Systematic Reviews and Meta- and Pooled Analyses

Allergies and Risk of Pancreatic Cancer: A Pooled Analysis From the Pancreatic Cancer Case-Control Consortium

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In order to quantify the risk of pancreatic cancer associated with history of any allergy and specific allergies, to investigate differences in the association with risk according to age, gender, smoking status, or body mass index, and to study the influence of age at onset, we pooled data from 10 case-control studies. In total, there were 3,567 cases and 9,145 controls. Study-specific odds ratios and 95% confidence intervals were calculated by using unconditional logistic regression adjusted for age, gender, smoking status, and body mass index. Between-study heterogeneity was assessed by using the Cochran *Q* statistic. Study-specific odds ratios were pooled by using a random-effects model. The odds ratio for any allergy was 0.79 (95% confidence interval (CI): 0.62, 1.00) with heterogeneity among studies ($P < 0.001$). Heterogeneity was attributable to one study; with that study excluded, the pooled odds ratio was 0.73 (95% CI: 0.64, 0.84) ($P_{\text{heterogeneity}} = 0.23$). Hay fever (odds ratio = 0.74, 95% CI: 0.56, 0.96) and allergy to animals (odds ratio = 0.62, 95% CI: 0.41, 0.94) were related to lower risk, while there was no statistically significant association with other allergies or asthma. There were no major differences among subgroups defined by age, gender, smoking status, or body mass index. Older age at onset of allergies was slightly more protective than earlier age.

allergic rhinitis; case-control studies; hypersensitivity; pancreatic neoplasms

Abbreviations: CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; OR, odds ratio; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

Relationships between the immune system and cancer risk can provide important clues about carcinogenesis. Associations between self-reported allergies and various cancers have been investigated in a number of epidemiologic studies (1–3); reduced risk for pancreatic cancer is among the most consistent findings. A meta-analysis of 14 pancreatic cancer studies showed a 30% reduced risk in those with any allergies and a 45% reduced risk in those with respiratory allergies such as hay fever in studies with direct interviews rather than proxies (4). Since the publication of the meta-analysis,

3 new case-control studies (5–8), 1 expanded case-control study (9), and a cohort study (10) have supported these results. A recent review of 11 published studies that reported on risks associated with any allergy (11) found statistically significantly reduced risk in most of the studies and consistently reduced risk for respiratory allergies such as hay fever and allergies to plants or pollen. Other allergies, such as those to animals, foods, and medications, have been less well studied, and associations with risk are unclear. Although asthma is often found in conjunction with respiratory allergies, it is not

consistently associated with risk, and several studies have shown no association (4, 11).

In contrast, cohort studies conducted in Sweden (12, 13) and the United States (14) in people with allergies have not found evidence that self-reported allergies, skin prick tests, or immunoglobulin E levels were associated with decreased risk of cancer overall or with specific cancers, including pancreatic cancer. Results from these cohort studies remain inconclusive because the patients studied were young and follow up was only for up to 13 years, resulting in only a handful of cases; in addition, data were not always available to adjust for potentially confounding factors such as cigarette smoking status.

Many questions remain about the reported associations between pancreatic cancer risk and history of allergies. Few studies have reported on whether or not the association between allergies and risk varies according to individual characteristics such as age, gender, cigarette smoking status, or body mass index. In addition, little is known about the influence of age at onset of allergies or the number of allergies and risk of pancreatic cancer. We conducted this pooled analysis of 10 studies in the international Pancreatic Cancer Case-Control Consortium (PanC4) in order to obtain a more precise estimate of risk associated with allergies and individual allergies, as well as to address these additional questions. Compared with a meta-analysis based only on published data, a pooled analysis using the original data allows for more consistent definitions of exposures, adjustment for the same potential confounders, and subgroup analyses.

MATERIALS AND METHODS

Study populations

The 10 studies that contributed data to this pooled analysis were identified through the Pancreatic Cancer Case-Control Consortium (<http://www.panc4.org>); their location, timing, methods, numbers of cases and controls, and prevalence of any allergy in controls are shown in Table 1. We included all the studies in the Pancreatic Cancer Case-Control Consortium that had data available on allergies, without regard to whether or not the results had been published. We obtained original data from each participating study. Patients with carcinoid or acinar histology were excluded. Proxy respondents were excluded from those studies where they had been included, since little is known about the agreement between proxy and direct interviews for questions on allergies. Each study obtained written, informed consent and approval from the institutional review board at its institution.

Variables

After obtaining original data on allergies from each participating study, we checked results for internal consistency, outliers, and missing variables. When published data were available, we compared them with the data we obtained. Questions and discrepancies were resolved in collaboration with the investigators who provided the data.

All the studies relied on respondent self-report to assess history of allergies. Questions on allergies varied among the

studies. Three studies (Surveillance of Environmental Aspects Related to Cancer (SEARCH), Shanghai, Louisiana State University) asked about allergies diagnosed or treated by a physician, while 2 others (National Cancer Institute (NCI), Toronto) asked about physician diagnosis of some but not all allergies. Most studies asked a general question on whether respondents ever had allergies, while others (University of California, San Francisco (UCSF), SEARCH, Shanghai) asked only about individual allergies. For the latter studies, we derived a variable for “any allergy” by considering respondents to have any allergy if they answered “yes” to any question about the specific allergies queried in the study. Asthma was not included in these definitions because it may or may not be related to allergy. Because the Milan study asked only about allergy to medications, we excluded this study from the summary of “any allergy” and used data from this study only in the summary of drug allergies. Details of the questions for each study are shown in Appendix Table 1. Although these studies asked about history of allergies, we use the term “any allergy” to describe this variable.

For each study, we determined the earliest reported age at onset of any allergy (excluding asthma) in controls and categorized cases and controls with any allergy as above or below the median age for the controls. The median age at onset ranged from 22 (Memorial Sloan-Kettering Cancer Center (MSKCC)) to 41 (Shanghai). Age at onset was also categorized by using the overall median age at onset in controls from all studies (age 30 years).

Statistical analysis

The analytical approach was a 2-stage process. In the first step, we calculated study-specific odds ratios using a logistic model with pancreatic cancer as the outcome. Within each study, odds ratios were adjusted for age (continuous), gender, race (white, black, Asian/Pacific Islander, other/mixed), cigarette smoking status (never, former, or current, including those who quit in the past year), and body mass index category (<25, 25–<30, ≥30). In separate analyses, we also included asthma as a covariate in studies that asked about asthma. Because information on body mass index was not available from Minnesota, this variable was not included as a covariate in study-specific analysis for this study. For 3 studies, there was no variation in race (Italy, SEARCH, and Shanghai), and for Toronto, information on race was available for 472 of 475 cases but for only 3 of 310 controls; for these studies, race was not included as a covariate when estimating study-specific odds ratios. To determine odds ratios, those with any allergy and with each individual allergy were compared with the reference category, those with no allergies. Those with asthma were compared with those without asthma.

The second step consisted of pooling the study-specific odds ratios by using a random-effects model where the outcomes are the estimated study-specific exposure-disease effects. The pooled summary odds ratio is a weighted average of the study-specific odds ratios. The weights are related to the inverse marginal variances of the study-specific odds ratios. More specifically, we calculated the pooled odds ratios and their standard errors using a weighted maximum

Table 1. Studies Included in the Analysis of Allergies and Risk of Pancreatic Cancer, International Pancreatic Cancer Case-Control Consortium

Study	Author, Year (Reference)	Location	Study Period	Median Age, years	Age Range, years	Matching Variables	Cases		Controls		
							No.	Source	No.	Source	Prevalence of Any Allergy, %
Milan	La Vecchia, 1990 (32)	Milan, Italy	1982–1999	57	17–86		362	Hospital	1,549	Hospital	9 (drugs only)
Italy	Lipworth, 2011 (33); Talamini, 2010 (34)	Northern Italy	1991–2008	63	34–80	Age, gender	322	Hospital	652	Hospital	11
Minnesota	Anderson, 2002 (35)	Minneapolis and St. Paul, Minnesota; Upper Midwest	1994–1998	68	25–94	Age, gender	254	Population-based and hospital-based cancer registries	676	Drivers' license lists (<65 years); HCFA (≥65 years)	21
SEARCH	Maisonnette, 2010 (9)	The Netherlands; Adelaide, Australia; Montreal and Toronto, Canada; Warsaw, Poland	1983–1989	65	28–87	Age, gender	318	Hospitals, cancer registries	1,321	Population registries	22
Shanghai	Dai, 1995 (36)	Shanghai, China	1992–1993	63	31–74	Age, gender	62	Cancer registry	247	Resident registry	23
LSU	Unpublished data	Louisiana	2001–2006	67	32–90	Age, gender, race	69	Cancer registry	158	Population-based files	30
Toronto	Anderson, 2009 (5)	Ontario (cases) and Greater Toronto (controls), Canada	2003–2006	66	20–89	None	475	Population-based cancer registry	310	RDD/property assessment rolls	35
NCI	Silverman, 1999 (37)	Atlanta, Georgia; Detroit, Michigan; New Jersey	1986–1989	63	30–81	Age, gender, race	461	Population-based cancer registry	2,036	RDD (<65 years); HCFA (≥65 years)	42
UCSF	Holly, 2003 (38)	San Francisco Bay Area, California	1995–1999	66	32–85	Age, gender, county	527	Cancer registry	1,696	RDD CMS/HCFA (≥65 years)	50
MSKCC	Olson, 2007 (8)	New York City Metropolitan Region, New York	2003–2010	63	27–90	None	717	Hospital	500	Hospital visitors	65
Total							3,567		9,145		

Abbreviations: CMS, Centers for Medicare and Medicaid Services; HCFA, Health Care Financing Administration; LSU, Louisiana State University; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; RDD, random digit dialing; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

likelihood-type approach that takes into account the variances of the study-specific odds ratios and other unexplained variation (15).

We tested for statistical significance of between-study heterogeneity using the Q test statistic (16). In sensitivity analyses, we evaluated heterogeneity after excluding each study and considering the remaining studies. To investigate factors potentially related to heterogeneity, we adjusted results for study location (North America vs. Europe, excluding the Shanghai study); study design (hospital or population based); prevalence of any allergy in the control group, classified as low (prevalence ranging from 11% to 22%), medium (ranging from 23% to 35%), and high (ranging from 42% to 65%); the median age at onset of any allergy; and the number of allergies queried, ranging from 1 (Italy, Louisiana State University, Toronto) to 8 (Minnesota). (Refer to Appendix Table 1 footnote a.) Milan was excluded from the last 2 analyses.

Using the same 2-stage process, we undertook stratified analyses with strata defined by age (≤ 63 and > 63 years, the median age in the controls), gender, cigarette smoking status (never, former, current), and body mass index (< 25 , $25\text{--}30$, ≥ 30). Stratified analyses were conducted for any allergy and for hay fever. Data from Shanghai were excluded from stratified analysis of hay fever because the numbers were too small.

We investigated earlier and later age at onset using categorical variables for both the study-specific medians and the overall median of 30 years and as a continuous variable using 5-year age increments.

SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) and R version 2.11 (<http://cran.r-project.org>) were used for all analyses. Forest plots were generated by using the forest function within library *rmeta*. All P values are 2 sided.

RESULTS

Characteristics of the 10 studies included in the pooled analysis are shown in Table 1, ordered by the prevalence of any allergy in the controls. Five studies were conducted in the United States, with the others conducted in Europe, Canada, and Shanghai. The majority of the studies were population based, and most used categorical matching for age and gender; no study used individual matching. The periods of data collection ranged from 1982 to 2010. For all studies combined (Table 2), cases and controls were similar with respect to age (median age, 64 and 63 for cases and controls, respectively) and gender (55% of cases and 58% of controls were men). Cases were somewhat better educated than controls. Most cases (86%) were white, while the percentage was somewhat lower for controls (80%).

Figure 1 shows the results of the pooled analysis for any allergy. Studies are ordered by the prevalence of any allergy in the controls. For any allergy, the association with risk was of borderline statistical significance: The summary odds ratio for 9 studies was 0.79 (95% confidence interval (CI): 0.62, 1.00), with significant heterogeneity among studies ($P_{\text{heterogeneity}} < 0.001$). Inclusion of asthma in the model did not change the results (data not shown).

Table 2. Demographic Characteristics of the Study Participants in the Pooled Analysis

Demographics	Cases		Controls	
	No.	%	No.	%
Pooled total	3,567		9,145	
Age, years				
<50	369	10	1,357	15
50–59	863	24	2,343	26
60–69	1,211	34	2,830	31
≥ 70	1,124	32	2,615	29
Median ^a	64		63	
Gender				
Male	1,950	55	5,304	58
Female	1,617	45	3,841	42
Education				
8th grade or less	851	24	2,810	31
9th to 11th grades	461	13	1,174	13
12th grade or high school graduate	699	20	1,473	16
Some college or college graduate	1,088	31	2,501	27
1 or more years of graduate school	453	13	1,157	13
Missing	15	0.4	30	0.3
Race				
White	3,073	86	7,332	80
Black	279	8	1,059	12
Asian/Pacific Islander	151	4	390	4
Other/mixed ^b	59	2	57	0.6
Missing	5	0.1	307	3
Cigarette smoking status				
Never	1,364	38	3,921	43
Former	1,265	35	3,081	34
Current ^c	880	25	2,051	23
Missing	58	2	92	1
Body mass index ^d				
<25	1,527	43	4,493	49
25–30	1,272	36	3,059	33
≥ 30	486	14	829	9
Missing ^e	282	8	764	8

^a Age range for cases: 17–92 years; range for controls: 21–94 years.

^b Includes those identified as “Hispanic” without designating race.

^c Current cigarette smoking status includes those who quit in the past year.

^d Body mass index: weight (kg)/height (m)².

^e No body mass index information was available for Minnesota.

Heterogeneity remained significant with each individual study removed, with the exception of the Minnesota study (data not shown). Exclusion of this study resulted in a sum-

Figure 1. Pooled results for any allergy. Study-specific odds ratios are adjusted for age, gender, cigarette smoking status, body mass index (except for Minnesota), and race (except for Italy, SEARCH, Shanghai, and Toronto). Asthma is not included in “any allergy.” CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; OR, odds ratio; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

mary odds ratio = 0.73 (95% CI: 0.64, 0.84) ($P_{\text{heterogeneity}} = 0.23$). Analysis of design factors indicated that heterogeneity remained statistically significant after adjustment for study location ($P_{\text{heterogeneity}} < 0.001$), study design ($P_{\text{heterogeneity}} < 0.001$), prevalence of any allergy in controls ($P_{\text{heterogeneity}} < 0.01$), age at onset of allergies ($P_{\text{heterogeneity}} < 0.001$), and number of allergies queried ($P_{\text{heterogeneity}} = 0.012$).

Associations with risk varied for specific allergies (Web Figure 1 available at <http://aje.oxfordjournals.org/>). Statistically significantly reduced risk was found for 6 studies of hay fever (summary odds ratio (OR) = 0.74, 95% CI: 0.56, 0.96) ($P_{\text{heterogeneity}} = 0.066$) and 4 studies of allergy to animals (summary OR = 0.62, 95% CI: 0.41, 0.94) ($P_{\text{heterogeneity}} = 0.15$). The summary odds ratio for eczema (OR = 0.74, 95% CI: 0.42, 1.30) indicated possibly reduced risk but was not statistically significant, and results were heterogeneous among 4 studies ($P_{\text{heterogeneity}} = 0.039$). There was no association overall for 5 studies of allergies to drugs (summary OR = 1.10, 95% CI: 0.73, 1.60) ($P_{\text{heterogeneity}} = 0.016$) or 4 studies of allergies to food (summary OR = 0.97, 95% CI: 0.51, 1.80) ($P_{\text{heterogeneity}} = 0.017$). Asthma was not associated with 6 studies of risk (summary OR = 0.91, 95% CI: 0.64, 1.30) ($P_{\text{heterogeneity}} = 0.18$). Including asthma as a covariate in the models for specific allergies did not alter the results (data not shown). We determined heterogeneity in results for specific allergies by removing each study individually, finding that different studies contributed to heterogeneity for different allergies (data not shown).

We analyzed whether the association between allergies and risk of pancreatic cancer differed in strata defined by age, gender, cigarette smoking status, and body mass index by comparing, within each stratum, those with any allergy or

hay fever to those with no allergy. Results were generally similar among subgroups (Table 3). Among those with a body mass index of 30 or higher, the risk of pancreatic cancer associated with any allergy appeared to be slightly lower in 8 studies (OR = 0.62, 95% CI: 0.43, 0.91) than among those with a body mass index of less than 30. Based on 5 studies, the association of hay fever with reduced risk of pancreatic cancer was slightly stronger in current smokers (OR = 0.61, 95% CI: 0.36, 1.03) compared with former smokers (OR = 0.76, 95% CI: 0.55, 1.06).

In considering whether age at onset influenced risk, we compared those with earlier or later age at onset with those having no allergies (Table 4). Two definitions of earlier or later age at onset were used: study-specific median age at onset and overall median age at onset, which was 30 years. For the former definition (study-specific median), in 9 studies (excluding Milan), later age at onset appeared to be slightly more strongly associated with reduced risk, with an odds ratio = 0.67 (95% CI: 0.58, 0.77) for later onset and odds ratio = 0.82 (95% CI: 0.66, 1.03) for earlier onset. Results were similar when we used the latter definition of age at onset (overall median). We also evaluated age at onset as a continuous variable, finding that risk of pancreatic cancer decreased by 3% for each 5-year increment in age at onset (95% CI: 0.96, 0.99) ($P_{\text{heterogeneity}} = 0.91$).

DISCUSSION

In this pooled analysis of case-control studies that examined the association between allergies and risk of pancreatic cancer, we found a reduced risk for individuals with self-reported allergies, although the overall result for any

Table 3. Association of Any Allergy and Hay Fever With Risk of Pancreatic Cancer Within Strata in the Pooled Analysis

Strata	Reference Category (No Allergy)	Summary OR ^a (Any Allergy)	95% CI	<i>P</i> _{heterogeneity Within Stratum}
<i>Any allergy vs. no allergy^b</i>				
Overall	1	0.79	0.62, 1.00	<0.001
Age, years				
≤63	1	0.74	0.61, 0.90	0.18
>63	1	0.80	0.58, 1.09	<0.001
Gender				
Male	1	0.77	0.57, 1.04	<0.01
Female	1	0.83	0.66, 1.03	0.12
Cigarette smoking status				
Never	1	0.82	0.67, 0.99	0.28
Former	1	0.78	0.55, 1.11	<0.01
Current ^c	1	0.71	0.60, 0.85	0.88
Body mass index ^d				
<25	1	0.75	0.65, 0.88	0.54
25–<30	1	0.77	0.64, 0.94	0.41
≥30	1	0.62	0.43, 0.91	0.38
<i>Hay fever vs. no allergy^e</i>				
Overall	1	0.74	0.56, 0.96	0.066
Age, years				
≤63	1	0.68	0.53, 0.86	0.39
>63	1	0.75	0.52, 1.07	0.11
Gender				
Male	1	0.68	0.40, 1.16	<0.01
Female	1	0.78	0.64, 0.95	0.63

Table continues

allergies was of borderline significance. Heterogeneity was statistically significant among the studies, attributable in part to the study from Minnesota that found an increased risk for those with each allergy. Exclusion of this study resulted in a statistically significant inverse association with any allergy that was not heterogeneous across studies and showed that risk of pancreatic cancer was reduced by 27% in those with allergy. Among the individual allergies studied, hay fever and allergy to animals showed significantly reduced risks, 26% and 38%, respectively. Although confidence intervals overlapped among subgroups, there was a suggestion that risk of pancreatic cancer associated with any allergy was more strongly reduced among those with a body mass index of 30 or higher and that risk associated with hay fever was more strongly reduced among current smokers. Risk was also slightly lower in those with later age at onset of allergies compared with those with earlier onset of allergies.

Table 3. Continued

Strata	Reference Category (No Allergy)	Summary OR ^a (Any Allergy)	95% CI	<i>P</i> _{heterogeneity Within Stratum}
Cigarette smoking status				
Never	1	0.69	0.49, 0.98	0.15
Former	1	0.76	0.55, 1.06	0.19
Current ^c	1	0.61	0.36, 1.03	0.23
Body mass index ^d				
<25	1	0.64	0.53, 0.78	0.64
25–<30	1	0.72	0.56, 0.93	0.53
≥30	1	0.71	0.40, 1.28	0.40

Abbreviations: CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; OR, odds ratio; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

^a Summary odds ratios are calculated from study-specific odds ratios adjusted for age (continuous), gender, cigarette smoking status, body mass index, and race. Each stratified analysis is adjusted for all the other variables except for the stratum variable.

^b Analysis includes Italy, Minnesota, SEARCH, Shanghai, Louisiana State University, Toronto, NCI, UCSF, and MSKCC. Milan was excluded because only drug allergies were ascertained.

^c Current cigarette smoking status includes those who quit in the past year.

^d Body mass index: weight (kg)/height (m)². Excludes Minnesota (body mass index not ascertained).

^e Analysis includes studies with data on hay fever (SEARCH, Minnesota, NCI, UCSF, MSKCC) except for Shanghai (excluded because of small numbers).

Although many allergies begin in early childhood, some begin later in life (17–19). Adult onset allergies may be attributable to workplace exposures (20) or to changes in exposures to allergens following a move. In addition, childhood allergies may be forgotten while more recent allergies are more readily recalled. The reasons for the anomalous findings in the Minnesota study are not clear. The section on allergies in that questionnaire was long and detailed, and it is possible that respondent fatigue led to fewer positive responses. The prevalence of allergies was relatively low in this study, 17% compared with 53% reporting at least 1 allergy in the National Health and Nutrition Examination Study (NHANES) 2005–2006 (21), although prevalence is probably lower in older individuals (22). Respondent fatigue might explain the higher reporting of allergies among cases than among controls, if, in the face of fatigue, controls were less motivated than cases to provide full and accurate information. One other case-control study (23), not included here, found a higher prevalence of allergies in pancreatic cancer cases; however, this hospital-based study did not provide any details on how controls were selected, making it difficult to evaluate possible reasons for this result.

Table 4. Association of Age at Onset of Allergy with Risk of Pancreatic Cancer in the Pooled Analysis

	Summary OR ^a	95% CI	<i>P</i> _{heterogeneity Within Stratum}
No allergies	1		
Early onset of first allergy ^b	0.82	0.66, 1.03	0.084
Late onset of first allergy ^b	0.67	0.58, 0.77	0.62
No allergies	1		
First allergy at age ≤30	0.79	0.66, 0.95	0.23
First allergy at age >30	0.70	0.59, 0.82	0.44
Age in 5-year increments (among those with any allergy)	0.97	0.96, 0.99	0.91

Abbreviations: CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; OR, odds ratio; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

^a Summary odds ratios are calculated from study-specific odds ratios adjusted for age (continuous), gender, cigarette smoking status, body mass index, and race.

^b Early onset is defined as ≤ the median onset age of study cases; late onset is defined as > the median onset age of study participants. Analysis includes Italy (median age at onset, 40 years), Minnesota (median age at onset, 25 years), SEARCH (median age at onset, 35 years), Shanghai (median age at onset, 41 years), Louisiana State University (median age at onset, 38 years), Toronto (median age at onset, 30 years), NCI (median age at onset, 27 years), UCSF (median age at onset, 27 years), and MSKCC (median age at onset, 22 years). Milan was excluded because only drug allergies were ascertained.

A meta-analysis of pancreatic cancer risk and allergies published in 2005 (4) included 14 studies, 4 of which were also in the present analysis (Shanghai, NCI, UCSF, and an earlier report from one SEARCH site (24)). In the meta-analysis, the summary estimate for any allergy was 0.82 (95% CI: 0.68, 0.99). The estimate was derived from a mixture of measures of “any allergy” provided in some reports as well as measures of individual allergies provided in other reports. Associations of any allergy and respiratory allergies were stronger in studies that used direct interviews only, rather than proxies. Comparison of the results of the meta-analysis in studies with direct interviews with results in the present pooled analysis leads to generally similar conclusions. Our recent review (11) included 11 studies that reported on any allergy in relation to risk, 6 of which were included in our pooled analysis presented here (SEARCH, Shanghai, Toronto, NCI, UCSF, MSKCC). Most studies reviewed found statistically significant reductions in risk for those with allergies. The review included data for hay fever from 12 studies, 5 of which were included in our pooled analysis (SEARCH, Shanghai, NCI, UCSF, MSKCC). Studies generally showed reduced risk associated with hay fever,

although the studies varied with respect to the strength and statistical significance of the findings.

Our study has several strengths, including the ability to harmonize exposures using the original data to construct a variable for “any allergy” that was not possible in the meta-analysis, to exclude proxy respondents, and to adjust uniformly for potential confounding variables. The large number of cases and controls from the combined studies allows for analysis of results in strata, as well as investigation of timing of onset of allergies.

The main drawback is the diversity in the way the questions on allergies were asked in the individual studies. In addition, analyses of specific allergies were based on fewer studies, ranging from 4 to 6. Although we intended to analyze the number of allergies reported as an indicator of severity, we were unable to accurately harmonize the data across studies because of the wide variation in how the questions were asked. There was not enough information on treatment of allergies from these studies to investigate whether this altered the association with risk; studies of glioma, where allergies are also related to lower risk, have shown mixed results for the influence of antihistamines (25–27). Reliability of responses to questions on allergies has rarely been assessed. In the Milan study, the investigators reinterviewed a subset of respondents 1–4 years after the original interview and found that reliability of self-reported drug intolerance was reasonably high, with a κ of 0.70 (28).

Case-control studies are subject to recall bias, although this is unlikely to be an important issue when studying allergies as this association with disease is not well known. Although few studies of general population cohorts have investigated allergies, 1 study reported a significantly reduced risk of death from pancreatic cancer for those reporting hay fever at baseline, but not for those with asthma (10).

The biological basis for reduced risk in individuals with allergies is not understood, although it is hypothesized that some aspect of heightened immune surveillance in individuals with allergies plays a role. Allergies are consistently associated with reduced risk of glioma (29) and lymphoma (30), and there is no obvious similarity among these 3 types of cancer. Allergies are characterized by a predominance of type 2 T-helper cells and the associated antiinflammatory cytokines such as interleukin-4, interleukin-10, interleukin-13, and transforming growth factor β , rather than type 1 T-helper cells characterized by proinflammatory cytokines such as interleukin-1 β , interleukin-6, interferon γ , and tumor necrosis factor α . These type 1 T-helper and type 2 T-helper pathways have different biological functions, but to date little is known about the relation between the associated cytokines and risk of pancreatic cancer. Stronger associations with specific allergies, such as hay fever and animals, may indicate that immunoglobulin E is an important factor, since these allergies are most strongly associated with serum levels of specific immunoglobulin E in cross-sectional studies (31). There may also be confounding variables unmeasured in these studies that account for the relationship between allergies and pancreatic cancer.

Overall, the results of this pooled analysis indicate that allergies are associated with reduced risk of pancreatic cancer and that hay fever and allergies to animals have the strongest

associations. It also indicates that large gaps continue to exist in our understanding of the apparently reduced risk for pancreatic cancer associated with allergies. Little information is available on risk in relation to some specific allergies, such as foods and drugs; the timing, number, and severity of allergies; or the influence of treatment for allergies.

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(Appendix follows)

Appendix Table 1. Specific Questions in Each Study

Study	First Author, Year (Reference)	General Question on Allergies	Specific Questions on Allergies ^{a,b}
Milan	La Vecchia, 1990 (32)	NA	Intolerance to drugs
Italy	Lipworth, 2011 (33); Talamini, 2010 (34)	Allergies	NA
Minnesota	Anderson, 2002 (35)	Ever had allergies to anything? Examples include foods, medications, plants/pollen, dust, insect bites, asthma, and hives.	Dust; pollen; ragweed; grass; mold; cigar; animals (dog, cat, bird, farm, feather, other); eggs; dairy; seafood; fruit; other food; insects; asthma; hives; eczema; hay fever; drugs (penicillin, sulfa, aspirin, antihistamine, steroids)
SEARCH	Maisonneuve, 2010 (9)	NA (derived)	Ever received medical treatment for asthma, eczema, hay fever, or other allergies?
Shanghai	Dai, 1995 (36)	NA (derived)	Ever diagnosed by a doctor as having food allergy, contact dermatitis, urticaria, asthma, allergic rhinitis, or drug allergy?
LSU	Unpublished data	Ever had asthma? Ever had allergies?	Ever been diagnosed by a physician as having asthma or allergies?
Toronto	Anderson, 2009 (5)	Ever had allergies or hay fever?	Has a doctor ever told you that you have asthma?
NCI	Silverman, 1999 (37)	NA (derived by NCI)	Hay fever or some other allergy to pollen. Has a doctor ever told you that you have asthma? Have you ever had eczema or a severe allergic reaction to an insect bite or sting? Do you have any other allergies (animals, dust and molds, drugs, household products, cosmetics, or anything else)?
UCSF	Holly, 2003 (38)	Ever been allergic to items listed on card (derived)?	House dust; animals (dogs, cats, horses, mice/rats/Guinea pigs); trees/grass/weeds/pollens; foods (eggs, dairy products, shellfish, other fish, wheat, peanuts, soy); bee/yellow jacket/hornet/wasp stings; mold; vaccination such as tetanus, mumps, or flu
MSKCC	Olson, 2007 (8)	Ever had allergies to foods, animals, pollen or hay fever, plants such as poison ivy, bee stings, molds, medicine, or vaccines?	What are you or have you been allergic to? (open-ended question)

Abbreviations: LSU, Louisiana State University; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not applicable; NCI, National Cancer Institute; SEARCH, Surveillance of Environmental Aspects Related to Cancer; UCSF, University of California, San Francisco.

^a Individual questions asked of respondents are shown in the order they appeared in the questionnaires and are separated by semicolons. For filter questions, where subsequent questions depend on a "yes" answer to the first question, subsequent questions are in parentheses. Exposures separated by "/" indicate that they were asked as one item.

^b In order to determine the number of allergies asked about in each study, we designated broad categories of allergies: animals, drugs, dust, eczema, food, hay fever, mold, and "other." Asthma was not included. The number of allergy categories for each study was as follows: Milan, not applicable; Italy, 1 (any allergy); Minnesota, 8 (animals, drugs, dust, eczema, food (dairy, eggs, fruit, seafood, other), hay fever (grass, hay fever, pollen, ragweed), mold, other (hives, insects, cigars, or other)); SEARCH, 3 (eczema, hay fever, other); Shanghai, 4 (drugs, food, hay fever, other (dermatitis)); Louisiana State University, 1 (any allergy); Toronto, 1 (any allergy); NCI, 6 (animals, drugs, dust, eczema, hay fever, other (cosmetics, household products, insects)); UCSF, 7 (animals, dust, eczema, food, hay fever, mold, other (insects, shot, vaccine)); MSKCC, 7 (animals, drugs, dust, food, hay fever, mold, other (insects, other)).