Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2014 March ; 23(3): 469–480. doi:10.1158/1055-9965.EPI-13-0965.

Association between allergies and risk of pancreatic cancer

Michelle Cotterchio[1,2], **Elizabeth Lowcock**[1], **Thomas J. Hudson**[3,4], **Celia Greenwood**[5], and **Steven Gallinger**[6,7]

[1] Prevention and Cancer Control, Cancer Care Ontario, Toronto, ON M5G 2L7, Canada

[2] Dalla Lana School of Public Health, University of Toronto, ON M5T 3M7, Canada

[3] Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada

[4] Department of Medical Biophysics and Department of Molecular Genetics, University of Toronto, Toronto, ON M5S 1A1, Canada

[5] Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC H3T 1E2, Canada

[6] Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON M5G 1X5, Canada

[7] Division of General Surgery, Toronto General Hospital, Toronto, ON M5G 2C4, Canada

Abstract

Background—Less than 10% of pancreatic cancer cases survive five years, yet its etiology is not well understood. Studies suggest allergies are associated with reduced pancreatic cancer risk. Our study collected additional information on allergies (including skin prick test results and differentiation of allergic/non-allergic asthma), and is the first to assess possible confounding by allergy medications.

Methods—A population-based case-control study was designed to comprehensively assess the association between allergy and pancreatic cancer risk. Pancreas cancer cases were diagnosed during 2011-2012, and identified through the Ontario Cancer Registry (345 cases). Population-based controls were identified using random digit dialing and age/sex frequency matched to cases (1285 controls). Questionnaires collected lifetime allergy history (type of allergy, age at onset, skin prick testing results), allergy medications, and established pancreas cancer risk factors. Logistic regression was used to estimate odd ratios and test potential confounders, including allergy medications.

Results—Hay fever was associated with a significant reduction in pancreatic cancer risk (AOR=0.68, 95% CI: 0.52-0.89), and reduction was greatest for those whose skin prick test was positive for hay fever allergens. No particular patterns were observed as regards age at onset and duration of allergy. Positive dust/mold allergy skin prick test and animal allergies were associated with a statistically significant reduced pancreatic cancer risk; AOR=0.49, 95% CI: 0.31-0.78 and AOR=0.68, 95% CI: 0.46-0.99, respectively. Asthma was not associated with pancreatic cancer risk.

Conclusions/Impact—These findings support the growing body of evidence that suggests certain allergies are associated with reduced pancreatic cancer risk.

Corresponding author: Michelle Cotterchio, Prevention and Cancer Control, Cancer Care Ontario, 620 University Avenue, Toronto, Ontario, M5G 2L7, Canada, T: 416-971-9800 x3205, F: 416-971-6888, michelle.cotterchio@cancercare.on.ca.

The authors have no conflicts of interest to declare.

Keywords

pancreas cancer; allergy; etiology

INTRODUCTION

Pancreatic cancer is a leading cause of cancer deaths with less than 10% of cases surviving five years (1,2), yet the etiology of pancreatic cancer is not well understood. Cigarette smoking continues to be identified as a strong established risk factor (3-5), and more recently, obesity has been consistently associated with increased risk (6-8). Recent literature suggests that heavy alcohol intake (9,10), non-O blood type (11), and *Helicobacter pylori* infection (12) modestly increase pancreatic cancer risk. While diabetes (13,14) and pancreatitis (15-17) increase risk, diabetes may also be an early manifestation (13,18), and pancreatitis is extremely rare. Genetics also plays a role; having a first degree relative with pancreas cancer doubles one's risk (19,20).

Several epidemiologic studies have examined the association between a history of allergies and pancreas cancer risk (21-29). A meta-analysis of ten case-control and four cohort studies concluded that allergies, especially respiratory allergies (e.g., hay fever), were associated with a statistically significant reduction in pancreatic cancer risk, while no association was observed for asthma (30). A recent review further supports this, and summarized that hay fever is associated with reduced pancreatic cancer risk while asthma findings are null, noting that literature on other allergies (food, drug, eczema) is inconclusive (16). A trend in reduced pancreas cancer risk was reported for increased number of allergies (22), but this has not been replicated (28). Some previous studies did not collect detailed allergy information, such as specific type of allergy (23) or age at onset (24,26,28). To our knowledge, no previous study collected information on skin prick testing, nor differentiated between allergic and non-allergic asthma. Furthermore, no previous study assessed the use of medications to treat allergy symptoms, yet it is important to rule out medications as a possible explanation of the reported allergy-pancreas cancer risk associations. There is no accepted biologic mechanism regarding how allergies may reduce the risk of pancreatic cancer, although enhanced cancer immune surveillance has been widely suggested (30-33).

This Canadian population-based case-control study improves upon previous studies to evaluate allergies and pancreatic cancer risk by collecting detailed information on allergy history (age at onset, duration, skin prick test results, sub-types, differentiation between allergic and non-allergic asthma), assessing pancreatic cancer risk factors as potential confounders, and being the first study to assess allergy medications as possible confounders.

METHODS

Case ascertainment, data collection, and response rate

Pancreas cancer cases were recruited by the Ontario Pancreas Cancer Study (OPCS) - an ongoing study (since 2003) conducted primarily for genetic research and part of the Pancreatic Cancer Genetic Epidemiology Consortium (34). In 2011, and in collaboration with the current study, an expanded epidemiology questionnaire, as well as food and allergy questionnaires, was implemented by the OPCS. The current study includes pancreatic cancer cases diagnosed between February 1, 2011 and August 31, 2012; cases were identified through the Ontario Cancer Registry, which employs a rapid-case ascertainment system (electronic pathology reporting). (International Classification of Diseases for Oncology Third Edition codes C25.0-25.9, with 25.4, neuroendocrine pancreas excluded). Men and women living in Ontario who were diagnosed with a pathologically confirmed

adenocarcinoma of the pancreas or adenocarcinoma metastasis, confirmed as pancreatic cancer by treating physicians, and aged ≤ 89 years, were approached by the OPCS to participate. Of the 345 participating cases, 252 were diagnosed with a pathologically confirmed adenocarcinoma of the pancreas and 93 had adenocarcinoma metastasis (pathology report), and were subsequently confirmed as pancreatic cancer cases by treating physicians.

Pancreas cancer cases were mailed a study package following passive physician consent. This package included four self-administered questionnaires: epidemiology, family history, allergy, and food (short 55-item). Cases were also asked if they would be willing to provide a blood sample. Within two weeks of the questionnaire mailing, a follow-up postcard was sent to cases who had not returned the package. Telephone calls were made two weeks later to non-responders. Telephone follow-up continued for several months in an effort to improve response rates. If no response was received after 10 weeks, a second questionnaire package was mailed. For cases that became deceased during this follow-up period, a proxy was requested to complete the questionnaires (n=37 proxies).

1,095 cases of pancreatic cancer were diagnosed between February 1, 2011 and August 31, 2012 and of these, 327 (30%) were deceased or ineligible (e.g., due to language barrier) leaving 768 eligible cases. The study was not able to mail questionnaire packages to 130 of these cases (57 had no address available, 46 had physicians that refused consent, and 27 cases had no known physician to obtain consent). Thus, 638 cases were mailed the study package, and of these, 137 (21%) refused, 30 (5%) provided only DNA, 126 (20%) were non-responders and 345 cases completed study questionnaires, resulting in a 54% response rate. The median lag between pancreas cancer diagnosis date and questionnaire completion was 3 months.

Control definition, data collection, and response rate

Population-based controls were identified using a modified random digit dialing procedure of households in Ontario and frequency matched (1:3) within 5-year age/sex groups to the expected case distribution. Throughout 2011, control recruitment was conducted by the survey research unit at the Institute for Social Research at York University (Toronto, Ontario). A sampling frame of phone numbers was derived from telephone directories and commercially available lists. Numbers that fell between or on either side of listed numbers were added to the sampling frame to capture unlisted/new numbers. In total, 11,629 households were telephoned; 5,054 households did not have an eligible member, 484 did not answer the phone, 31 did not provide age, and 4,065 refused (eligibility of these households unknown). In total, 1,995 households with an eligible man or woman in a required age-group were identified (one person from each household was randomly selected). Of the 1,995 eligible participants, 261 (13%) persons refused and 1,734 persons agreed to participate in our Ontario Cancer Risk Factor Study (87% response rate). These 1,734 persons (controls) were then mailed a study package that included three self-administered questionnaires: epidemiology, allergy, and food (short 55-item). Controls were also sent a form asking whether they would be willing to donate a blood/saliva sample. A reminder postcard was mailed 2 weeks after the questionnaire package. Telephone follow-up of non-responders was initiated after 4 weeks, and again after 8 weeks. If no response was received after 10 weeks, a second questionnaire package was mailed. Questionnaires were completed by 1,285 controls, for a response rate of 74%. Research Ethics Board approval for this study was obtained from the University of Toronto and Mount Sinai Hospital, Toronto, Canada.

Allergy variables

The allergy questionnaire collected information regarding lifetime history of allergies, including hay fever, eczema/atopic dermatitis, and allergies to dust/mold, animals/pets, insect bites/stings, food, medication, chemicals/metals. Subjects that reported having any of these allergies were asked more detailed questions regarding age at onset, duration, self-reported results of skin prick testing, and use of medications to treat allergies (oral, eye drop, nasal spray, inhaled; antihistamine, steroid, leukotriene modifier, mast cell stabilizer, β2 adrenergic agonists). The allergy questionnaire also asked about lifetime history of asthma, including type (allergic or non-allergic) and medications used to treat asthma. In addition, all participants were asked about use of antihistamines, nasal sprays or steroids for reasons other than allergies/asthma. Eight pages of allergy/asthma medication photos were included in the allergy questionnaire appendix to help subjects with recall.

Subjects were categorized as yes or no to ever having had each of the allergies queried; those reporting a particular type of allergy were further categorized based on their skin prick testing results (whether they tested positive to an allergen belonging to that type of allergy). 'Any allergy' was defined as having reported any of the 8 types of allergy (asthma not included); participants who responded no to all allergy types were categorized as not having any allergy. A composite variable reflecting respiratory allergies/allergic rhinitis was defined as having hay fever, dust/mold or animal/pet allergy (35), since respiratory allergy was most strongly associated with reduced pancreas cancer risk in previous studies (30). 'Atopy' was defined as a history of hay fever, dust/mold allergy, animal/pet allergy, eczema/atopic dermatitis or allergic asthma because these conditions are likely the most valid indicators of IgE mediated allergy; other allergies (chemical/metal, medication, food, insect) were not included as 'atopy' because some persons reporting these conditions likely had intolerances (e.g., to foods or medications) or type IV hypersensitivity reactions (e.g., to nickel), rather than IgE mediated allergies (misclassified). Allergy history was also categorized based on onset and duration, and on the number of allergic conditions reported. Medications used for the treatment of allergies or asthma were classified according to type (antihistamine, corticosteroid, leukotriene modifier, mast cell stabilizer, β2 adrenergic agonist) and route of administration (oral, inhaled, nasal spray, eye drop).

Statistical data analysis

The distributions of subject characteristics, established pancreas cancer risk factors and allergy history were described among pancreatic cancer cases and population controls. Multivariate logistic regression was used to estimate the age-adjusted odds ratios (AOR) and 95% confidence intervals (CI) for the association between allergic diseases and pancreas cancer risk; conducted using SAS version 9.2 (SAS Institute Inc.). Possible confounding by pancreas cancer risk factors (family history of pancreas cancer, body mass index (BMI), pancreatitis, type 2 diabetes, blood type, cigarette smoking, alcohol consumption) was evaluated by adding each potential confounder to the regression models and assessing the impact on the AORs for any allergy, respiratory allergy (hay fever, dust/mold or animal/pet allergy), and atopy. A variable was considered a confounder if any of the three AORs changed by >10% (36); none of the variables met this definition and therefore the AOR is presented in all tables. For completeness, Table 2 also contains the multivariate odds ratio (MVOR) in which BMI, diabetes, and smoking variables were forced into the AOR model. Confounding by medications used to treat allergies/asthma (antihistamines, corticosteroids, leukotriene modifiers, mast cell stabilizers, β2 adrenergic agonists) was similarly assessed. Some medications were minimal negative confounders of the allergy associations (changed AOR away from the null); however, we elected to be conservative and not include these medications as covariates so as not to overestimate the strength of association observed

between allergies and pancreas cancer risk. Smoking status was assessed as an effect modifier of the allergy-pancreas cancer relationship.

RESULTS

The distributions of subject characteristics and established pancreas cancer risk factors among cases and controls are shown in Table 1, along with age-adjusted odds ratio (AOR) estimates. As expected, family history of pancreas cancer, pancreatitis, type 2 diabetes, non-O blood type, and cigarette smoking were associated with increased risk of pancreas cancer.

Table 2 contains the individual and combined allergy variables. Hay fever was associated with a significant reduction in pancreatic cancer risk (AOR=0.68, 95% CI: 0.52-0.89), and this reduction was even greater for those whose allergy skin prick test was positive for hay fever allergens (AOR=0.43, 95% CI: 0.26-0.72). Similarly, having a positive dust/mold allergy skin prick test was associated with a statistically significant risk reduction (AOR=0.49, 95% CI: 0.31-0.78); however, self-reported dust/mold allergy was of borderline significance. Animal/pet allergy was associated with a significant reduction in pancreatic cancer risk (AOR=0.68, 95% CI: 0.46-0.99), and this reduction was even greater for those who were skin prick test positive. Hay fever, dust/mold and animal/pet allergies were reported by 37%, 21% and 17% of the controls, respectively. No statistically significant associations were found between pancreatic cancer risk and each of the following allergies: insects, food, medication, chemical/metal, and eczema/atopic dermatitis. In addition, asthma was not associated with pancreatic cancer risk. All combined/derived allergy variables were associated with reduced pancreatic cancer risk. For example, hay fever, dust/mold or animal/pet allergy (“respiratory allergy”) was significantly associated with reduced pancreatic cancer risk (AOR=0.66, 95% CI: 0.51-0.86).

Table 3 contains age of allergy onset, time since allergy onset, and allergy duration for several individual and combined allergy variables. For hay fever, no particular patterns were observed as age at onset, time since onset, and duration all showed consistent associations with reduced risk. No particular pattern was observed as regards dust/mold allergy or animal/pet allergy age at onset, time since onset, and duration, with all point estimates below 1, although as expected with reduced power CI's were wider. Of note, the magnitude of the association was strongest for age at onset 18-35 years for both animal allergy and dust allergy. No statistically significant associations were seen with eczema/atopic dermatitis, though most point estimates were below 1. For the combined hay fever, dust/mold or animal/pet allergy variable, a slightly stronger reduction in risk was observed as age at allergy increased, with an OR of 0.68 for age onset less than 18 years of age, and 0.51 for aged 36 or older.

Having more than one allergic condition conferred a similar reduction in pancreatic cancer risk as having only one allergic condition (Table 4). For example, having one atopic condition is associated with reduced pancreatic cancer risk (AOR=0.67, 95% CI: 0.49-0.92), as is having three or more atopic conditions (AOR=0.62, 95% CI: 0.41-0.94).

Smoking status showed no statistically significant interaction ($p>0.05$) with individual nor combined allergy variables and pancreatic cancer risk (data not shown); however, after stratification, the reductions in risk associated with allergies were more evident among ever smokers as compared with never smokers [e.g., hay fever allergy: ever smoker (AOR=0.57, 95% CI: 0.39-0.82) versus never smoker (AOR=0.91 95% CI: 0.60-1.37)].

DISCUSSION

Our current finding that self-reported hay fever was associated with a significant reduction in pancreatic cancer risk is consistent with the growing body of literature on this topic (21,22,28,29). We reported a halving of pancreatic cancer risk for persons having a positive skin prick test for hay fever allergens; we are the first to assess this. Similar to other studies, we found that animal/pet allergies (22,28,29) and dust/mold allergies (22) were also associated with a significant reduction in pancreatic cancer risk. We did not observe a statistically significant association between eczema/atopic dermatitis and pancreas cancer risk, which is consistent with most previous studies (21,27,29), although others have reported a reduction in risk (22,24). Consistent with prior studies, we did not observe a reduction in pancreas cancer risk associated with the less common allergies to medications (21,25,28,29), insect stings (21,22), and foods (22,25,28,29), although it is possible conditions were misreported as allergies when they were really intolerances or other non-IgE mediated reactions. Similar to one study (28), but not another (22), we found that having more than one allergic condition conferred a similar reduction in pancreatic cancer risk as having only one allergic condition. Lastly, similar to the two other studies to assess interaction with smoking status (29,37), we found no statistically significant interaction between smoking, allergies and pancreatic cancer risk, although the reductions in risk were more evident among ever smokers as compared with never smokers. Since we did not observe a pattern with duration of allergy our findings should be interpreted cautiously and need to be replicated.

Previous studies to examine the association between asthma and pancreas cancer risk had slightly inconsistent findings, with a meta-analysis reporting no association (30). Our findings are consistent with the majority of studies reporting no association (e.g., 21,23,27,29), although two studies found a reduced pancreas cancer risk associated with asthma (22,24). The majority of asthma is allergic (triggered by allergens; skin prick test positive), however, a sub-set of asthma is non-allergic (e.g., triggered by cold air, exercise) and typically has a later onset (38). Previous studies did not differentiate between these two types of asthma, thus it is possible that if only allergic asthma is associated with cancer risk and all asthma was captured then misclassification may be responsible for the inconsistent findings. Our study is the first cancer study to differentiate between allergic asthma and non-allergic asthma. Although our study collected information on the type of asthma, we still did not observe an association with pancreas cancer risk, suggesting asthma may not be associated with pancreatic cancer risk in the same way atopic conditions such as hay fever and allergies to pets/dust/mold appear to be.

Allergies are hypersensitivity disorders of the immune system occurring in response to allergens (e.g., pollen), and include hay fever, allergic rhinitis, atopic dermatitis, and atopic asthma. Allergy is mediated by immunoglobulin E (IgE) antibodies; allergen-specific IgE is produced by B cells in response to the release of cytokines (e.g., interleukins) by type 2 helper T cells (Th2) that have encountered the allergen (39,40). IgE antibodies bind to receptors on mast cells and other effector cells, and subsequent exposure to the allergen causes the release of chemicals, such as histamine, which results in allergic inflammation (39,40). While it is not well understood why allergies develop, both genetic predisposition (41,42) and environmental influences are important (43). The hygiene hypothesis suggested several decades ago proposes that childhood infections protect against the development of allergy, and thus the development of allergic disease may be a consequence of reduced microbial exposure, due to improved sanitation, vaccination, and antimicrobial agents (44,45). A lack of Th1-activating exposures to microorganisms may skew the helper T cell (Th) immune response towards Th2-driven allergy (46). In addition, climate, housing, and

lifestyle may alter exposure to allergens, and thus risk of allergic disease (47-49), and pollutants may interact with allergens to enhance IgE-mediated immune responses (50,51).

There is no accepted biologic mechanism regarding how allergies may reduce the risk of pancreatic cancer, although it has been suggested that persons with allergies may display enhanced tumor immune surveillance (30-33), where the immune system identifies (via tumor-specific antigens or release of stress molecules) and then eliminates cancerous cells (52,53). While there has been some speculation regarding possible biologic mechanisms, none are established. Allergic conditions have generally been associated with higher levels of allergen-specific IgE (54), and it has been suggested that IgE antibodies may recognize tumor antigens since the molecular epitope pattern determines whether an allergen elicits IgE synthesis/binding, and tumor cell antigens may exhibit similar epitope patterns, and therefore may also trigger IgE responses (55). IgE antibodies have been shown to be elevated in pancreatic cancer cases, compared to controls, and when isolated from pancreatic cancer patients have been shown to target pancreatic cancer antigens with subsequent cytotoxicity against pancreatic cancer cells (56). It has also been suggested that cells with IgE receptors (e.g., eosinophils, mast cells, dendritic cells) may act as antibody-dependent effector cells in an anti-tumor immune response (57,58); these cells are involved in allergic inflammation (59), and are also recruited to the tumor microenvironment (60). Stimulated eosinophils release cytotoxins that can kill tumor cells, and it has been proposed that eosinophils from allergic individuals may be more effective at inducing tumor cell death than those from non-allergic individuals (61,62). Mast cell involvement with the allergy-cancer relationship is unclear as they release chemicals that may induce tumor cell death (e.g., TNF and IL-4) but can also release VEGF which promotes growth (63,64). Dendritic cells present tumor antigens to, and activate cytotoxic lymphocytes (e.g., cytotoxic T (T_C) cells, natural killer (NK) cells) that are central to the innate immune system in eliminating tumor cells (53,65). Dendritic cells express IgE receptors, and it has been hypothesized that IgE could mediate the cross-presentation of tumor antigens by dendritic cells, and thus elicit strong T_C cell response (66). While the role of NK cells in allergy is not well understood (67), one recent study found individuals with allergic rhinitis exhibit a higher proportion of NK cells, and greater NK cytotoxicity, than non-atopic controls (68); thus, one could speculate that allergies may be related to the enhanced ability of innate immune system cells to eliminate tumor cells. Lastly, it has been suggested that allergy symptoms such as sneezing may serve to expel particles and adhering carcinogens (69,70).

There is an inherited component to allergies (41,42), and future studies that comprehensively assess the possible link between variants in immunologic genes and pancreatic cancer risk are warranted. It is interesting that a recent pathway-based analysis of pooled GWAS data reported that Th1/Th2 immune response genes (in particular variants in TGFBR2, CCL18, IL13RA2) were associated with pancreatic cancer risk (71). To our knowledge, the only other assessment of immunologic variants was a small study that found no association between three IL-4 gene variants and pancreatic cancer risk (28).

A limitation of prior studies was the inability to evaluate allergy medications as possible confounders. Many prescription and over the counter medications are used to reduce allergy symptoms (antihistamines, corticosteroids, leukotriene modifiers, mast cell stabilizers) (72). It is possible that the protective effect observed between allergies and pancreas cancer risk may be due to medications taken to relieve allergy symptoms; however, this has never been assessed. It has been reported that cromolyn (one type of mast cell stabilizer) reduced pancreatic tumor growth in mice (73), although it is rarely prescribed. It is important to rule out allergy medications as a possible explanation (confounder) of the allergy-pancreas cancer risk association. Our study was the first to collect detailed information on the use of each of these medications and assess confounding by allergy medication use. We found that

the reduction in pancreatic cancer risk observed for persons with allergies was not due to allergy medications. Another important strength of our study is that information on skin prick testing was obtained, and this has never been assessed in prior pancreatic cancer studies although it is likely a more reliable measure of allergy, and as expected the magnitude of associations observed in our study were strongest for those with skin prick positive results reported.

There are a few limitations to this study. While it is possible self-reported allergic conditions may result in misclassification of atopic status as defined by serum IgE levels (74), self-reported lifetime prevalence is the best measure in the context of a case-control study, as post-diagnostic biologic measures are not relevant to risk. Cohort studies with pre-diagnostic IgE or skin prick test measures would be ideal; however, IgE/skin prick tests are not routinely conducted in cancer cohort studies. Self-reported hay fever has been shown to be highly correlated with sensitization to plant pollens (75), suggesting self-report may be a valid measure of allergy; however, no formal validation study has been published. Selection bias is always a concern in case-control studies; however, the distribution of all but one risk factor was as expected suggesting our dataset was unbiased. The one exception was BMI (one year ago), and this may be because a large proportion of our subjects were elderly (≥65 years), and BMI is not an ideal measure of obesity due to loss of muscle mass and changes in the distribution of body fat (76). It is also possible that case-control studies may underestimate the association with BMI due to the weight loss pancreas cancer patients undergo prior to diagnosis (77). The prevalence of allergies among our controls is consistent with other North American estimates suggesting our sample was not biased; the lifetime prevalence of any allergic condition (hay fever, rhinitis, allergy, eczema) in the US NHANES survey was 53% (74), which is comparable to our observed prevalence of 53% for any atopy.

These findings support the growing body of evidence suggesting certain allergies are associated with reduced pancreatic cancer risk. Future research directions that may help elucidate the possible association between allergies and pancreatic cancer include the conduct of cohort studies that evaluate biologic measures of allergy (e.g., serum IgE) and subsequent cancer risk. In addition, while smoking status showed no significant interaction with allergies and pancreatic cancer risk, the risk reductions were more evident among ever smokers as compared with never smokers and future studies with larger sample sizes and greater power should assess this further. Finally, further investigation of the possible link between variants in immunologic genes and pancreatic cancer risk is reasonable.

Acknowledgments

The authors would like to thank Ayelet Borgida for her dedication, as project co-ordinator, to the Ontario Pancreas Cancer Study.

GRANT SUPPORT

This research was funded by the Canadian Institutes of Health Research (grant # MOP-106631 to M. Cotterchio), and the National Institutes of Health (RO1 CA97075 to S. Gallinger, as part of PACGENE consortium). Thomas Hudson is a recipient of a Senior Investigator Award from the Ontario Institute for Cancer Research, through generous support from the Ontario Ministry of Research and Innovation.

REFERENCES

1. Canadian Cancer Statistics 2013. Canadian Cancer Society; Toronto, ON: 2013. Canadian Cancer Society's Advisory Committee on Cancer Statistics..
2. American Cancer Society. Cancer Facts & Figures 2013. American Cancer Society; Atlanta: 2013.

3. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010; 28:645–56. [PubMed: 21088417]
4. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008; 393:535–45. [PubMed: 18193270]
5. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge B, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009; 170:403–13. [PubMed: 19561064]
6. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012; 23:843–52. [PubMed: 21890910]
7. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010; 170:791–02. [PubMed: 20458087]
8. Larsson S, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer. 2007; 120:1993–1998. [PubMed: 17266034]
9. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer. 2010; 126:1474–86. [PubMed: 19816941]
10. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012; 23:374–82. [PubMed: 21536662]
11. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. Eur J Cancer. 2010; 46:3345–50. [PubMed: 20833034]
12. Trikudanathan G, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. JOP. 2011; 12:26–31. [PubMed: 21206097]
13. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer. 2011; 47:1928–37. [PubMed: 21458985]
14. Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer Causes Control. 2011; 22:189–97. [PubMed: 21104117]
15. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010; 24:349–58. [PubMed: 20510834]
16. Olson SH. Selected medical conditions and risk of pancreatic cancer (review). Mol Carcinog. 2012; 51:75–97. [PubMed: 22162233]
17. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012; 23:2964–70. [PubMed: 22767586]
18. Magruder JT, Elahi D, Andersen DK. Diabetes and pancreatic cancer: chicken or egg? Pancreas. 2011; 40:339–51. [PubMed: 21412116]
19. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Fam Cancer. 2009; 8:109–17. [PubMed: 18763055]
20. Jacobs EJ, Chanock SJ, Fuchs CS, Lacroix A, McWilliams RR, Steplowski E, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Int J Cancer. 2010; 127:1421–28. [PubMed: 20049842]
21. Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe KD, Swanson GM, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer. 1999; 80:1830–37. [PubMed: 10468306]
22. Holly EA, Eberle CA, Bracci PM. Prior history of allergies and pancreatic cancer in the San Francisco Bay area. Am J Epidemiol. 2003; 158:432–41. [PubMed: 12936898]

23. Eppel A, Cotterchio M, Gallinger S. Allergies are associated with reduced pancreas cancer risk: A population-based case-control study in Ontario, Canada. Int J Cancer. 2007; 121:2241–45. [PubMed: 17582608]
24. Maisonneuve P, Lowenfels AB, Bueno-de-Mesquita HB, Ghadirian P, Baghurst PA, Zatonski WA, et al. Past medical history and pancreatic cancer risk: Results from a multicenter case-control study. Ann Epidemiol. 2010; 20:92–98. [PubMed: 20123159]
25. Dai Q, Zheng W, Ji BT, Shu XO, Jin F, Zhu JL, et al. Prior immunity-related medical conditions and pancreatic-cancer risk in Shanghai. Int J Cancer. 1995; 63:337–40. [PubMed: 7591227]
26. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. J Natl Cancer Inst. 1986; 76:49–60. [PubMed: 3455742]
27. Jain M, Howe GR, St Louis P, Miller AB. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. Int J Cancer. 1991; 47:384–89. [PubMed: 1993545]
28. Olson SH, Orlow I, Simon J, Tommasi D, Roy P, Bayuga S, et al. Allergies, variants in IL-4 and IL-4R alpha genes, and risk of pancreatic cancer. Cancer Detect Prev. 2007; 31:345–51. [PubMed: 18031948]
29. Olson S, Hsu M, Satagopan J, Maisonneuve P, Silverman D, Lucenteforte E, et al. Pancreatic Cancer Case-Control Consortium. Allergies and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case-Control Consortium. Am J Epidemiol. 2013; 178:691–00. [PubMed: 23820785]
30. Gandini S, Lowenfels AB, Jaffee EM, Armstrong TD, Maisonneuve P. Allergies and the risk of pancreatic cancer: a meta-analysis with review of epidemiology and biological mechanisms. Cancer Epidemiol Biomarkers Prev. 2005; 14:1908–16. [PubMed: 16103436]
31. Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, et al. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy. 2008; 63:1255–66. [PubMed: 18671772]
32. Rittmeyer D, Lorentz A. Relationship between allergy and cancer: an overview. Int Arch Allergy Immunol. 2012; 159:216–25. [PubMed: 22722389]
33. Severson RK, Davis S, Thomas DB, Stevens RG, Heuser L, Sever LE. Acute myelocytic leukemia and prior allergies. J Clin Epidemiol. 1989; 42:995–01. [PubMed: 2809658]
34. Petersen GM, de Andrade M, Goggins M, Hruban RH, Bondy M, Korczak JF, et al. Pancreatic Cancer Genetic Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2006; 15:704–10. [PubMed: 16614112]
35. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol. 2001; 108(1 Suppl):S2–8. [PubMed: 11449200]
36. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993; 138:923–36. [PubMed: 8256780]
37. Anderson L, Cotterchio M, Gallinger S. Lifestyle, dietary and medical history factors associated with pancreatic cancer risk in Ontario, Canada. Cancer Causes Control. 2009; 20:825–34. [PubMed: 19194662]
38. Barnes PJ. Intrinsic asthma: not so different from allergic asthma but driven by superantigens? Clin Exp Allergy. 2009; 39:1145–51. [PubMed: 19538350]
39. Corry DB, Kheradmand F. Induction and regulation of the IgE response. Nature. 1999; 402(6760 Suppl):B18–23. [PubMed: 10586891]
40. Poulsen LK, Hummelshoj L. Triggers of IgE class switching and allergy development. Ann Med. 2007; 39:440–56. [PubMed: 17852040]
41. Davila I, Mullol J, Ferrer M, Bartra J, del Cuvillo A, Montoro J, et al. Genetic aspects of allergic rhinitis. J Investig Allergol Clin Immunol. 2009; 19(Suppl 1):25–31.
42. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011; 242:10–30. [PubMed: 21682736]
43. Davies RJ, Rusznak C, Devalia JL. Why is allergy increasing?--environmental factors. Clin Exp Allergy. 1998; 28(Suppl 6):8–14. [PubMed: 9988428]
44. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989; 299:1259–60. [PubMed: 2513902]

45. Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis”. Thorax. 2000; 55(Suppl 1):S2–10. [PubMed: 10943631]
46. Romagnani S. The Th1/Th2 paradigm and allergic disorders. Allergy. 1998; 53(46 Suppl):12–15. [PubMed: 9825989]
47. Beggs PJ. Impacts of climate change on aeroallergens: past and future. Clin Exp Allergy. 2004; 34:1507–13. [PubMed: 15479264]
48. Platts-Mills TA, Woodfolk JA, Chapman MD, Heymann PW. Changing concepts of allergic disease: the attempt to keep up with real changes in lifestyles. J Allergy Clin Immunol. 1996; 98(6 Pt 3):S297–06. [PubMed: 8977541]
49. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. Lancet. 1999; 353:1485–88. [PubMed: 10232315]
50. Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. J Allergy Clin Immunol. 1999; 104:1183–88. [PubMed: 10588999]
51. Kim BJ, Kwon JW, Seo JH, Kim HB, Lee SY, Park KS, et al. Association of ozone exposure with asthma, allergic rhinitis, and allergic sensitization. Ann Allergy Asthma Immunol. 2011; 107:214–19. [PubMed: 21875539]
52. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007; 117:1137–46. [PubMed: 17476343]
53. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol. 2011; 29:235–71. [PubMed: 21219185]
54. Pastorello EA, Incorvaia C, Ortolani C, Bonini S, Canonica GW, Romagnani S, et al. Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens. J Allergy Clin Immunol. 1995; 96(5 Pt 1):580–87. [PubMed: 7499673]
55. Jensen-Jarolim, E.; Mechtcheriakova, D.; Pali-Schoell, I. The targets of IgE: allergen- associated and tumor-associated molecular patterns.. In: Penichet, ML.; Jensen-Jarolim, E., editors. Cancer and IgE: introducing the concept of allergooncology. 1st edn.. Humana Press; New Jersey: 2010. p. 231-54.
56. Fu SL, Pierre J, Smith-Norowitz TA, Hagler M, Vowne W, Pincus MR, et al. Immunoglobulin E antibodies from pancreatic cancer patients mediate antibody-dependent cell-mediated cytotoxicity against pancreatic cancer cells. Clin Exp Immunol. 2008; 153:401–09. [PubMed: 18803764]
57. Karagiannis, S.; Nestle, FO.; Gould, HJ. IgE interacts with potent effector cells against tumors: ADCC and ADCP.. In: Penichet, ML.; Jensen-Jarolim, E., editors. Cancer and IgE: introducing the concept of allergooncology. 1st edn.. Humana Press; New Jersey: 2010. p. 185-13.
58. Karagiannis SN, Bracher MG, Hunt J, McCloskey N, Beavil RL, Beavil AJ, et al. IgE-antibody-dependent immunotherapy of solid tumors: cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells. J Immunol. 2007; 179:2832–43. [PubMed: 17709497]
59. Barnes PJ. Pathophysiology of allergic inflammation. Immunol Rev. 2011; 242:31–50. [PubMed: 21682737]
60. Murdoch C, Muthana M, Coffelt SB, Lewis CE. The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer. 2008; 8:618–31. [PubMed: 18633355]
61. Gatault S, Legrand F, Delbeke M, Loisieau S, Capron M. Involvement of eosinophils in the anti-tumor response. Cancer Immunol Immunother. 2012; 61:1527–34. [PubMed: 22706380]
62. Legrand F, Driss V, Delbeke M, Loiseau S, Hermann E, Dombrowicz D, et al. Human eosinophils exert TNF-α and granzyme A-mediated tumoricidal activity toward colon carcinoma cells. J Immunol. 2010; 185:7443–51. [PubMed: 21068403]
63. Theoharides TC, Conti P. Mast cells: the Jekyll and Hyde of tumor growth. Trends Immunol. 2004; 25:235–41. [PubMed: 15099563]
64. Conti P, Castellani ML, Kempuraj D, Salini V, Vecchiet J, Tete S, et al. Role of mast cells in tumor growth. Ann Clin Lab Sci. 2007; 37:315–22. [PubMed: 18000287]

65. Fernandez NC, Lozier A, Flament C, Ricciardi-Castognoli P, Bellet D, Suter M, et al. Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo. Nat Med. 1999; 5:405–11. [PubMed: 10202929]
66. Platzer B, Dehlink E, Turley SJ, Fiebiger E. How to connect an IgE-driven response with CTL activity? Cancer Immunol Immunother. 2012; 61:1521–25. [PubMed: 22042251]
67. Deniz G, Akdis M. NK cell subsets and their role in allergy. Expert Opin Biol Ther. 2011; 11:833–41. [PubMed: 21426239]
68. Mesdaghi M, Vodjgani M, Salehi E, Hadjati J, Sarrafnejad A, Bidad K, et al. Natural killer cells in allergic rhinitis patients and nonatopic controls. Int Arch Allergy Immunol. 2010; 153:234–38. [PubMed: 20484921]
69. Profet M. The function of allergy: immunological defense against toxins. Q Rev Biol. 1991; 66:23–62. [PubMed: 2052671]
70. Zacharia BE, Sherman P. Atopy, helminths, and cancer. Med Hypotheses. 2003; 60:1–5. [PubMed: 12450762]
71. Li D, Duell EJ, Yu K, Risch HA, Olson SH, Kooperberg C, et al. Pathway analysis of genome-wide association study data highlights pancreatic development genes as susceptibility factors for pancreatic cancer. Carcinogenesis. 2012; 33:1384–90. [PubMed: 22523087]
72. Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. Otolaryngol Head Neck Surg. 2007; 136(6 Suppl):S107–24. [PubMed: 17512862]
73. Arumugam T, Ramachandran V, Logsdon CD. Effect of cromolyn on S100P interactions with RAGE and pancreatic cancer growth and invasion in mouse models. J Natl Cancer Inst. 2006; 98:1806–18. [PubMed: 17179482]
74. Hoppin JA, Jaramillo R, Salo P, Sandler DP, London SJ, Zeldin DC. Questionnaire predictors of atopy in a US population sample: Findings from the National Health and Nutrition Examination Survey, 2005-2006. Am J Epidemiol. 2011; 173:544–52. [PubMed: 21273397]
75. Chan-Yeung M, Anthonisen NR, Becklake MR, Bowie D, Sonia Buist A, Dimich-Ward H, et al. Geographical variations in the prevalence of atopic sensitization in six study sites across Canada. Allergy. 2010; 65:1404–13. [PubMed: 20557300]
76. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, DiFrancesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. Int J Obes (Lond). 2005; 29:1011–29. [PubMed: 15925957]
77. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer. 2003; 89:519–523. [PubMed: 12888824]

Table 1

Age group-adjusted odds ratio estimates for established pancreas cancer risk factors

	Cases		Controls		AOR
Characteristic	**N=345**	**%**	**N=1285**		**(95% CI)**
Family History of Pancreas Cancer[a]					
No	298	91	1168	96	1.00
Yes	29	9	49	4	2.36 (1.46-3.82)
Pancreatitis					
No	325	95	1261	99	1.00
Yes	17	5	15	1	4.44 (2.18-9.05)
Diabetes (Type 2)[b]					
No	270	78	1113	87	1.00
Yes	74	22	162	13	1.74 (1.28-2.38)
Blood Type					
Type O	64	19	342	28	1.00
Non-Type O	98	29	347	28	1.56 (1.10-2.22)
Don't know	173	52	537	44	—
Cigarette Smoking					
Never	135	39	581	45	1.00
Ever	207	61	701	55	1.28 (1.00-1.63)
>0-<8.5 pack years	54	17	224	18	1.06 (0.74-1.50)
8.5-<22 pack years	60	18	238	19	1.12 (0.80-1.58)
≥22 pack years	78	24	230	18	1.42 (1.03-1.95)
Alcohol Consumption					
Never	120	35	415	33	1.00
Former	27	8	89	7	1.06 (0.66-1.72)
Current	193	57	769	60	0.87 (0.67-1.13)
Light to moderate (1-20 drinks/wk)	155	47	666	54	0.81 (0.62-1.06)
Heavy (21+ drinks/wk)	30	9	74	6	1.41 (0.88-2.26)
Body Mass Index (kg/m^2)[c]					
<25.0	119	35	412	32	1.00
25.0-<30.0	110	33	522	41	0.74 (0.55-0.99)
≥30.0	107	32	343	27	1.14 (0.84-1.54)
Gender					
Male	175	51	680	53	—
Female	170	49	605	47	—
Age (y)[d]					
<60	86	25	450	35	—
60-64	74	21	288	22	—
65-69	65	19	221	17	—
70-89	120	35	326	25	—

AOR, age group-adjusted odds ratio; CI, confidence interval.

[a] - First degree relatives

[b] - Prior to one year before questionnaire completion

[c] – One year before questionnaire completion

[d] - Age at pancreas cancer diagnosis for cases; age at questionnaire completion for controls

Table 2

Odds ratio estimates for history of any allergy and individual allergic conditions.

	Cases		Controls		OR	MVOR
Type of Allergy	**N=345**	**%**	**N=1285**		**(95% CI)**	**(95% CI)**
Hay Fever						
No	239	72	777	63	1.00	1.00
Yes	92	28	464	37	0.68 (0.52-0.89)	0.68 (0.52-0.90)
Skin prick test positive[a]	18	5	146	12	0.43 (0.26-0.72)	0.43 (0.26-0.74)
No skin prick test reported	43	13	214	17	-	-
Dust or Mold Allergy						
No	275	84	947	79	1.00	1.00
Yes	52	16	253	21	0.75 (0.54-1.04)	0.74 (0.53-1.04)
Skin prick test positive[a]	22	7	163	14	0.49 (0.31-0.78)	0.47 (0.29-0.76)
No skin prick test reported	14	4	56	5	-	-
Animal/Pet Allergy						
No	292	89	1024	83	1.00	1.00
Yes	37	11	212	17	0.68 (0.46-0.99)	0.68 (0.46-1.00)
Skin prick test positive[a]	14	4	104	8	0.52 (0.29-0.92)	0.52 (0.28-0.94)
No skin prick test reported	10	3	66	5	-	-
Insect Bite/Sting Allergy						
No	306	93	1118	91	1.00	1.00
Yes	23	7	110	9	0.75 (0.47-1.20)	0.80 (0.50-1.29)
Skin prick test positive[a]	1	0	5	0	0.80 (0.09-6.92)	0.83 (0.09-7.31)
No skin prick test reported	10	3	56	5	-	-
Food Allergy						
No	298	91	1136	91	1.00	1.00
Yes	31	9	111	9	1.10 (0.72-1.68)	1.08 (0.70-1.67)
Skin prick test positive[a]	8	2	27	2	1.15 (0.51-2.58)	1.06 (0.45-2.51)
No skin prick test reported	15	5	44	4	-	-
Medication Allergy						

Type of Allergy	Cases N=345	%	Controls N=1285		OR (95% CI)	MVOR (95% CI)
No	243	75	989	80	1.00	1.00
Yes	79	25	250	20	1.28 (0.96-1.71)	1.34 (0.99-1.80)
Skin prick test positive[a]	4	1	11	1	1.54 (0.48-4.91)	1.67 (0.51-5.50)
No skin prick test reported	49	15	143	12	-	-
Chemical or Metal Allergy						
No	289	91	1129	91	1.00	1.00
Yes	30	9	109	9	1.11 (0.72-1.70)	1.05 (0.68-1.64)
Skin prick test positive[a]	3	1	17	1	0.78 (0.22-2.68)	0.83 (0.24-2.87)
No skin prick test reported	16	5	52	4	-	-
Eczema/Atopic Dermatitis						
No	276	84	1015	81	1.00	1.00
Yes	54	16	235	19	0.89 (0.64-1.24)	0.89 (0.64-1.24)
Skin prick test N/A						
Hay Fever, Dust/Mold or Animal/Pet Allergy						
No	222	66	680	55	1.00	1.00
Yes	113	34	555	45	0.66 (0.51-0.86)	0.66 (0.51-0.85)
Skin prick test positive[a]	30	9	214	17	0.46 (0.30-0.70)	0.45 (0.30-0.69)
No skin prick test reported	51	15	253	20	-	-
Any Allergy[b]						
No	139	43	454	36	1.00	1.00
Yes	186	57	796	64	0.81 (0.63-1.04)	0.83 (0.65-1.08)
Skin prick test positive[a]	43	13	261	21	0.58 (0.40-0.84)	0.60 (0.41-0.88)
No skin prick test reported	107	33	429	34	-	-
Asthma						
No	297	89	1100	87	1.00	1.00
Yes	38	11	164	13	0.89 (0.61-1.30)	0.89 (0.60-1.30)
Allergic Asthma[c]	18	5	70	6	1.03 (0.60-1.77)	1.05 (0.61-1.80)
Non-allergic Asthma	9	3	56	4	0.61 (0.30-1.26)	0.65 (0.32-1.35)

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2015 March 01.

Type of Allergy	Cases N=345	%	Controls N=1285		OR (95% CI)	MVOR (95% CI)
Type unknown	11	3	38	3	—	—
Atopy[d]						
No	196	59	578	47	1.00	1.00
Yes	136	41	650	53	0.66 (0.51-0.84)	0.66 (0.51-0.85)

AOR, age group-adjusted odds ratio (none of the covariates assessed were identified as confounders)

MVOR, age group, BMI, diabetes and smoking adjusted odds ratio (variables forced into model)

CI, confidence interval

[a]- skin prick test reported as positive to an allergen belonging to this class of allergy (numbers may not add to total as negative skin prick test results not shown)

[b]- any allergy includes hay fever, allergies to dust/mold, animals/pets, insect bites/stings, food, medication, chemicals/metals, and eczema/atopic dermatitis

[c]– triggered by allergens or positive skin prick allergy test reported (atopic asthma)

[d]- atopy: hay fever, allergies to dust/mold, animal/pet, eczema/atopic dermatitis, and allergic asthma

Table 3

Odds ratio estimates for age at onset and duration of allergic conditions

	Cases		Controls		AOR
Allergy Onset/Duration	**N=345**	**%**	**N=1285**		**(95% CI)**
No *Hay Fever*	239	72	777	63	1.00
Hay Fever	92	28	464	37	0.68 (0.52-0.89)
Age at onset					
0-17 years	20	6	124	10	0.58 (0.35-0.95)
18-35 years	30	9	134	11	0.81 (0.53-1.24)
36+ years	18	5	116	9	0.50 (0.30-0.84)
Time since onset					
<25 years	18	5	130	10	0.50 (0.30-0.83)
25-39 years	23	7	110	9	0.78 (0.48-1.26)
40+ years	27	8	134	11	0.65 (0.42-1.00)
Duration					
1-15 years	16	5	111	9	0.50 (0.29-0.86)
16-35 years	28	8	118	10	0.87 (0.56-1.35)
36+ years	23	7	128	10	0.59 (0.37-0.95)
No *Dust/Mold Allergy*	275	84	947	79	1.00
Dust/Mold Allergy	52	16	253	21	0.75 (0.54-1.04)
Age at onset					
0-17 years	12	4	67	6	0.70 (0.37-1.33)
18-35 years	7	2	75	6	0.35 (0.16-0.76)
36+ years	11	3	41	3	0.90 (0.45-1.78)
Time since onset					
<25 years	8	2	44	4	0.69 (0.32-1.49)
25-39 years	5	2	69	6	0.28 (0.11-0.71)
40+ years	16	5	70	6	0.80 (0.45-1.40)
Duration					
1-15 years	4	1	37	3	0.41 (0.14-1.16)
16-35 years	8	2	56	5	0.55 (0.26-1.18)
36+ years	15	5	74	6	0.74 (0.42-1.31)
No *Animal/Pet Allergy*	292	89	1024	83	1.00
Animal/Pet Allergy	37	11	212	17	0.68 (0.46-0.99)
Age at onset					
0-17 years	14	4	68	6	0.86 (0.47-1.57)
18-35 years	3	1	56	5	0.21 (0.07-0.69)
36+ years	6	2	37	3	0.57 (0.24-1.37)
Time since onset					
<25 years	5	2	42	3	0.47 (0.18-1.21)
25-39 years	6	2	53	4	0.47 (0.20-1.12)
40+ years	11	3	66	5	0.63 (0.33-1.21)

	Cases		Controls		AOR
Allergy Onset/Duration	**N=345**	**%**	**N=1285**		**(95% CI)**
Duration					
1-15 years	5	2	34	3	0.59 (0.23-1.52)
16-35 years	6	2	42	3	0.58 (0.24-1.39)
36+ years	10	3	62	5	0.63 (0.32-1.25)
No *Eczema/Atopic Dermatitis*	276	84	1015	81	1.00
Eczema/Atopic Dermatitis	54	16	235	19	0.89 (0.64-1.24)
Age at onset					
0-17 years	14	4	60	5	0.92 (0.51-1.68)
18-35 years	8	2	50	4	0.64 (0.30-1.37)
36+ years	10	3	55	4	0.68 (0.34-1.35)
Time since onset					
<25 years	11	3	56	4	0.79 (0.41-1.54)
25-39 years	7	2	41	3	0.71 (0.31-1.60)
40+ years	14	4	67	5	0.76 (0.42-1.38)
Duration					
1-15 years	10	3	76	6	0.51 (0.26-1.01)
16-35 years	7	2	40	3	0.72 (0.32-1.64)
36+ years	11	3	27	2	1.59 (0.77-3.26)
No *Hay Fever, Dust/Mold or Animal/Pet Allergy*	222	66	680	55	1.00
Hay Fever, Dust/Mold or Animal/Pet Allergy	113	34	555	45	0.66 (0.51-0.86)
Age at onset					
0-17 years	31	9	155	13	0.68 (0.45-1.04)
18-35 years	28	8	153	12	0.62 (0.40-0.96)
36+ years	22	7	133	11	0.51 (0.31-0.82)
Time since onset					
<25 years	22	7	147	12	0.51 (0.32-0.82)
25-39 years	24	7	124	10	0.68 (0.42-1.09)
40+ years	34	10	170	14	0.61 (0.41-0.92)

AOR, age group-adjusted odds ratio (none of the covariates assessed were identified as confounders)

CI, confidence interval

Numbers may not add to total due to missing values

Table 4

Odds ratio estimates for number of allergic conditions

	Cases		Controls		AOR
Number of Allergic Conditions	**N=345**	**%**	**N=1285**		**(95% CI)**
Number of Allergies[a]					
None	139	43	454	36	1.00
1	80	25	313	25	0.87 (0.64-1.19)
2	44	14	206	17	0.75 (0.51-1.10)
3+	62	19	277	22	0.78 (0.56-1.09)
Number of Atopic Conditions[b]					
None	196	59	578	47	1.00
1	67	20	309	25	0.67 (0.49-0.92)
2	38	11	179	15	0.67 (0.45-0.98)
3+	31	9	162	13	0.62 (0.41-0.94)
Number of Hay Fever, Dust/Mold or Animal/Pet Allergies					
None	222	66	680	55	1.00
1	62	19	294	24	0.68 (0.49-0.93)
2	34	10	148	12	0.75 (0.50-1.12)
3	17	5	113	9	0.51 (0.30-0.87)

AOR, age group-adjusted odds ratio (none of the covariates assessed were identified as confounders)

CI, confidence interval

[a] - allergies included: hay fever, allergies to dust/mold, animals/pets, insect bites/stings, food, medication, chemicals/metals, and eczema/atopic dermatitis

[b] - atopic conditions: hay fever, allergies to dust/mold, animal/pet, eczema/atopic dermatitis and allergic asthma