 (0.34–1.03)
Three or more	43	11	28	13	0.64 (0.35–1.17)

^a Adjusted for age (continuous), gender, smoking (never, past, current), education (high school graduate, college, graduate school). Reference category is those with no allergies.

among those with allergies who carried the T allele, and significantly decreased risk among those without allergies who carried the T allele. Since the numbers of cases and controls in the strata were small, these results should be considered preliminary and require replication.

Although the cytokine IL-4 and its receptor are central to antibody switching to IgE and allergic symptoms and there is strong evidence of genomic linkage of the region including IL-4 to serum total IgE [28] and to asthma and

atopy [29], association of genotypes in IL-4 with either IgE or allergies is not consistent. For the C-589T polymorphism, some studies have shown higher levels of IgE or higher prevalence of allergies among individuals with the TT genotype [6,30–32] although sometimes only among certain subgroups, such as those with positive skin prick tests [31] or evidence of exposure to an allergen [30]. Other studies have found no relation between the IL-4 C-589T genotype and total serum IgE or allergen-specific IgE [33–37]. The C3017T polymorphism has been less frequently studied, with two studies showing associations with allergic phenotypes [31,32]. In contrast to some of these results, which showed the variants related to increased risk, our results indicated that the T allele in each of these polymorphisms was associated with lower risk of allergies in controls.

For the Gln576Arg polymorphism in IL-4Rα, the minor allele has been associated with lower IgE or lower prevalence of allergies in a number of studies [34,38–40], although others found no association [35,41–43]. Our results were consistent with lower prevalence of allergies in controls with the minor allele, but were not statistically significant. There are several linked nonsynonymous polymorphisms in IL-4Rα, and stronger associations with allergic phenotypes have been found for pairs of variants, including the Gln576Arg change, than for single variants [39,42,44].

The literature on allergies and related genes is difficult to evaluate for several reasons. Most of these studies have

Table 3
Association of genotypes in IL-4 and IL-4Rα with pancreatic cancer

	Cases		Controls		OR (95% CI)
	n = 149	%	n = 135	%	
IL-4 C-589T					
CC	101	68	96	71	1
CT	39	26	26	19	1.43 (0.81–2.52)
TT	9	6	13	10	0.66 (0.27–1.61)
Any T	48	32	39	29	1.17 (0.71–1.94)
IL-4 G3017T					
GG	73	49	66	49	1
GT	55	37	53	39	0.94 (0.57–1.55)
TT	21	14	16	12	1.19 (0.57–2.46)
Any T	76	51	69	51	1.00 (0.63–1.59)
IL-4Rα A576G					
AA Gln/Gln	104	70	89	66	1
AG Gln/Arg	38	26	41	30	0.79 (0.47–1.34)
GG Arg/Arg	7	5	5	4	1.20 (0.37–3.91)
Any G any Arg	45	31	46	34	0.84 (0.51–1.38)

Table 4

Association of genotypes in *IL-4* and *IL-4Rα* with pancreatic cancer according to presence of allergies

	Cases ^a n = 78	Controls ^a n = 95	OR (95% CI) ^a	Cases ^b n = 71	Controls ^b n = 40	OR (95% CI) ^b
<i>IL-4</i> C-589T						
CC	53	72	1	48	24	1
Any T	25	23	1.48 (0.76–2.88)	23	16	0.72 (0.32–1.61)
<i>IL-4</i> G3017T						
GG	36	53	1	37	13	1
Any T	42	42	1.47 (0.81–2.69)	34	27	0.44 (0.20–0.99)
<i>IL-4Rα</i> A576G						
AA	57	65	1	47	24	1
Any G	21	30	0.80 (0.41–1.55)	24	16	0.77 (0.34–1.71)

^a Have allergies.^b Do not have allergies.

focused on asthma; while many individuals with asthma have atopy, there are many with atopy who do not have asthma [45]. Studies of pancreatic cancer have found associations with hay fever or other respiratory allergies or dermatologic allergies but less often with asthma [4]. Phenotypes have been defined in various ways, such as by use of skin prick tests, total serum IgE, radioallergosorbent test (RAST) for specific allergens, and self report.

As in other studies of pancreatic cancer, our case population did not include those whose disease was most rapidly fatal. The risks associated with other factors, such as smoking, obesity, family history, and pancreatitis, are similar to those found in other studies (reviewed in [46,47]). Spouse controls share some exposures with cases and not all patients have spouses and visitor controls come from an undefined source population. However, an advantage of this control group is that it consists of individuals likely to come to MSKCC if they developed cancer. In addition, conditions such as allergies and genotypes are unlikely to be shared by spouses. Our questions on allergies did not allow us to evaluate the length of time individuals were affected or severity. In addition, our questionnaire did not include questions about medications for allergies, so are unable to evaluate any possible associations of these medications with risk. Since the genetic analysis was a pilot study, we were not able to include a larger sample or other genotypes for these or other genes.

In conclusion, we confirmed earlier studies showing decreased risk of pancreatic cancer in individuals with allergies and found no overall association of the genotypes we studied in *IL-4* and *IL-4Rα* with risk. However, in stratified analyses, we did find evidence that risk of pancreatic cancer differed for genotypes of *IL-4* G3017T according to presence of allergies. These results require confirmation in other studies. Future work focusing on other genetic variants related to allergic response should provide better understanding of the association between allergies and reduced risk of pancreatic cancer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cdp.2007.10.002.

Conflict of interest

None disclosed.

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Supplementary Tables

Supplementary table I.

**Distribution of genotypes in *IL-4* and *IL-4Rα* according to race
(cases and controls combined)**

	#	(%)	#	(%)	#	(%)		
	Whites		Blacks		Others		Whites vs Blacks	Whites vs Others
	<i>n</i> =255		<i>n</i> =14		<i>n</i> =15		p-value	
<i>IL-4</i> C-589T								
CC	194	(76)	2	(14)	1	(7)	<0.0001	<0.0001
CT	53	(21)	5	(36)	7	(47)		
TT	8	(3)	7	(50)	7	(47)		
Any T	61	(24)	12	(86)	14	(93)		
<i>IL-4</i> G3017T								
GG	138	(54)	0	(0)	1	(7)	<0.0001	<0.0001
GT	101	(40)	4	(29)	3	(20)		
TT	16	(6)	10	(71)	11	(73)		
Any T	117	(46)	14	(100)	14	(93)		
<i>IL-4Rα</i> A576G								
AA Gln/Gln	183	(72)	1	(7)	9	(60)	<0.0001	0.49
AG Gln/Arg	68	(27)	5	(36)	6	(40)		
GG Arg/Arg	4	(2)	8	(57)	0	(0)		
Any G Any Arg	72	(28)	13	(93)	6	(40)		

Overall $\chi^2=123.1$ df= 4 p<0.001

Supplementary table II.**Observed and expected distribution of genotypes in *IL4***

	<i>IL-4</i> G3017T genotypes					
	Homozygous wild-type		Heterozygous		Homozygous variant	
	<i>n</i>		<i>n</i>		<i>n</i>	
	Observed	Expected	Observed	Expected	Observed	Expected
<i>IL-4</i> C-589T genotypes						
Homozygous wild-type	65	47	30	38	1	11
Heterozygous	1	13	22	10	3	3
Homozygous variant	0	6	1	5	12	2

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Supplementary table III.**Risk of allergies in controls according to genotypes, all controls and Caucasians only**

	All controls			Caucasians only		
	#	#	OR (95% CI)	#	#	OR (95% CI)
	Allergies	No allergies		Allergies	No allergies	
	<i>n</i> =95	<i>n</i> =40		<i>n</i> =86	<i>n</i> =35	
<i>IL-4</i> C-589T						
CC	72	24	1	70	24	1
Any T	23	16	0.48 (0.22-1.05)	16	11	0.50 (0.20-1.22)
<i>IL-4</i> G3017T						
GG	53	13	1	53	13	1
Any T	42	27	0.38 (0.18-0.83)	33	22	0.37 (0.16-0.83)
<i>IL-4Rα</i> A576G						
AA	65	24	1	61	22	1
Any G	30	16	0.69 (0.32-1.49)	25	13	0.69 (0.30-1.59)

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Supplementary table IV.		
Association of genotypes in <i>IL-4</i> and <i>IL-4Rα</i> with pancreatic cancer, all participants and Caucasians only		
	All participants (149 cases/ 135 controls) OR (95%)	Caucasians Only (134 cases/ 121 controls) OR (95% CI)
<i>IL-4</i> C-589T		
CC	1	1.
Any T	1.17 (0.71-1.94)	1.18 (0.66-2.11)
<i>IL-4</i> G3017T		
GG	1	1.
Any T	1.00 (0.63-1.59)	1.03 (0.63-1.69)
<i>IL-4Rα</i> A576G		
AA Gln/Gln	1	1.
Any G Any Arg	0.84 (0.51-1.38)	0.74 (0.43-1.28)

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