Review

Allergies and the Risk of Pancreatic Cancer: A Meta-analysis with Review of Epidemiology and Biological Mechanisms

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Abstract

Previous reports suggest that allergic disorders may protect against various types of cancer, but the association between history of allergy and pancreatic cancer risk has not been well studied. We did a systematic review and meta-analysis of published studies to evaluate the association of any type, and specific types, of allergy and the risk of pancreatic cancer. We did a comprehensive literature search using MEDLINE, PUBMED, and the ISI Web of Science databases to identify potential relevant case-control and cohort studies. Pooled relative risks (RR) and 95% confidence intervals (95% CI) were calculated using the fixed- and random-effects model. Fourteen population-based studies (4 cohort and 10 case-control studies) with a total of 3,040 pancreatic cancer cases fulfilled our inclusion criteria. A history of allergy was associated with a reduced risk of pancreatic cancer (RR, 0.82; 95% CI, 0.68-0.99). The risk reduction was stronger for allergies related to atopy (RR, 0.71; 95% CI, 0.64-0.80), but not for asthma (RR, 1.01; 95% CI, 0.77-1.31). There was no association between allergies related to food or drugs and pancreatic cancer (RR, 1.08; 95% CI, 0.74-1.58). Overall, there was no evidence of publication bias. Allergies, in particular those related to atopy, seem to be associated with a decreased risk of pancreatic cancer. The hyperactive immune system of allergic individuals may, therefore, in some way lead to increased surveillance and protect against pancreatic cancer development. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1908–16)

Introduction

Although the incidence of pancreatic cancer is low, because of its aggressive nature it is the fourth most common cause of death from cancer in the United States (1). Smoking is the major etiologic factor that has been linked to this lethal tumor, but only ~25% of all pancreatic cancer are attributable to this cause (2). Furthermore, most smokers will never develop pancreatic or other types of cancer, suggesting that detoxifying mechanisms and/or the body's innate immune system protect us against cancer.

It is reasonable to assume that the immune system in allergic individuals would differ from that of nonallergic individuals, and that this difference might be responsible for quantitative differences in cancer incidence rates or in responsiveness to therapy. Indeed, several studies have suggested that the overall incidence of cancer is lower in allergic individuals than in nonallergic persons (3-12). One potential source of protection against cancer may be through increased immune surveillance in allergic individuals. The concept of immune surveillance hypothesizes that the immune system is capable of detecting and eliminating neoplastic and preneoplastic cells before they are clinically diagnosed. Many immune cell types may be involved in surveillance, but the cytokine IFN-γ system is central to the surveillance mechanism. The hyperactive immune system of allergic individuals may, therefore, in some way lead to increased surveillance.

With respect to pancreatic cancer, some studies have looked at allergy as a risk factor, but usually only as part of a comprehensive report where the primary focus has been on other risk factors, such as smoking or diet. Also, the results have been unclear because of the wide heterogeneity of terms used to define allergy. Additional uncertainty derives from the fact that, in some studies, information was obtained from proxy interviews or was based on hospital controls: These types of studies could be an important source of bias. We, therefore, did a meta-analysis and a sensitivity analysis of all published epidemiologic studies to quantitate the association between atopic allergy and pancreatic cancer.

Materials and Methods

Definition of Exposures and Outcome. The exposure variables include various types of allergy: We classified in the ''atopy allergy'' group patients with allergic and other types of asthma, atopic dermatitis (eczema), rhinitis (hay fever and year-around rhinitis), allergy to natural antigens, allergy to animals or plants, hives, urticaria, and reaction to insect bites and stinging insects. In subsequent analyses, we considered separately patients with (*a*) asthma, (*b*) respiratory allergy to natural antigen (including allergies to animal, plants, and dust), (*c*) eczema and other skin reaction (urticaria, hives, and contact dermatitis), and (*d*) reaction to insect bites and stinging insects. Finally, we classified in the ''systemic allergy'' group patients with reaction to food, medications, and chemical and commercial products that often are more irritant than allergenic.

For the outcome variable (pancreatic cancer), we relied upon the definition as published in each report.

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Data Sources and Search Strategy. Published reports were obtained from the following databases using validated search strategies (13-15): Ovid MEDLINE database (1966 to July 2004); ISI Web of Science Science Citation Index Expanded (SCI Expanded); and PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). Other sources were found in the reference lists of the retrieved articles and preceding reviews on the topic. The following search terms (both as MeSH terms and as keywords) were used to identify potentially relevant studies in the three databases mentioned above: pancreatic cancer, malignancy, atopy, atopic disease, allergy, allergic disease, asthma, eczema, hives, hay fever, and rhinitis. The search was limited to human studies but no language or time restrictions were applied.

Selection of Articles. All searches were made independently by two abstractors (S. Gandini and P. Maisonneuve); in case of disagreement or uncertainty, a third reviewer (A. Lowenfels) was consulted. Primary inclusion criteria were developed for the selection of all relevant articles (i.e., case-control, cohort, or cross-sectional studies) published as an original article. Secondary criteria were then identified to set apart studies with comparable features:

- The studies should have sufficient information to allow adequate estimation of the relative risk (RR) and 95% confidence intervals (95% CI: i.e., they should report either adjusted odds ratios or RRs or crude data and SEs, variance, CIs, or *P* values of the significance of the estimates). An estimate of the RR and its variance are required to calculate a weighted pooled estimate of the RR for allergy.
- The studies should be independent to avoid giving double weight to some estimates.
- The populations studied should be homogeneous. In particular, when available, population-based estimates were preferred to estimates based on hospital controls and fully hospital-based studies were initially excluded. This decision has been discussed and evaluated in the sensitivity analysis.

Extraction and Classification of the Data. For each study, the following data were retrieved:

- Study: publication year, study design, study location, mean age of study population, type of interviews.
- Exposure: definition of the types of allergy studied.
- Cases: number and source of cases, participation rates of cases, accrual period.
- Controls: number and source of controls, matching design, blinding of interviewers, response rates of controls, exclusion of specific types of diseases/cancer among controls.
- Statistics: statistical methods used, adjustment for confounding variables (demographic factors, such as age and sex, and baseline host characteristics such as smoking), type of effect estimates (odds ratio, RR, standardized incidence ratio) with corresponding measures of precision.

Statistical Methods. Because pancreatic cancer is a rare disease, we ignored the distinction between the various measures of RR (i.e., odds ratio, rate ratio, risk ratio). We transformed the various estimates of RR and their CIs into log RR and we calculated the corresponding variance using the formula proposed by Greenland (16). When estimates were not given, we calculated them from tabular data and we used Woolf's formula to evaluate the SE of the log odds ratio. When standardized incidence rates were presented, we used the number of cases to estimate the SE of the log(standardized incidence rates). Finally, ''test-based'' estimates were considered when only significance levels were published.

We assessed the homogeneity of the effect across studies using the large sample test based on the χ^2 statistic. Because the χ^2 test has limited power, we considered statistically significant heterogeneity at the $P = 0.10$ level of association (17). The summarized RR was estimated pooling the study-specific estimates by the classic fixed-effects and random-effects models according to the heterogeneity test. When several measures of RR were given for a single study, even if heterogeneity was not statistically significant, random-effects models were used, including the two sources of variation (within and between studies), to take into account also correlation within study. Random-effects models were fitted using SAS (Proc Mixed) with restricted maximum likelihood estimate; thus, the resulting estimate for the between-study variance is identical to the iterated DerSimonian-Laird estimator (18, 19).

We carried out subgroup analyses and meta-regression with ANOVA models to investigate between-study and between-estimates heterogeneity. We did a sensitivity analysis to evaluate the influence of various inclusions criteria and specific studies on the pooled estimates and on heterogeneity. We assessed whether publication bias might affect the validity of the estimates using two funnel-plot–based approaches: Copas and Shi sensitivity analysis (20) and the funnel plot regression of ln(RR) on the sample size, weighted by the inverse of the pooled variance (21).

Results

Fourteen population-based studies (4 cohort and 10 case-control studies) with a total of 3,040 pancreatic cancer cases, published between 1981 and 2003, fulfilled our inclusion criteria (Table 1; refs. 22–36). Six of them provided estimates partially based on proxy interviews and for two of them, separate estimates restricted to direct interviews were also given. Most studies reported estimates for several types of allergies. Only one study examined the association between atopy, determined by skin-prick testing, and cancer (ref. 33; Table 2).

The pooled RR indicated a significant protective effect for ''any allergy'' against pancreatic cancer (RR, 0.82; 95% CI, 0.68-0.99; Fig. 1). For allergies related to atopy, the inverse association was even stronger (RR, 0.71; 95% CI, 0.64-0.80). The protective effect was present for respiratory allergy excluding asthma (RR, 0.63; 95% CI, 0.52-0.76; Fig. 2) and for dermal allergy (RR, 0.66; 95% CI, 0.49-0.89; Fig. 3) but not for asthma, which is not always related to atopy (RR, 1.01; 95% CI, 0.77-1.31; Fig. 4). Only seven studies have reported on allergies related to food or drugs, showing no association with pancreatic cancer risk (RR, 1.08; 95% CI, 0.74-1.58; Table 3). When restricting the meta-analysis to the eight studies, which provided risk estimates adjusted for smoking, the protective effect for any allergy became stronger (RR, 0.75; 95% CI, 0.65-0.87).

Face-to-Face versus Proxy Interviews. Because of the rapidly fatal course and extreme morbidity of pancreatic cancer, often case-control studies relied on information collected from relatives or friends (proxy respondents). It is obvious that for some lifestyle or personal history characteristics, such as allergy, data collected by proxy are likely to be less accurate and less reliable than data collected from face-to face interviews. When separate estimates for proxy and for direct interviews were available from a single study, it seemed that the inverse association between history of allergies and pancreatic cancer was stronger in direct interviews (24, 30). In fact, most pooled estimates (except for dermal allergy) decreased noticeably when restricted to direct interviews (Table 3). For any allergy, it was possible to obtain a pooled estimate based on 10 studies (RR, 0.70; 95% CI, 0.51-0.97).

Sensitivity Analysis. We did a sensitivity analysis to assess the influence of various studies or various study characteristics

on the pooled estimates: Initially, we excluded the study by Lin et al. (22) from the analysis for several reasons: The study was carried out in 115 hospitals, between 1972 and 1975, but no description of the control group was given; it was not stated whether the hospital controls may have respiratory problems or diseases related to allergy and, therefore, may be subject to introduce a bias in the study results; the study was carried out before computed tomography scan and, therefore, the diagnosis of pancreatic cancer might not have been always accurate; only the number and the frequency of allergic cases and controls were given, which did not allow us to calculate adjusted estimates. After inclusion of this study, the pooled RR for any allergy lost statistical significance (RR, 0.88; 95% CI, 0.70-1.11) and heterogeneity became substantial ($P = 0.005$). Similar results were found for atopic allergy, with the pooled RR showing just a marginal protective effect (RR, 0.82; 95% CI, 0.62-1.07) and again with appearance of significant heterogeneity ($P = 0.008$), providing strong support for exclusion of the study from the main meta-analysis.

The heterogeneity observed for any allergy was driven by a single study (35) that has peculiar characteristics: This study was part of the α-Tocopherol, β-Carotene Cancer Prevention Study and was restricted to male smokers with no medical problems who might have limited their long-term participation to the trial. In this study, ''bronchial asthma'' (with no mention of allergy), was associated with a significant 2-fold risk for developing pancreatic cancer but it might well have been a marker of cigarette dose, as discussed by the authors. After exclusion of this study from the meta-analysis, the pooled RR for any allergy improved in significance (RR, 0.79; 95% CI, 0.65-0.95) and heterogeneity disappeared ($P = 0.32$). Similar results were found for atopic allergy, with the pooled RR showing a strong protective effect (RR, 0.61; 95% CI, 0.43-0.86) with no sign of heterogeneity ($P = 0.29$).

The cohort study by Erikkson et al. (33) concerns a very young population (median age is 31 and 90th percentile is 55 years) and is the only one using skin prick test. The authors showed that such test was negative for many subjects who declared suffering from asthma, rhinitis, or urticaria; therefore, assessment of allergy in this cohort differs from the other studies. Still, in view of the very wide CIs of the RR estimate and the very low weight of this study based on one single case of pancreatic cancer, its inclusion did not influence the pooled RR. Similarly, the study by Kalapothaki et al. (31) based on very few cases did not influence the overall estimates.

In contrast, the study by Holly et al. (36), the most recent, is also the largest one. Its estimates, which have a considerable weight on the pooled RR, derive from very detailed measures. After exclusion of this study from the meta-analysis, the pooled RR for any allergy was of borderline statistical significance (RR, 0.83; 95% CI, 0.67-1.04), whereas the estimate for atopic allergy remained similar (RR, 0.73; 95% CI, 0.59-0.91).

We did further analysis to evaluate if the inclusion of multiple estimates from a single study may have influenced the pooled RR, giving too much weight to some studies. This was not a problem for asthma, eczema, or for reactions to mosquito bites because no more than one estimate per study was available for these categories. Instead, in case of multiple estimates for a single allergy category, such as ''respiratory allergy to natural antigens,'' we arbitrarily choose the one that we retained to be most relevant: in that case, we preferred ''allergy to plant'' and ''hay fever'' to ''allergy to animals,'' ''allergy to house dust,'' or ''allergy to mold,'' which we retained less specific or less common forms of allergy. After exclusion of the multiple estimates, heterogeneity was not significant ($P = 0.74$) and the fixed-effects model applied did not show a considerable change (RR, 0.74; 95% CI, 0.65-0.83). This confirmed that the random-effects model applied to the main analyses, which takes into account correlation within each study, was conservative because it produced larger CIs.

Finally, the Funnel-plot–based approaches did not suggest any indication for publication bias.

Discussion

Atopy and Cancer Development. Results from this meta-analysis support evidence of a reduced risk of pancreatic cancer among persons with a history of allergic conditions. The inverse association is moderate and the overall estimate of borderline significance. However, such association has been noted for several other forms of cancer: In 1960, Fisherman (37) suggested that natural defenses against cancer may explain (*a*) the differences between a cancer-prone and a cancer-resistant person; (*b*) the differences in tumor growth

Table 1. Characteristics of studies included in the meta-analysis or sensitivity analysis

First author, year (reference)	Study	Country	Accrual period	Study subjects
Lin, 1981 (22)*	Case-control	United States, 115 hospitals	1972-1975	109 cases
Gold, 1985 (23)	Case-control	United States, Baltimore	1978-1980	201 cases
Mack, 1986 (24)	Case-control	United States, LA county	1976-	490 cases
McWhorter, 1988 (25)	Cohort	United States, NHANESI	1971-1975	11 incident case
Mills, 1988 (26)	Cohort	United States, California	1976-1983	40 deaths
Farrow, 1990 (27)	Case-control	United States, Washington	1982-1986	148 married men
La Vecchia, 1990 (28)	Case-control	Italy, Greater Milan area	1983-1988	247 cases
Jain, 1991 (29)	Case-control	Canada, Toronto	1983-1986	249 cases
Bueno de Mesquita, 1992 (30)	Case-control	The Netherlands, central part	1984-1988	176 cases
Kalapothaki, 1993 (31)	Case-control	Greece, Athens	1991-1992	181 cases
Dai, 1995 (32)	Case-control	China, Shanghai	1992-1993	108 cases
Eriksson, 1995 (33)	Cohort	Sweden, Halmstad	1976-1989	1 incident case
Silverman, 1999 (34)	Case-control	United States, Atlanta, Detroit, New Jersey	1986-1989	484 cases
Stolzenberg-Solomon, 2002 (35)	Cohort	Finland	1985-1988	172 cases
Holly, 2003 (36)	Case-control	United States, San Francisco	1994-2001	532 cases

*Excluded from the main pooled estimates.

rate, invasiveness, and curability; (*c*) the occasional rare spontaneous disappearance of cancer. In his study, the prevalence of atopy was significantly lower (3.2%) among 1,185 patients with malignancy than among a control group of 294 noncancerous patients (12.9%), findings later confirmed by Vena et al. (3). Allergic conditions have been associated with reduced risk of cancer of the oral cavity, pharynx, larynx, colon and rectum (7), esophagus (7, 32), stomach (4), breast (4, 12), malignant melanoma, body of the uterus (4), glioma (5, 6), multiple myeloma (4), acute myelocytic leukemia (8), childhood acute lymphoblastic leukemia (9, 10), and non–Hodgkin's lymphoma (11). Still, in several studies, the authors were not able to identify such risk reduction (38–42). Mills et al. (43), who found elevated risk of prostate and breast cancer but decreased risk of ovarian cancer in person who reported any type of allergic history, concluded that the association between allergy and cancer is complex and depends on the specific allergy and the specific organ site under consideration.

Atopy, Natural T Cells, and Prognosis of Cancer Patients. Several studies have also shown the importance of tumor immunity on cancer prognosis. Recently, Pompei et al. (44) not only found that the prevalence of allergy was lower in a series of 1,055 consecutive cancer patients than in a control group (8% versus 16-37%), but that allergic patients had a 20% higher probability of being cured and a 50% lower risk of tumor progression compared with nonallergic patients, suggesting that allergy-related overactive immune system is associated with cancer prognosis. Natural T cells, and notably the $CD4^+$ subset, are related to atopy and total IgE levels (45). Also, the number of IFN-γ–producing $CD8^+$ T cells is related to asthma severity, to bronchial hyperresponsiveness, and to blood eosinophilia (46). In some types of cancer, such as colorectal, esophageal, or gallbladder carcinoma, immunohistochemical identification of tumor-infiltrating $CD8^+$ T lymphocytes has been shown to correlate with an improved overall survival (47, 48). In a single case report, the long-term survival of a 65-year-old man who underwent pancreaticoduodenectomy with portal vein resection for pancreatic cancer has been attributed to the response of $CD8^+$ T cells to the cancer (49). This finding was corroborated by a study based on tumor specimens obtained from 80 patients with pancreatic adenocarcinomas, which showed that $CD4/8^{+/+}$ status was an independent favorable prognostic factor after surgical treatment (50). Using an animal model, Karagiannis et al. (51) established that IgE antibodies commonly involved in allergic responses could trigger an immune response against ovarian cancer. In their experiment, injection of tumor-bearing mice with peripheral blood mononuclear cells and MOv18 IgE led to infiltration of monocytes into the tumors and prolonged survival of the mice, providing evidence that tumor-specific IgE antibodies may be exploited for immunotherapy of cancer.

Immune Surveillance of Cancer and the Pancreas. The concept of immune surveillance and editing stresses the importance of the immune system in eliminating preneoplastic cells and thus safeguarding the body against cancer through an IFN-γ–dependent mechanism. The immune cells that have been implicated in surveillance are natural killer (NK) cells, NK-T cells, CTLs, and γδ T cells. These cells come from both the innate (NK and NK-T cells) and adaptive, antigen-specific (γδ, αβ T cells) immune system. All of these cells have the potential to survey the pancreas; most of these cells are active during allergic responses.

During transformation, preneoplastic cells may lose MHC expression or express potentially immunogenic tumor antigens. Loss of MHC expression could lead to recognition by the innate immune system, whereas expression of potential tumor-specific antigens could lead to recognition by T cells. Under conditions of stress (i.e., allograft rejection, inflammation, or neoplastic transformation), the pancreas has been shown to up-regulate the MHC-like molecules MIC-A and MIC-B (52-54). MIC-A and MIC-B act through the NKG2D costimulatory molecule and directly activate or costimulate NK cells, γδ T cells, $CD8^+$ T cells, and NK-T cells, thus allowing for surveillance of the pancreas by the innate and adaptive immune system (55).

A case for a link between allergy and immune surveillance could be made for the cell types mentioned above. Cells of the innate immune system (NK and NK-T cells) would be expected to be part of the immune surveillance process. Recent conflicting data has been presented on whether NK-T cells are a part of the immune surveillance process in relation to allergy. Allergy is mediated by type 2 responses, which are characterized by the cytokines interleukin (IL)-4 and IL-10. Conflicting data from Oishi (56) and Saikai (57) have shown that during allergic

Table 1. Characteristics of studies included in the meta-analysis or sensitivity analysis (Cont'd)

Histologic confirmation	Type of interview	Control subjects	Pair matching and adjustments
100%	Direct	109 hospital controls	Matched for age, sex, race, marital status
62%	75% proxy	201 population controls	Matched on age, sex, race; adjusted for religion, alcohol, and smoking
100%	75% proxy	490 neighborhood controls	Matched on age, sex, race and neighborhood
Hospital records or death certificate	Proxy for disabled/ deceased persons	6,108 adults	Adjusted for age, sex, race, and smoking
70%	Mailed questionnaire	34,000 Seventh-Day Adventists	Adjusted for age and sex
46%	Wives	188 population controls	Adjusted for age
100%	Direct	1,089 hospital controls	Adjusted for age and sex
69%	66% proxy	505 population controls	Matched on age, sex, proxy status; adjusted for calories, fiber, smoking
68%	39% proxy	487 population controls	Adjusted for age, sex, proxy and smoking
100%	Direct only	181 hospital visitors	Age, sex and hospital
Cancer registry data	Direct	275 population controls	Adjusted for age, sex, income, and smoking
Cancer registry data	Hospital data	6,593 patients with skin prick test	Adjusted for age, sex, year
85%	Direct	2,099 population controls	Adjusted for age, sex, race, region, alcohol, body mass index, caloric intake, income, marital status and smoking
80%	Direct	29,048 male smokers part of the α-Tocopherol, β-Carotene Cancer Prevention Study	Adjusted for age, smoking, diabetes, occupation, high blood pressure
100%	Direct	1,701 population controls	Adjusted for age and sex and other potential confounders

Table 2. Summary of published study results

First author, year	Source or type of allergy	Direct + proxy interviews, RR (95% CI)	Direct interview only, RR (95% CI)	Classification group
Lin, 1981*	Allergy; eczema; dermatitis	—	2.56 (1.34-4.89)	Any allergy
Gold, 1985	Allergic disorders	0.97 (0.50-1.90)	—	Any allergy
Mack, 1986	Any allergic disease	0.6 (0.4-0.8)	0.2 (0.1-0.5)	Any allergy
	Asthma	0.7 (0.4-1.1)	0.2 (0.1-0.8)	Asthma
	Eczema; hives	0.2 (0.1-0.5)	0.2 (0.03-0.7)	Dermal
	Hay fever; plants; animals	0.5 (0.3-0.9)	0.2 (0.05-0.7)	Respiratory
	Drugs; cosmetics and household products	0.9 (0.5-1.6)	0.4 (0.1-1.6)	Systemic
McWhorther, 1988	Asthma, hay fever, hives, food, or other allergies	1.69 (0.49-5.83)	—	Any allergy
Mills, 1988	Asthma	—	0.87 (0.21-3.63)	Asthma
	Reaction to poison ivy, oak or other plants	—	0.99 (0.44-2.27)	Dermal
	Reaction to bee sting	—	0.43 (0.06-3.16)	Insect bites
	Hay fever	—	0.66 (0.23-1.87)	Respiratory
	Drugs	—	0.67 (0.07-5.98)	Systemic
	Chemicals	—	1.53 (0.37-6.30)	Systemic
Farrow, 1990	Asthma	1.1 (0.4-3.2)	—	Asthma
	Plants	0.7 (0.3-1.8)	—	Respiratory
	Animals	1.2 (0.4-3.4)	—	Respiratory
	Drugs	1.7 (1.0-3.0)	—	Systemic
	Foods	2.1 (0.8-5.5)	—	Systemic
La Vecchia, 1990	Drugs	—	0.94 (0.56-1.57)	Systemic
Jain, 1991	Asthma	0.52 (0.16-1.70)	—	Asthma
	Eczema	0.68 (0.31-1.51)	—	Dermal
	Hay fever	0.47 (0.18-1.27)	—	Respiratory
	Other allergies	1.26 (0.69-2.28)	—	—
Bueno de Mesquita, 1992	Any allergy	0.57 (0.36-0.90)	0.43 (0.23-0.81)	Any allergy
	Eczema	0.75 (0.42-1.32)	0.71 (0.34-1.48)	Dermal
	Asthma, hay fever, others	0.41 (0.21-0.82)	0.22 (0.08-0.63)	Respiratory
Kalapothaki, 1993	Allergic asthma	—	0.50 (0.04-5.57)†,‡	Asthma
Dai, 1995	Any conditions	—	0.6 (0.4-1.1)	Any allergy
	Asthma	—	1.0 (0.3-3.2)	Asthma
	Contact dermatitis	—	0.5 (0.1-1.7)	Dermal
	Urticaria	—	0.5 (0.2-1.3)	Dermal
	Mosquito bites	—	1.0 (0.3-3.1)	Insect bites§
	Allergic rhinitis	—	0.3 (0.1-1.4)	Respiratory
	Drugs	—	1.1 (0.5-2.4)	Systemic
	Food	—	0.3 (0.0-2.6)	Systemic
Eriksson, 1995	Positive skin prick test to inhalant allergens	—	1.22 (0.03-6.80)‖	Respiratory
Silverman, 1999	Any allergic condition	—	0.7 (0.5-0.9)	Any allergy
	Asthma	—	1.0 (0.6-1.5)	Asthma
	Eczema	—	1.1 (0.7-1.9)	Dermal
	Insect bite/sting	—	0.8 (0.6-1.2)	Insect bites
	Hay fever	—	0.6 (0.5-0.9)	Respiratory
	Animals	—	0.5 (0.2-1.1)	Respiratory
	Dust or mold	—	0.6 (0.3-1.1)	Respiratory
	Drugs	—	1.4 (1.0-1.9)	Systemic
	Household products	—	1.5 (0.8-2.9)	Systemic
Stolzenberg-Solomon, 2002	Bronchial asthma	—	2.16 (1.17-3.98)	Asthma
	Allergic skin lesions	—	0.59 (0.29-1.20)	Dermal
Holly, 2003	Eczema	—	0.66 (0.46-0.93)	Dermal
	Other allergies	—	0.77 (0.63-0.95)	—
	Insect bites or stings	—	0.65 (0.41-1.00)	Insect bites
	House dust	—	0.72 (0.54-0.94)	Respiratory
	Plants	—	0.77 (0.62-0.96)	Respiratory
	Mold	—	0.49 (0.32-0.75)	Respiratory
	Any animals	—	0.66 (0.47-0.93)	Respiratory
	Food	—	0.74 (0.51-1.10)	Systemic

*Excluded from main meta-analysis.
†RR, 0.25; 95% CI, 0.03-2.24 for hospital controls; RR, 0.33; 95% CI, 0.01-12.4 for all.
‡Estimates calculated on crude data.
§Strong reaction to mosquito bites.
‖Standardized incidence rates for severe and intermediate atopy were published separately.

responses, the number of NK-T cells is reduced, or increases over time during constant exposure to allergen, respectively, thus creating a possible link between NK-T cells in allergy and immune surveillance.

A link between NK cell immune surveillance and allergy would be unexpected because the predominant cytokine milieu during allergic responses (IL-4, IL-13) does not correspond to what is expected during immune editing (IFN-γ). Recent evidence, however, suggests that allergy, specifically asthma, may not be tipped so heavily toward a type 2 (IL-4, IL-13) response. Kuepper et al. (58) have shown increased type 1 CTL activity (IFN-γ) in asthmatics that depends on the activation and cell-to-cell contact with NK cells, suggesting that NK cells may be active during an allergic response.

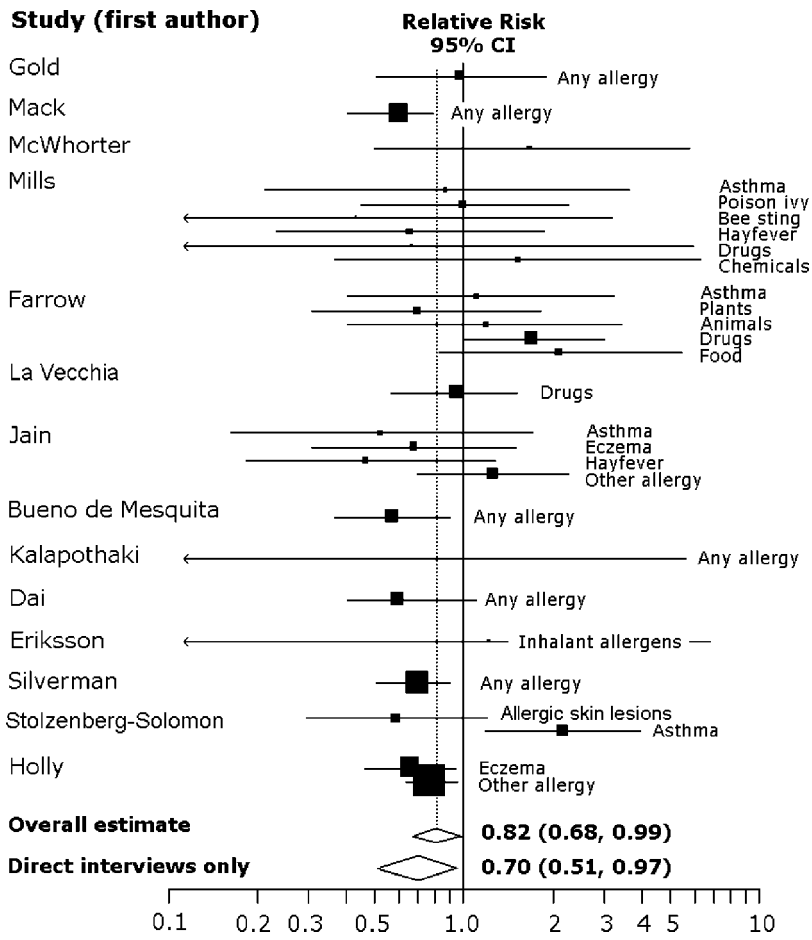

Figure 1. Meta-analysis: Forest plot and pooled RR of the association between any allergy and pancreatic cancer using the random-effects model.

γδ T cells may also be a bridge between immune surveillance and allergy. γδ T cells are a subset of T cells that are not MHC-restricted, have varied receptor diversity, and an unknown antigenic target(s). They can be activated by MIC-A protein expression making them more like innate effectors, but they have many proposed roles, including tissue repair, tumor rejection, and regulation of inflammation (59). They have been shown to be potent IFN-γ secretors and should counteract type 2 allergic responses. In fact, a lack of γδ T cells has been correlated with

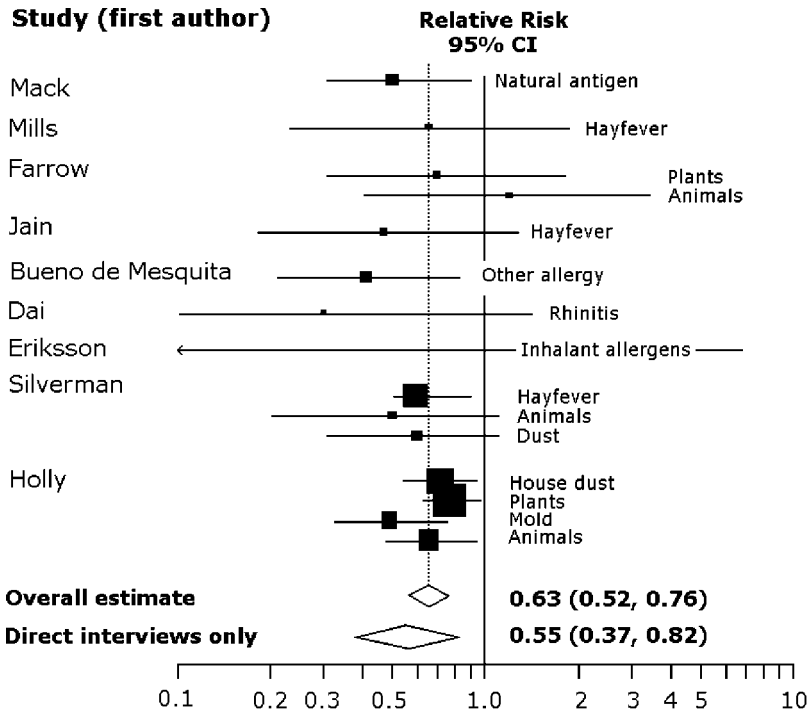

Figure 2. Meta-analysis: Forest plot and pooled RR of the association between respiratory allergy and pancreatic cancer using the random-effects model.

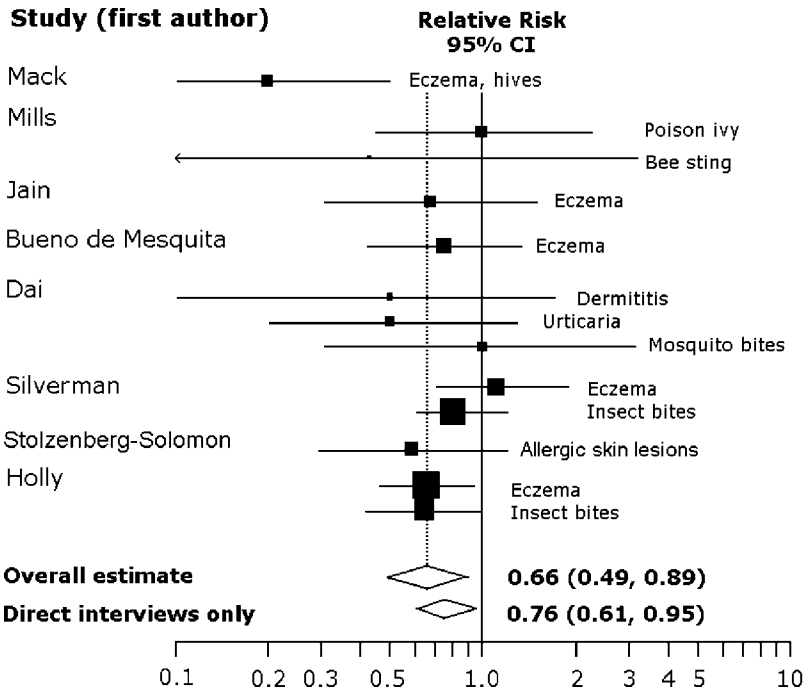

Figure 3. Meta-analysis: Forest plot and pooled RR of the association between dermal allergy and pancreatic cancer using the random-effects model.

increased contact hypersensitivity in the skin (60). However, many groups have shown that γδ T cells in asthma are increased and show increased IL-4 and tumor necrosis factor secretion. Because they are essential for IgE and eosinophil infiltration in allergic asthma airway inflammation (61–63) and because of their increase and ability to recognize the MIC-A/B proteins, γδ T cells may connect allergy and immunosurveillance.

The cells of the adaptive immune response, α/β T cells, are also involved in immune surveillance and could cross-over from allergic responses. Antigen-specific T helper cells and CTLs are thought to be important in immune surveillance and are traditionally associated with type 1 responses that secrete IL-2 and IFN-γ. Dutton et al. (64, 65), however, have shown the effectiveness of type 2 CTL cells in antitumor response. These CTLs are as lytic as traditional IFN-γ–secreting CTLs, but secrete and respond to IL-4. As stated above, classic IFN-γ–secreting CTLs have been found in asthmatics that rely on the activation and cell-to-cell contact with NK cells. Recent data in murine and human studies have shown the existence of T helper 1 responses (IFN-γ secreting) contributing to airway inflammation in asthmatics (66-68). These data suggest that the hypersensitivity found in allergic responses may lead to a broader activation of the immune system and to increased immune surveillance against tumors.

A Possible Link between Allergy and Tumor Immunotherapy? Although many tumor immunotherapies have focused on type 1 responses, some early murine tumor models using IL-4–secreting tumor vaccines showed success and one recent study suggests that IL-4 may enhance type 1

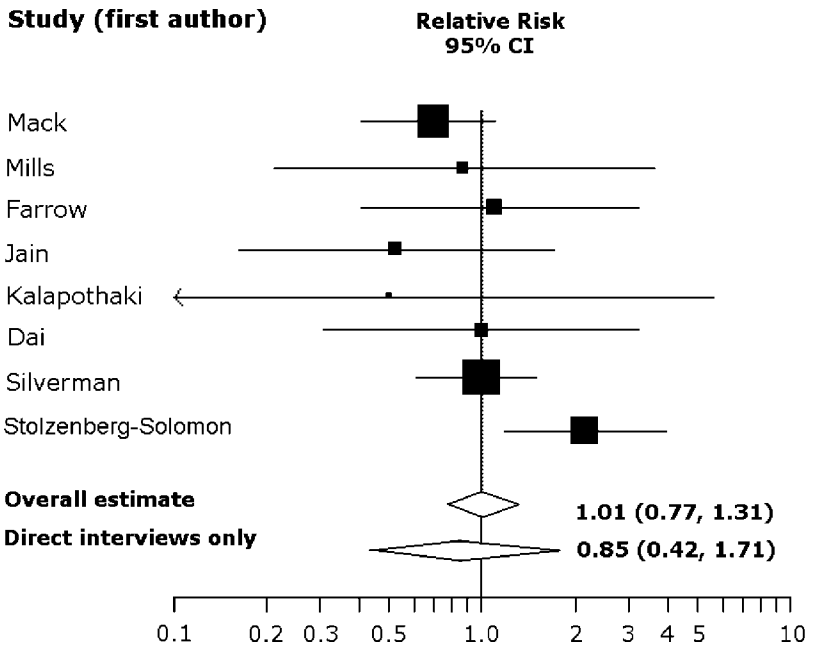

Figure 4. Meta-analysis: Forest plot and pooled RR of the association between asthma and pancreatic cancer using the random-effects model.

Table 3. Overall estimates of RR of pancreatic cancer by subgroups

	No. studies* (*n*)	Direct + proxy interviews RR (95% CI)	χ^2 $P^\dagger$	No. studies* (*n*)	Direct interviews only, RR (95% CI)	χ^2 $P^\dagger$
Any allergy	14	0.82 (0.68-0.99)	0.07	10	0.70 (0.51-0.97)	0.02
Atopic allergy	13	0.71 (0.64-0.80)	0.12	9	0.64 (0.43-0.95)	0.04
Respiratory	9	0.63 (0.52-0.76)	0.68	7	0.54 (0.32-0.82)	0.30
Asthma	8	1.01 (0.77-1.31)	0.22	6	0.85 (0.42-1.71)	0.01
Any dermal	8	0.66 (0.49-0.89)	0.21	7	0.76 (0.61-0.95)	0.68
Eczema, hives...	8	0.66 (0.42-1.03)	0.08	7	0.72 (0.52-0.98)	0.40
Insect bites	4	0.74 (0.57-0.97)	0.79	4	0.74 (0.57-0.97)	0.79
Systemic (drugs, food, ...)	7	1.08 (0.74-1.58)	0.08	6	0.95 (0.60-1.50)	0.09

*Published studies for which we have at least one estimate.
†*P* value for heterogeneity χ^2 test.

responses possibly by acting on dendritic cells (69-71). Evidence for a possible link between allergy and tumor immunotherapy of pancreatic cancer was seen in studies designed to enhance the activation and maturation of dendritic cells. Pancreatic cancer cells engineered to secrete granulocyte macrophage colony-stimulating factor, a potent dendritic cell activator, were used as a vaccine in a clinical trial against minimal residual disease. Five of 14 patients receiving the vaccine showed a significant increase in eosinophils both systemically and at the vaccine site. Three of these patients went on to have prolonged long-term survival (>39 months; ref. 72). In addition, one of these three patients had experienced multiple recurring systemic rashes and recall responses at old vaccine sites that seem to be mediated by eosinophils and T cells. Given the predominance of eosinophils in classic allergic reaction, these data suggest a link between the mediators of allergy and the classic type 1 antitumor responses.

In conclusion, although this meta-analysis is based on studies that were not all designed to address appropriately this association, its results provide some evidence that, unlike other exposure variables such as smoking or pancreatitis, which increase the risk of pancreatic cancer, allergies, particularly atopic allergy, may protect against pancreatic cancer. The notion that the immune system itself could regulate cancer development through a functional cancer immunosurveillance process has led to the development of monoclonal antibody therapies and cancer vaccines. However, current knowledge is insufficient to suggest a practical way to immunize high-risk patients against pancreatic cancer, but there is sufficient information to justify continued efforts to stimulate the immune system as a therapeutic measure in the treatment of pancreatic cancer.

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