Title

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Journal

Cancer Epidemiology Biomarkers & Prevention, 23(7)

ISSN

1055-9965

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Publication Date

2014-07-01

DOI

10.1158/1055-9965.epi-13-1359

Peer reviewed

Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2014 July ; 23(7): 1414–1420. doi:10.1158/1055-9965.EPI-13-1359.

Serum IgE and risk of pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

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Abstract

Epidemiologic studies have consistently found that self-reported allergies are associated with reduced risk of pancreatic cancer. Our aim was to prospectively assess the relationship between serum IgE, a marker of allergy, and risk. This nested case-control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) included subjects enrolled in 1994-2001 and followed through 2010. There were 283 cases of pancreatic cancer and 544 controls matched on age, gender, race, and calendar date of blood draw. Using the ImmunoCAP system, we measured total IgE (normal, borderline, elevated), IgE to respiratory allergens, and IgE to food allergens (negative or positive) in serum collected at baseline. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. We assessed interactions with age, gender, smoking, body mass index, and time between randomization and case diagnosis. Overall, there was no association between the IgE measures and risk. We found a statistically significant interaction by baseline age: in those aged >65, elevated risks were observed for borderline total IgE (OR=1.43; 95% CI, 0.88-2.32) and elevated total IgE (OR=1.98; 95% CI, 1.16-3.37) and positive IgE to food allergens (OR=2.83; 95% CI, 1.29-6.20); among

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The authors have no conflict of interest to report.

participants <65, ORs were <1. Other interactions were not statistically significant. The reduced risk of pancreatic cancer associated with self-reported allergies is not reflected in serum IgE.

Keywords

pancreatic cancer; allergies; IgE; biomarkers

Introduction

Pancreatic cancer is a deadly disease, with 5-year survival only 6% (1). A consistent finding in epidemiologic studies is reduced risk associated with self-reported allergies (2-5). Very little is known about the biologic basis of this association, which is found in other cancers as well (5). For pancreatic cancer, evidence of reduced risk is most consistent for respiratory allergies, while asthma is not associated with risk. Although few studies have investigated food allergies, there is little evidence of an association with risk (3).

Individuals with allergies are characterized by high levels of serum IgE, both total IgE and allergen-specific IgE. We hypothesized that measures of total IgE and specific IgE to respiratory allergens would be inversely associated with risk of pancreatic cancer; we did not have a specific hypothesis about IgE to food allergens. Tests of total and specific IgE may point towards a functional allergy pathway that cannot be inferred from self-reported allergy. We tested this hypothesis in the National Cancer Institute's prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO).

Materials and Methods

Study population

We used a nested case-control design within PLCO, a randomized trial investigating the effects of screening for prostate, lung, colorectal, and ovarian cancers (6). From 1994 to 2001, >150,000 men and women aged 55-74 at entry were randomized at ten screening centers to receive screening or usual care. Participants were eligible if they were not currently undergoing treatment for any cancer (except nonmelanoma skin cancer) and had not been diagnosed with one of the cancers under study. Participants completed baseline questionnaires on background characteristics and provided a blood sample. Questions on allergies were not included.

Cases had confirmed incident primary pancreatic adenocarcinomas diagnosed from 1994 through 2010 (ICDO3 codes C250-C259, excluding histology codes for endocrine neoplasms). They were identified by an annual mail survey to participants or next of kin and search of cancer registries and death certificates.

A total of 295 pancreatic cancer cases were identified. Controls unaffected by pancreatic cancer were alive in the year of the matched cases' diagnosis and were matched to each case in a 2:1 ratio on age at randomization (<60, 60-64, 65-69, >70), year of birth (in 5-year groups from 1920-1924 to 1945-1949), gender, race, and calendar date of blood draw (in 2-month groups, beginning with January/February). Twelve cases and 26 controls were

excluded from analysis because they had missing information on all three IgE measures; in addition, 20 more controls were excluded because their matched cases were excluded, resulting in a total of 283 cases and 544 matched controls.

The PLCO study was approved by the institutional review boards of the screening centers and the National Cancer Institute. This analysis was reviewed by the institutional review board at Memorial Sloan Kettering Cancer Center.

Measurement of total and allergen-specific IgE

Blood samples were collected at study entry, processed within two hours, and stored at -70°C. IgE measures were undertaken in the Laboratory for Molecular Epidemiology at the University of California San Francisco using the ImmunoCAP Fluorescent Enzyme Immunoassay system (Thermo Fisher Scientific, Kalamazoo MI)(7). ImmunoCAP is a fluorescent assay in which the solid phase is a flexible, hydrophobic cellulose polymer to which allergen has been covalently linked. The system has a very high binding capacity and minimal non-specific binding. For allergen-specific IgE, ImmunoCAP's Phadiatop combines specific respiratory allergens that identify about 97% of individuals with respiratory allergies in the U.S.; information on the specific allergens included is not provided. The food panel includes peanuts, tree nuts, shellfish, milk, egg, and codfish. Laboratory technicians were blinded to case-control status. We categorized the IgE measures using standard cut points: for total IgE, normal (<25kU/L), borderline (25-100kU/L), and elevated (>100kU/L); for IgE for respiratory allergens and food allergens, negative (<0.35 kU/L) or positive (i.e., detectable) (>0.35kU/L). For total IgE, we additionally analyzed risk for those with very elevated levels (>310 kU/L, the 90^{th} percentile). In the UCSF laboratory, the range of coefficients of variation percent for measures of total IgE is 2.0-2.8 within assays and 5.3 to 9.1 between. For specific IgE, the corresponding ranges are 5-6 and 10-11.

Statistical analysis

We prepared descriptive statistics for cases and controls of demographic characteristics (education, marital status, occupation), design factors (study center and season of blood draw), and risk factors for pancreatic cancer (cigarette smoking, body mass index (BMI, weight(k)/ height(m^2)), diabetes, alcohol intake, and family history of pancreatic cancer. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI). In the controls, we determined the associations of total and specific IgE measures with demographic characteristics, design factors and risk factors, using χ^2 tests to compare groups. For total IgE, results were log transformed to adjust for skewness in order to determine the geometric mean and standard deviation and to assess the linear association of total IgE with risk. To identify potential confounding factors, we entered each of the demographic, design, and risk factors individually into the conditional logistic models and included those factors that changed the risk estimate by >5%. Confounders included in final models were cigarette smoking for total IgE and IgE to respiratory allergens and study center for IgE to food allergens.

We explored whether the risk of pancreatic cancer associated with serum IgE varied by age at baseline (<65 or >65), gender, smoking history (never smokers and former smokers who

quit ≥15 yrs ago; current smokers and former smokers who quit <15 yrs ago), and BMI (dichotomized at the median value, 26.55). Stratum-specific odds ratios and 95% confidence intervals were estimated from multivariable conditional logistic regression models with cross-product terms composed of the IgE measure and the potential effect modifier variable. To determine whether the association between IgE and risk varied by the length of time between randomization and diagnosis, we categorized cases and matched controls into groups of 0-5, 6-9, and 10-15 years between randomization and diagnosis and analyzed using conditional logistic regression with interaction terms.

All statistical analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Characteristics of cases and controls are shown in Table 1. Slightly more than half the cases and controls were aged >65 at baseline. Sixty-two percent were men, 90% were white, and 38% were college graduates. Cases were more likely to be current or recent cigarette smokers and more likely to report having diabetes.

For total IgE, the distribution of results in controls was as follows: normal, 41% (n=224); borderline, 35% (n=192); elevated, 23% (n=126). Men were more likely than women to have borderline or elevated total IgE, as were current smokers and those who quit <15 years ago (data not shown in tables). Twenty-eight percent of controls (n=150) had positive IgE to respiratory allergens. They were more likely to be men and non-white, more likely to be currently working, and less likely to report family history of pancreatic cancer. There was a higher percentage with positive results from the University of Colorado, Georgetown University, and Hawaii. Six percent of controls (n=35) had positive results for IgE to foods. They were more likely to be younger (<65), women, and not married, although these results were not statistically significant.

There were no differences between cases and controls in the IgE measures (Table 2). For total IgE, the adjusted odds ratios were 0.84 (95% CI, 0.59-1.20) for borderline IgE and 1.22 (95% CI, 0.84-1.78) for elevated IgE, compared to normal levels. For a higher category of total IgE (>310 kU/L), risk was slightly higher (OR=1.42; 95% CI, 0.85-2.37). There was no association with risk when total IgE was analyzed as a log-transformed continuous variable (OR=1.04; 95% CI, 0.95-1.15, data not shown in tables). For positive results for IgE to respiratory allergens, the adjusted odds ratio was 1.16 (95% CI, 0.84-1.61) and for food allergens, the adjusted odds ratio was 1.57 (95% CI, 0.90-2.74).

Associations of the total and food IgE measures varied according to age (Table 3), with higher IgE related to increased risk in those aged >65, while in those <65, ORs were <1. For total IgE, OR=1.43 (95% CI, 0.88-2.32) for borderline and OR=1.98 (95% CI, 1.16-3.37) for elevated IgE in older respondents, in contrast to OR=0.45 (95% CI, 0.26-0.77) for borderline and 0.71 (95% CI, 0.41-1.24) for elevated IgE in younger respondents ($p_{interaction}$ 0.003). The patterns were consistent when we examined a higher category of total IgE (>310kU/L) (data not shown). IgE to food was positively associated with risk for older respondents (OR=2.83; 95% CI, 1.29-6.20) but not for younger respondents (OR=0.80; 95% CI,

0.34-1.91) ($p_{interaction}$ 0.03). The pattern was similar for IgE to respiratory allergens but neither the odds ratios within strata nor the interaction was significant.

For other stratified analyses, there were few differences between stratum-specific odds ratios and no statistically significant interactions (data not shown in tables). There was no pattern of association according to time between randomization and diagnosis for any of the IgE measures (Table 3). For IgE to respiratory allergens, there was a suggestion that positive results were inversely associated with risk in those with 10-15 years between randomization and diagnosis (OR=0.80; 95% CI, 0.43-1.48). We investigated whether there was a difference between younger and older age groups in time from randomization to diagnosis, but results were very similar (mean 90.8 months in cases aged <65 and 88.7 in cases aged >65).

Discussion

In the sample as a whole, there were no statistically significant associations of the three measures of IgE with risk. Although there is a well-documented relationship between self-reported allergies and reduced risk of pancreatic cancer (2-5), the concordance between self-reported allergy and serum IgE measures is notably poor (8, 9): in data from the National Health and Nutrition Examination Survey (NHANES), only 52% of those who reported any allergy had positive results for IgE to one or more of 10 specific IgEs studied (9). Few studies of pancreatic cancer have included questions about food allergies and findings to date are inconsistent (4). It may be particularly difficult for people to distinguish between IgE-mediated sensitivity and other types of food intolerance.

The finding of differences in risk according to age was unexpected and was not related to time between enrollment and diagnosis. Older individuals generally have lower levels of IgE (10); whether the cases harbored higher IgE levels over the long term or whether some immune factor triggered this closer to the time of diagnosis cannot be determined. Our findings on differences in age groups could also be due to chance.

Only one study to date has reported on total IgE and IgE for airborne allergens in relation to risk of pancreatic cancer (11). This Swedish study linked records from patients at an immunology clinic to records from a cancer registry and concluded that there were no increased or decreased risks. This study is limited by the young age of the patients with allergies (65% <40 years) and the short average follow-up (<7 years). In glioma, another cancer for which self-reported allergies are also related to reduced risk, three prospective studies studied serum IgE (12-14). While some measures showed reduced risk with higher IgE, overall there were few significant findings and little consistency among studies.

The proportion of controls in this study with positive IgE measures was similar to those reported in other recent studies, for borderline and elevated total IgE (10, 15), IgE to panels of specific respiratory allergens (9, 15-17), and IgE to foods (8, 18). Total IgE (19-21) and IgE to respiratory allergens (20, 22) have been found to be stable over time in individuals for about 10 years, although less is known about the stability over time for food IgE in adults.

Strengths of this study include a sample size large enough to identify an inverse OR of ~0.60 for borderline and elevated total IgE and for respiratory allergies, although there was less power for food allergies. Higher IgE levels are used clinically to identify food allergies (23, 24), but there were too few exposed to evaluate higher levels in our study. In addition, the longest time between cohort entry and diagnosis was 15 years, with a median follow-up of 7 years. Although pancreatic cancer often appears to develop and metastasize quickly, there is recent evidence that it develops, like other cancers, over a period of about 20 years (25).

In conclusion, the reported association of self-reported allergies with reduced risk of pancreatic cancer is not reflected in lower levels of IgE among cases, suggesting that this association operates through some mechanism other than a systemic immune response to allergens.

Acknowledgments

Financial support: This project was supported by U01CA150138 to Dr. Olson.

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Table 1

Characteristics of cases and controls

Characteristic	Cases (N=283) N (%)	Controls (N=544) N (%)	OR (95% CI)
Age (y), median (range)	65 (55 - 74)	65 (55 - 74)	
<60	52 (18)	101 (19)	NA
60-64	78 (28)	148 (27)	NA
65-69	97 (34)	187 (34)	NA
≥70	56 (20)	108 (20)	NA
Gender			
Female	108 (38)	206 (38)	NA
Male	175 (62)	338 (62)	NA
Race			
White, non-Hispanic	255 (90)	491 (90)	NA
Black, non-Hispanic	9 (3)	18 (3)	NA
Hispanic	4 (1)	7 (1)	NA
Asian	14 (5)	26 (5)	NA
Pacific Islander	1 (0)	2 (0)	NA
Education			
High school or less	84 (30)	166 (31)	1
Post-high school and some college	91 (32)	175 (32)	1.00 (0.69-1.45)
College graduate	57 (20)	85 (16)	1.31 (0.84-2.05)
Post graduate	51 (18)	117 (22)	0.84 (0.54-1.30)
Employment status			
Working	85 (30)	184 (34)	1
Retired	156 (55)	282 (52)	1.32 (0.90-1.92)
Other (homemaker, disabled, unemployed)	42 (15)	76 (14)	1.26 (0.78-2.06)
Marital status			
Married or living as married	220 (78)	433 (80)	1
Not married	63 (22)	111 (20)	1.10 (0.77-1.56)
Study center			
University of Minnesota	75 (27)	122 (22)	1
University of Pittsburgh	42 (15)	57 (10)	1.17 (0.67-2.02)
Henry Ford Health System	31 (11)	62 (11)	0.73 (0.39-1.38)
University of Utah	27 (10)	61 (11)	0.65 (0.37-1.15)
Marshfield Clinic Research Foundation	25 (9)	70 (13)	0.53 (0.29-0.97)
Washington University in St. Louis	24 (8)	50 (9)	0.72 (0.39-1.32)
University of Colorado	20 (7)	47 (9)	0.62 (0.33-1.20)
Georgetown University	15 (5)	28 (5)	0.79 (0.38-1.65)
Pacific Health Research and Education Institute (Honolulu)	13 (5)	25 (5)	0.58 (0.09-3.73)
University of Alabama at Birmingham	11 (4)	22 (4)	0.74 (0.27-2.05)
Season of blood draw			
Spring/summer/fall (Mar-Oct)	202 (71)	397 (73)	1

Characteristic	Cases (N=283) N (%)	Controls (N=544) N (%)	OR (95% CI)
Winter (Nov-Feb)	81 (29)	147 (27)	1.27 (0.71-2.28)
Smoking			
Never	106 (37)	272 (50)	1
Former quit ≥ 15 years ago	73 (26)	158 (29)	1.25 (0.86-1.81)
Former quit < 15 years ago	50 (18)	76 (14)	1.67 (1.08-2.57)
Current	54 (19)	38 (7)	3.88 (2.36-6.37)
Body Mass Index (BMI: kg/m^2)			
<25	96 (34)	192 (35)	1
25-30	118 (42)	248 (46)	0.96 (0.68-1.35)
>=30	67 (24)	102 (19)	1.34 (0.89-2.01)
Median (Range)	26.6 (18.2 - 46.3)	26.6 (18.3 - 46.9)	
Diabetes			
No	245 (87)	496 (91)	1
Yes	38 (13)	46 (8)	1.74 (1.09-2.8)
Family history of pancreatic cancer			
No	264 (94)	507 (94)	1
Yes or possibly	18 (6)	34 (6)	1.06 (0.58-1.91)
Months until diagnosis of pancreatic cancer, median (range)	94.6 (3.6 - 181.5)	NA	

Odds ratios estimated using conditional logistic regression

Columns may not add to total because of missing values

NA – not applicable

Table 2

Risk of pancreatic cancer associated with measures of IgE

	Cases (N=283) N (%)	Controls (N=544) N (%)	Odds Ratio (95% CI)
Total IgE			
Normal (<25 kU/L)	113 (40)	224 (41)	1
Borderline (25-100 kU/L)	87 (31)	192 (35)	0.84 (0.59-1.20)
Elevated (>100 kU/L)	81 (29)	126 (23)	1.22 (0.84-1.78)
>100-310 kU/L	45 (16)	79 (15)	1.09 (0.68-1.73)
>310 kU/L	36 (13)	47 (9)	1.42 (0.85-2.37)
Median (Range)	32.7 (1 - 12662)	31.9 (1 - 4099)	
Geometric Mean (SD)	41.3 (5.26)	35.5 (4.66)	
IgE to respiratory allergens			
Negative (<35 kU/L)	198 (70)	392 (72)	1
Positive (≥35 kU/L)	85 (30)	150 (28)	1.16 (0.84-1.61)
IgE to food allergens			
Negative (<35 kU/L)	257 (91)	506 (93)	1
Positive (≥35 kU/L)	26 (9)	35 (6)	1.57 (0.90-2.74)

Odds ratios estimated using conditional logistic regression adjusting for smoking (for total IgE and IgE to respiratory allergens; never, former quit >15 years ago, former quit <15 years ago, current) or study center (for IgE to food allergens)

Table 3

Interactions of IgE measures with age groups and length of time until case diagnosis

	Age		Interaction p
	<65	≥65	
Total IgE			
Cases/ Controls	130/247	151/295	
Normal	1	1	0.003
Borderline	0.45 (0.26-0.77)	1.43 (0.88-2.32)	
Elevated	0.71 (0.41-1.24)	1.98 (1.16-3.37)	
IgE to respiratory allergens			
Cases/ Controls	130/247	153/295	
Negative	1	1	0.25
Positive	0.94 (0.58-1.53)	1.39 (0.89-2.18)	
IgE to food allergens			
Cases/ Controls	130/247	153/294	
Negative	1	1	0.03
Positive	0.80 (0.34-1.91)	2.83 (1.29-6.20)	

	Years between enrollment and diagnosis			
	0-5 Years	6-9 Years	10-15 Years	
Total IgE				
Cases/ Controls	98/188	105/200	78/154	
Normal	1	1	1	
Borderline	0.64 (0.35-1.17)	1.14 (0.64-2.01)	0.79 (0.40-1.55)	0.63
Elevated	1.26 (0.66-2.41)	1.45 (0.77-2.76)	0.96 (0.49-1.91)	
IgE to respiratory allergens				
Cases/ Controls	98/188	107/200	78/154	
Negative	1	1	1	0.36
Positive	1.37 (0.76-2.46)	1.35 (0.80-2.28)	0.80 (0.43-1.48)	
IgE to food allergens				
Cases/ Controls	98/188	107/200	78/153	
Negative	1	1	1	0.98
Positive	1.47 (0.53-4.07)	1.56 (0.64-3.81)	1.68 (0.63-4.48)	

Stratum-specific odds ratios estimated using conditional logistic regression models with interaction terms and adjusting for smoking (for total IgE and IgE to respiratory allergens; never, former quit >15 years ago, former quit <15 years ago, current) or study center (for IgE to food allergens)