



## Prior History of Allergies and Pancreatic Cancer in the San Francisco Bay Area

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Data from a large population-based case-control study conducted in the San Francisco Bay Area between 1994 and 2001 were analyzed to examine the association between pancreatic cancer and history of allergic conditions. Pancreatic cancer cases ( $n = 532$ ) had to be 21–85 years of age and were identified using rapid case ascertainment. Random digit dialing and Health Care Financing Administration lists (age,  $\geq 65$  years) were used to obtain 1,701 controls who were frequency-matched to cases by sex and age within 5 years. In-person interviews were conducted and detailed allergy history data were obtained for all participants. Prior history of any allergy was associated with a reduced risk estimate for pancreatic cancer (odds ratio (OR) = 0.77, 95% confidence interval (CI): 0.63, 0.95). Inverse associations were observed for common allergens, including house dust (OR = 0.72, 95% CI: 0.54, 0.94), cats (OR = 0.59, 95% CI: 0.41, 0.85), plants (OR = 0.77, 95% CI: 0.62, 0.96), and mold (OR = 0.49, 95% CI: 0.32, 0.75), and for all allergic symptoms, although some confidence intervals included unity. Trends were observed for decreased risks associated with increasing number of allergies ( $p = 0.0006$ ) and severity of allergic symptoms ( $p = 0.003$ ). These results provide support for the plausibility that immune function in relation to allergies may play a role in the etiology of pancreatic cancer.

allergy and immunology; pancreatic neoplasms

Abbreviations: RDD, random digit dialing; Th1, T helper cell type 1; Th2, T helper cell type 2.

Pancreatic cancer is the fourth leading cause of cancer mortality among men and women in the United States (1). An estimated 30,700 new cases and 30,000 deaths due to this disease are expected to occur in the United States in 2003 (2). Fewer than 50 percent of patients survive for 3 or more months after diagnosis, and the 5-year survival rate is less than 4 percent (1). Few consistent risk factors beyond cigarette smoking and older age have been identified (3, 4), and cigarette smoking explains only about 25 percent of the disease (5).

Several medical conditions may influence the risk of pancreatic cancer. Diabetes mellitus is the most common medical condition associated with pancreatic cancer risk. A recent literature review and a meta-analysis indicated that diabetes diagnosed at least 5 years prior to the diagnosis of pancreatic cancer may confer increased risk (6, 7). Other medical conditions associated with increased risk include gallbladder disease or cholecystectomy, chronic pancreatitis,

and ulcer or gastrectomy (for a review, see Anderson et al. (8)). In contrast, decreased risks have been reported for allergic conditions (8).

Results from several studies that examined risk factors for pancreatic cancer suggested a reduced risk of pancreatic cancer among patients with any allergic conditions, although the results varied (9–13). The purpose of this analysis was to determine the relation between pancreatic cancer risk and history of allergies in a large population-based case-control study.

### MATERIALS AND METHODS

#### Study population

A population-based case-control study of 532 pancreatic cancer cases and 1,701 controls was conducted between 1994 and 2001 in the San Francisco Bay Area in California (14–18). Patients with primary adenocarcinoma of the

exocrine pancreas were identified by the Northern California Cancer Center using rapid case ascertainment in the six San Francisco Bay Area counties of Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara. All pancreatic cancer patients between 21 and 85 years of age who were residents of one of the six counties at the time of diagnosis between 1994 and 1999 and who were alive and able to complete an interview in English were eligible for inclusion in this study. Diagnoses were confirmed by the participants' physicians and finally by Surveillance, Epidemiology, and End Results abstracts that included histologic confirmation of the disease based on surgery and/or autopsy. A total of 735 patients were ineligible because they died before we could contact them, and 84 could not complete an interview in English. Of the 719 eligible San Francisco Bay Area patients, 140 were too ill, 20 had physician-indicated contraindications for contact, 68 refused to participate, 19 could not be located, five did not participate for other reasons, and 467 completed the study interview. Additionally, 65 out-of-area cases identified through clinical records at the University of California, San Francisco, Medical Center were eligible to participate because they met all study criteria other than that for place of residence at the time of diagnosis. Diagnoses were confirmed using pathology reports and medical records for the out-of-area patients who completed interviews. This provided us with a total of 532 pancreatic cancer patients.

Control participants were obtained using random digit dialing (RDD) and Health Care Financing Administration (now Centers for Medicare & Medicaid Services) lists for persons aged 65 years or older. Control participants were frequency-matched to cases by sex and age within 5 years. Out-of-area controls also were identified using RDD and were frequency-matched to out-of-area cases by telephone area code and prefix and by sex and age. Written informed consent was obtained from each study participant prior to interview. A total of 1,701 eligible control participants completed interviews. Of these, 59 percent were obtained by RDD in the San Francisco Bay Area, 4 percent were obtained by out-of-area RDD, and 37 percent were obtained from the Health Care Financing Administration lists. Response rates for eligible control participants were 60 percent for the San Francisco Bay Area, 69 percent for out-of-area RDD, and 53 percent for the Health Care Financing Administration.

### Interviews

No proxy interviews were conducted. Detailed interviews were conducted in person in the participants' homes or at another location of choice for Bay Area participants and by telephone for out-of-area participants. Carefully trained, experienced interviewers used structured questionnaires.

The questionnaire was designed to collect extensive information about potential pancreatic cancer risk factors, including demographic data and information on occupational history, smoking history, diet, and family and personal medical history (including history of allergic conditions). Data were collected for the following allergens: house dust, animals (cats, dogs, and other animals), plants (trees, grass,

weeds, and pollen), foods (eggs, dairy food, shellfish or seafood, wheat, peanuts, citrus fruit, and other foods specified by the respondent), insect stings, and mold. Data also were collected on reactions to vaccines (tetanus, mumps, influenza, and other vaccines). A card that listed the allergens of interest was provided to the study participant, and the interviewer asked whether the participant had ever been allergic to any of the items on the card. If a positive response to a specific allergen was indicated, the participant was given a list of symptoms and asked whether the allergic reaction included any of the following: runny nose, burning or watery eyes, sneezing or congestion, wheezing or asthma, hives, severe swelling, or anaphylactic shock. The interviewer also asked at what age the participant had first noticed the allergy and at what age the participant had had the most recent allergic reaction to the specific allergen. Participants were asked to report the duration of exposure in years for animals and in months per typical year for plants and mold, or the total number of reactions to a specific allergen such as foods, insect stings, or immunizations. They also were asked about periodic allergy shots (defined as daily, weekly, or monthly), their ages at the first and last allergy shots, the total number of months or years for which the shots had been received, and whether a doctor had ever told them that they had eczema.

### Statistical analyses

Statistical analyses were completed using SAS software (version 8; SAS Institute, Inc., Cary, North Carolina). Unconditional logistic regression was used to obtain odds ratios and 95 percent confidence intervals as estimates of relative risk. All estimates were adjusted for age and sex. Potentially confounding factors, including race (White/non-White), education, and smoking (ever vs. never, where ever smoking was defined as having smoked more than 100 cigarettes or having smoked at least one cigar or pipe per month for at least 6 months), were evaluated and were included in the final models if the risk estimate was changed by 10 percent or more. Other factors, including body mass index, height, and diabetes, were not considered as potential confounders because they were not associated with allergy history in this population.

The referent group for all analyses was participants who reported that they had never been allergic to house dust, animals, trees, grass, weeds, or pollen, foods, bee, yellow jacket, or wasp stings, mold, or vaccines and had not experienced any accompanying symptoms of runny nose, burning or watery eyes, sneezing or congestion, wheezing or asthma, hives, severe swelling, or anaphylactic shock. Because too few participants reported having had reactions to vaccines, those results are not reported individually but were used to compute other variables, including total number of allergies and allergy severity. A score for number of allergies was computed as the total number of different major allergens reported by each person. Continuous variables were categorized into quartiles or tertiles based on the frequency distribution among the controls. Severity of reported allergic reactions was evaluated using the most severe symptom experienced. Reactions were defined as mild (runny nose,

**TABLE 1. Demographic characteristics of pancreatic cancer patients and control participants, San Francisco Bay Area, California, 1994–2001**

Characteristic	Cases ( <i>n</i> = 532)		Controls ( <i>n</i> = 1,701)	
	No.	%	No.	%
Age (years)				
22–39	5	1	27	2
40–49	37	7	137	8
50–59	119	22	438	26
60–69	172	32	473	28
70–79	160	30	498	29
80–85	39	7	128	8
Sex				
Female	241	45	818	48
Male	291	55	883	52
Race				
Caucasian	442	83	1,471	86
African American	46	9	78	5
Asian	35	7	119	7
Other	9	2	33	2
Hispanic origin	25	5	114	7
Education (highest level completed)				
High school or less	235	44	534	31
College	200	38	754	44
Graduate studies	97	18	413	24

burning/watery eyes, sneezing/congestion), moderate (wheezing/asthma, hives, severe swelling), or severe (anaphylactic shock). Routes of exposure to allergens were evaluated for comparison with other investigators' work (19) and were categorized as respiratory (house dust, animals, plants, molds), dermal (insect stings or bites), or digestive (foods).

Tests of linear trend in risk for ordinal categorical variables were conducted using logistic models. All statistical tests were two-sided. Results were considered significant at  $p \leq 0.05$  and borderline-significant at  $p \leq 0.10$ .

## RESULTS

The demographic characteristics of the pancreatic cancer patients and controls are presented in table 1. Participants ranged in age from 22 years to 85 years; the median age was 67 years for women and 66 years for men. History of any allergy was associated with a reduced risk of pancreatic cancer (table 2). Inverse associations were observed for several allergens, including house dust, animals, plants, some foods, insect bites or stings, and mold. Many of the odds ratios for individual food allergies were based on sparse data and had wide confidence intervals that included unity. However, odds ratios for more common allergens, including house dust, dogs, cats, plants, insect bites or stings, and

mold, had a narrow range between 0.49 and 0.82, with most confidence intervals excluding unity (table 2).

Total number of allergies, specific symptoms, and severity of allergies were also examined (table 3). A trend of decreasing risk with increasing number of allergies was observed. All allergic symptoms were evaluated independently of a specific allergen, and all were associated with reduced risk estimates for pancreatic cancer, although some confidence intervals included unity. In addition, a trend of decreasing risk was observed with increasing severity of symptoms and older age at first allergy. Latency between age at first reported allergy and diagnosis or interview was evaluated. The odds ratio was lowest for persons who reported having had the first occurrence of their allergy within 5 years of diagnosis or interview (<5 years: odds ratio = 0.44, 95 percent confidence interval: 0.20, 0.93;  $\geq 5$  years: odds ratio = 0.88, 95 percent confidence interval: 0.65, 0.98). Duration of exposure was evaluated as the total number of years of living or working with an animal that caused allergic reactions and the total number of months plants or molds triggered allergies in a typical year. Linear trends of decreasing risk with increasing duration of exposure were observed for each of these factors (table 3). Results regarding the likely route of exposure showed that respiratory allergy was the most common.

History of allergy shots showed that persons who had received allergy shots for 2 years or less had a greater

**TABLE 2. Odds ratios for pancreatic cancer in relation to allergic reactions to specific allergens, San Francisco Bay Area, California, 1994–2001\***

Allergen	Cases (n = 532)		Controls (n = 1,701)		Odds ratio†	95% confidence interval
	No.	%	No.	%		
No allergies	314	59	879	52	1.0‡	
Any allergy	211	40	781	46	0.77	0.63, 0.95
House dust	87	16	351	21	0.72§	0.54, 0.94
Plants¶	166	31	617	36	0.77	0.62, 0.96
Mold	27	5	160	9	0.49	0.32, 0.75
Any animals	52	10	226	13	0.66	0.47, 0.93
Dogs	23	4	83	5	0.82	0.50, 1.3
Cats	42	8	207	12	0.59	0.41, 0.85
Other animals#	12	2	41	2	0.86	0.44, 1.7
Insect bites or stings	24	5	107	6	0.65	0.41, 1.0
Any foods	39	7	152	9	0.74	0.51, 1.1
Eggs	3	1	18	1	0.49	0.14, 1.7
Dairy products	7	1	25	1	0.82	0.35, 1.9
Seafood or shellfish	16	3	52	3	0.89	0.50, 1.6
Wheat	2	<1	10	1	0.59	0.13, 2.7
Peanuts	6	1	12	1	1.5	0.55, 4.0
Citrus fruit	5	1	25	1	0.58	0.22, 1.5
Other foods**	18	3	63	4	0.82	0.45, 1.4

\* Data may not sum to the totals because six cases and 39 controls who reported having had allergies but no allergic reactions were excluded, and data on some participants were missing.

† Adjusted for age and sex.

‡ Referent.

§ When adjusted for age, sex, and smoking, the odds ratio was 0.82 (95% confidence interval: 0.65, 1.0).

¶ Trees, grass, weeds, or pollen.

# Horses, rodents, cattle, rabbits, or birds.

\*\* Other fruits, vegetables, and grains reported by fewer than seven participants for a specific food.

reduced risk than persons who had not received allergy shots (table 4). Although having received allergy shots for more than 2 years also resulted in a reduced risk estimate, the confidence interval included unity. The risk estimate for allergy shots did not differ by age at first allergy shot. However, when time since last allergy shot was evaluated, the greatest reduced risk was observed for persons who had received allergy shots within 5 years of diagnosis or interview, although the confidence interval included unity.

History of physician-diagnosed eczema was asked about separately, and risk estimates were computed for ever having had eczema versus never having had it and for eczema combined with allergy history (table 5). An inverse association between history of eczema and pancreatic cancer was observed. When eczema was evaluated in combination with other allergy history data, risk estimates were reduced for persons who reported allergies only, persons who reported eczema only, and persons who reported both allergies and eczema, with similar effects observed for groups that included eczema.

## DISCUSSION

Results from our large, population-based case-control study support evidence from earlier epidemiologic studies of pancreatic cancer that suggested a reduced risk of pancreatic cancer among persons with a general history of allergic conditions (9–13, 20–22). In addition to the data in the earlier investigations, we collected detailed data about specific allergens, frequency, duration, and allergic symptoms. Using these data, we observed evidence of a dose-response effect associated with allergy characteristics in addition to our main-effect results. Odds ratios were consistently reduced for individual allergens, for people who reported having allergies to an increasing number of allergens, and for increasing severity of reported allergic symptoms, although some estimates were based on few exposed cases. In a Medline search of articles that have been published in English since 1975, we found no investigations that reported data on allergy symptoms, symptom severity, age at first allergy, and other information on duration of exposure in relation to pancreatic cancer risk.

**TABLE 3. Odds ratios for pancreatic cancer in relation to allergy characteristics, San Francisco Bay Area, California, 1994–2001\***

Factor	Cases (n = 532)		Controls (n = 1,701)		Odds ratio†	95% confidence interval
	No.	%	No.	%		
Total no. of allergies						
0	314	59	879	52	1.0‡	
1	111	21	335	20	0.93	0.73, 1.2
2	53	10	200	12	0.75	0.54, 1.0
≥3	47	9	243	14	0.56	0.39, 0.79
<i>p</i> for trend						<0.001
Allergy symptoms						
Runny nose	159	30	542	32	0.84	0.67, 1.0
Burning or watery eyes	152	29	545	32	0.80	0.64, 1.0
Sneezing or congestion	168	32	644	38	0.75	0.60, 0.93
Wheezing or asthma	44	8	238	14	0.53	0.37, 0.75
Hives	37	7	116	7	0.92	0.62, 1.4
Severe swelling	33	6	117	7	0.82	0.54, 1.2
Anaphylactic shock	3	1	23	1	0.38	0.11, 1.3
Severity of symptoms§						
Mild	121	23	393	23	0.88	0.67, 1.1
Moderate	87	16	361	21	0.69	0.53, 0.91
Severe	3	1	23	1	0.37	0.11, 1.3
<i>p</i> for trend						0.003
Route of exposure¶						
Respiratory	200	38	717	42	0.80	0.65, 0.98
Dermal	24	5	107	6	0.65	0.41, 1.0
Digestive	39	7	152	9	0.74	0.51, 1.1
Age (years) at first allergy						
≤15	79	15	265	16	0.86	0.65, 1.2
16–35	66	12	254	15	0.75	0.55, 1.0
>35	66	12	262	15	0.71	0.52, 0.95
<i>p</i> for trend						0.007
Duration of exposure						
Plants# (no. of months in a typical year)						
<4	97	18	310	18	0.88	0.67, 1.1
≥4	67	13	302	18	0.62	0.46, 0.84
<i>p</i> for trend						0.002
Molds (no. of months in a typical year)						
<6	16	3	76	4	0.57	0.33, 1.01
≥6	9	2	74	4	0.33	0.16, 0.67
<i>p</i> for trend						<0.001
Animals (total no. of years)						
<2	23	4	81	5	0.80	0.49, 1.3
2–19	19	4	73	4	0.73	0.43, 1.2
≥20	9	2	73	4	0.35	0.17, 0.71
<i>p</i> for trend						0.002

\* Data may not sum to the totals because six cases and 39 controls who reported having had allergies but no allergic reactions were excluded, and data on some participants were missing.

† Adjusted for age and sex.

‡ Referent.

§ Mild symptoms include runny nose, burning or watery eyes, and sneezing or congestion; moderate symptoms include wheezing or asthma, hives, and swelling; severe symptoms include anaphylactic shock.

¶ The respiratory route of exposure includes house dust, animals, plants, and molds; the dermal route includes insect stings or bites; and the digestive route includes eggs, dairy food, nonshellfish seafood, shellfish, wheat, peanuts, citrus fruit, and other foods.

# Trees, grass, weeds, or pollen.

**TABLE 4. Odds ratios for pancreatic cancer in relation to history of allergy shots, San Francisco Bay Area, California, 1994–2001\***

Factor	Cases (n = 532)		Controls (n = 1,701)		Odds ratio†	95% confidence interval
	No.	%	No.	%		
Total duration of allergy shots						
No allergies	314	59	879	52	1.0‡	
Allergies but no allergy shots	159	30	592	35	0.77	0.62, 0.96
≤2 years	19	4	92	5	0.59	0.36, 0.99
>2 years	29	5	96	6	0.87	0.56, 1.3
Age (years) at first allergy shot						
≤33	27	5	99	6	0.79	0.51, 1.2
>33	25	5	89	5	0.79	0.50, 1.3
Allergy shot latency (years)§						
≤5	10	2	45	3	0.64	0.32, 1.3
>5	40	8	143	8	0.80	0.55, 1.2

\* Data may not sum to the totals because six cases and 39 controls who reported having had allergies but no allergic reactions were excluded, and data on some participants were missing.

† Adjusted for age and sex.

‡ Referent.

§ Latency for cases = diagnosis age minus age at last allergy shot; latency for controls = interview age minus age at last allergy shot.

Some of the discrepancies between our results and those from earlier investigations may be associated with the use of proxy data in other studies. Exposure data collected from proxy participants may be inaccurate and may introduce biases (23). The inconsistency in results from analyses of allergy data collected using proxy respondents is reflected in one earlier study that used both direct and proxy interviews and reported greater reduced risk estimates for direct respondents alone (10). Additionally, researchers observed that next-of-kin proxy respondents overreported the presence of

asthma and hay fever in comparison with reports by cases who were interviewed in person in a large population-based study (13). Compared with other population-based studies that did not use proxy interviews (12, 13) or that reported risk estimates separately for direct and combined interviews (10, 11), our results similarly showed inverse associations between history of allergies and pancreatic cancer.

Investigation of specific allergens indicated that although all individual allergens were associated with a reduced risk of pancreatic cancer, the magnitude of the effect varied. The

**TABLE 5. Odds ratios for pancreatic cancer in relation to history of eczema (ever vs. never) and history of both allergies and eczema, San Francisco Bay Area, California, 1994–2001\***

Factor	Cases (n = 532)		Controls (n = 1,701)		Odds ratio†	95% confidence interval
	No.	%	No.	%		
Eczema						
Never	487	92	1,492	88	1.0‡	
Ever	42	8	200	12	0.66	0.46, 0.93
Allergies and eczema						
Neither	298	56	808	48	1.0‡	
Allergies only	183	34	648	38	0.78	0.63, 0.97
Eczema only	14	3	68	4	0.57	0.31, 1.0
Both allergies and eczema	27	5	128	8	0.59	0.38, 0.92

\* Data may not sum to the totals because six cases and 39 controls who reported having had allergies but no allergic reactions were excluded, and data on some participants were missing.

† Adjusted for age and sex.

‡ Referent.

estimate for general history of allergies reflected the estimate for plants reported by more than 75 percent of participants with allergies. Mold allergies were associated with the greatest reduction in pancreatic cancer risk, although the confidence interval overlapped the confidence intervals for other allergens. The few other epidemiologic studies that collected nonproxy data and investigated specific allergens either did not evaluate mold allergies or combined mold with other allergens (12, 13). For comparable allergens such as insect stings, hay fever, and animals, the associated risk estimates reported by other investigators were similar to those obtained in our analyses (12, 13). Similar to our results, another study that tallied the total number of allergic conditions combined with allergic symptoms found that a greater number of conditions was associated with a greater reduction in risk (12). However, the estimates were not significant.

All dust, plant, mold, and cat allergic reactions were associated with reduced risk, with confidence intervals that excluded unity. The allergic signs and symptoms of runny nose, watery eyes, and sneezing often occurred in combination among participants with allergies in our study, and all had similar reduced risks. To our knowledge, no other study of pancreatic cancer that collected nonproxy data evaluated these mild reactions. Of the three studies that interviewed patients directly and evaluated more severe reactions (12, 13, 22), two reported no effect for asthma (12, 13), whereas one reported a reduced risk for hives, although the confidence interval was imprecise (12). Investigators using data from a cohort of male smokers observed a positive association between bronchial asthma and pancreatic cancer risk but did not specify whether the bronchial asthma was allergy-related (24). The severe reaction of anaphylactic shock is rare (1 percent of our participants with allergies); therefore, it is not surprising that it was not evaluated in other, smaller investigations of pancreatic cancer and allergic conditions. In our study, anaphylactic shock was associated with a reduced risk of pancreatic cancer, although the estimate was based on few exposed patients and was imprecise. Because we collected data on a range of types of reactions, we were able to create a unique allergy severity scale to differentiate the effect of severity of allergies on pancreatic cancer risk. Our results showing a decreasing risk associated with increasing allergy severity provide further evidence that allergies are likely to play a role in the etiology of pancreatic cancer. Additionally, we observed a reduced risk estimate for a history of physician-diagnosed eczema. Other studies that used nonproxy data reported inconsistent results for eczema alone, with both reduced (11) and increased (13) risks being observed.

We observed no trend in decreased risk with increasing number of years of allergy shots. The one study that investigated total number of allergy shots similarly reported no trend with increasing number of shots (13). Interestingly, we observed a greater inverse association with pancreatic cancer risk among persons who had received allergy shots within 5 years of diagnosis or interview than among persons who had allergies but had received no allergy shots. These results are consistent with the pattern we observed for other allergy characteristics and suggest that persons who were still receiving allergy shots were likely to have had more severe allergies that may differentially affect biologic processes

complementary to the etiologic pathway of pancreatic cancer.

Other allergy-related factors evaluated in our study and not reported by other investigators, such as increasing age at first allergy, increasing duration of exposure, and route of exposure, were associated with decreased risks of pancreatic cancer. Nearly all of our analyses of dose-related factors associated with allergies consistently showed reduced risks of pancreatic cancer, whether measured as longer duration, greater number of allergies, or more severe reactions. These detailed data provide additional support for the plausibility that immune function related to allergies may play a role in the etiology of pancreatic cancer. Advances in the understanding of cancer and immunology may help to explain how allergies and other related biologic processes might influence immune function and the development of pancreatic cancer.

Recent studies have used premises of the "hygiene hypothesis" (25) and the "Th1/Th2 paradigm" (26, 27) to investigate the roles of T helper cell type 1 (Th1) and T helper cell type 2 (Th2) in allergic conditions and tumor immunity. Evidence indicates that Th2 inflammatory responses marked by the production of immunoglobulin E antibody-producing B cells are essential factors in the pathophysiology of allergies (28), whereas Th1 responses have stronger antitumor effects (29). Our analyses showed that although long-standing allergies were associated with reduced risk, first-time allergies were less likely to be reported shortly before diagnosis with pancreatic cancer. Similar to the association between parasitic infections and allergies (30), pancreatic cancer may dominate the Th2 pathway suppressing allergic conditions. However, immunologic factors that influence pancreatic and other cancers are ambiguous and undoubtedly involve a complex array of mechanisms that are not completely understood (26, 27, 31). Enhanced natural immune surveillance that results from a hypersensitive immune system in persons with a history of allergies may be a plausible mechanism with which to explain the observed reduced risk estimates (32, 33). In addition, specific components of the allergic cascade and similar associations with other diseases may help to elucidate the role of allergies in the etiology of pancreatic cancer. Histamine released as an allergic response may positively impact antitumor immunity through its ability to boost Th1-type responses (via histamine-1 receptor binding) (34) and to protect natural killer cells and T cells (via histamine-2 receptor binding) from the damaging effects of reactive oxygen metabolites (35, 36). Alternatively, the mechanism may be similar to that underlying the inverse association between atopy and helminth infections (both Th2-driven) and/or between atopy and measles and tuberculosis (diseases that mediate immunosuppression via cytokines dominant in pancreatic cancer patients (30, 37)). An inverse association with history of allergies has also been observed in epidemiologic studies for other gastrointestinal cancers, including colorectal (38, 39) and liver (40) cancers, non-Hodgkin's lymphoma (41–43), and glioma (19, 44). Detailed data from previous studies that examined the association between allergies and pancreatic cancer are limited. A recent study that examined the association between history of allergies and risk of adult glioma

included several variables similar to those in our study and proved useful for comparing results (19). We observed reduced risk estimates for all self-reported allergy symptoms that were similar to those reported in the glioma study (19). Reduced risk estimates for all routes of likely allergen exposure also were comparable between studies. Although these studies examined different cancer sites, support for observations associated with specific variables lends credence to a role for allergies in cancer immunology.

A major strength of this study is that, in addition to being the largest population-based pancreatic cancer case-control study to date, only direct interviews with study participants were conducted. Thus, we were able to avoid the potential inaccuracies associated with proxy data. To our knowledge, this is also the first published study to have examined the association between detailed allergy data such as duration, symptoms and their severity, and pancreatic cancer. In addition, we observed evidence of a dose-response associated with specific allergic characteristics. Our study questionnaire was designed to elicit a variety of types of information that allowed us to evaluate potential confounders. Another advantage of our study is that it did not require physician diagnosis of allergic conditions. Diagnosis of allergic conditions by a physician may influence study participants' self-reported history of allergies (45). Thus, because persons with minor allergic symptoms may not be compelled to seek the advice of a physician (45), such strict study criteria could have eliminated a large number of exposed cases and controls. Factors such as physicians' diagnostic practices and study participants' memories of their diagnoses also may affect participants' perceptions of their allergy history (45). Our study collected data on allergic symptoms in addition to specific allergens to circumvent these issues and to better identify persons who suffered from allergic conditions.

Some potential limitations of our study deserve consideration. Selection bias is a concern with diseases, such as pancreatic cancer, that are characterized by short survival and high mortality rates. Our study design sought to minimize this bias by identifying population-based participants using rapid case ascertainment for cases. However, the disease may have been different among persons who died before interview. Using abstract data from the Surveillance, Epidemiology, and End Results registry, we found that interviewed patients were more likely to be male, were more likely to be White, and were slightly younger and that their tumor characteristics more often were unknown in comparison with noninterviewed patients. Based on these few characteristics, noninterviewed patients may have been sicker than interviewed patients, but we cannot assume that this was related to differential risk factors by group. Noninterviewed patients may have waited longer to seek medical attention, may have been misdiagnosed initially, or may have had more aggressive disease. Proxy interviews would not alleviate this problem, because evidence indicates that medical history, including allergies, is often reported inaccurately by proxy respondents (13). Recall bias, where cases report more allergies than controls, is possible. However, this is less likely given that the possibility of an association between allergy and pancreatic cancer is not commonly known. Additionally, such reporting by cases would have

resulted in increased risk estimates rather than the observed decreased estimates. When researchers ask people to recall prior events, there often is a concern that inaccurate information may be obtained. However, for history of allergies, such reporting errors are unlikely, because allergies are aggravating and usually persistent conditions that are not easily forgotten. Because most allergies are recurrent conditions, it is likely that any reporting error that did occur was nondifferential, and this would have resulted in estimates closer to the null. It is also possible that more pancreatic cancer patients had asymptomatic allergic conditions and therefore would have underreported allergic conditions. This may be related to coexisting infections or conditions and would result in residual confounding. Residual confounding due to an unknown or unmeasured exposure may be possible for the observed association and the lower allergy prevalence in the patients.

The complex nature of allergic conditions and thus allergy-related questions may have introduced the possibility of misclassification of length of exposure in our study. Asking the question "At what age did you first notice your allergy?" to ascertain age at first allergy may have been problematic, since there could have been a discrepancy between the time when a person first noticed a symptom or reaction as an allergy and the time when the allergy actually originated. Additionally, allergies may be dependent on a variety of factors such as a person's location and the season of the year. Allergic reactions also may be confused with minor irritations, and this could result in misclassification of exposure. To avoid eliciting erroneous responses regarding allergic conditions, we worked with an allergist to develop the allergy portion of our questionnaire. We did not inquire about topics such as drugs or smoke, because often these factors are irritants rather than allergens. We avoided, to the best of our ability, the confusion between irritation and a true allergic response.

Allergy history was self-reported and was not biologically confirmed at diagnosis by performance of skin-prick tests or measurement of immunoglobulin E levels. However, such information obtained from cases in a case-control study may not be useful, because there is no way to know whether the pancreatic cancer affected the allergic response or immunoglobulin E levels. Additionally, it has been reported that cigarette smoking (46, 47) and sex-related differences may influence immunoglobulin E levels (48), further complicating the use of such biologic information. Thus, self-reported history of allergies may be the best measure of exposure in a case-control study.

In summary, we observed consistent reduced risk estimates for pancreatic cancer associated with allergy history. We also consistently observed dose-response effects for total number, severity, and duration of allergies—all evidence that supports a role for allergic conditions in the pathogenesis of pancreatic cancer. Future epidemiologic studies of pancreatic cancer designed to collect detailed information on allergies, including ages at first and last allergy, severity, and duration, are needed to confirm our results. Continued investigation of immune system function in cancer development is essential.

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