

References

1. Alam M, Burki NK. Chronic eosinophilic pneumonia: a review. *South Med J*. 2007; 100(1):49–53.
2. Matsuda Y, Tachibana K, Sasaki Y, Tsuyuguchi K, Kitaichi M, Inoue Y. Tracheo-bronchial lesions in eosinophilic pneumonia. *Respir Invest*. 2014;52:21–27.
3. Ishiguro T, Takayanagi N, Uozumi R, et al. The long-term clinical course of chronic eosinophilic pneumonia. *Intern Med*. 2016;55:2373–2377.
4. Marchand E, Etienne-Mastroianni B, Chanez P, et al. Idiopathic chronic eosinophilic pneumonia and asthma: how do they influence each other? *Eur Respir J*. 2003;22:8–13.
5. Shin YS, Jin HJ, Yoo HS, et al. Successful treatment of chronic eosinophilic pneumonia with anti-Ig E therapy. *J Korean Med Sci*. 2012;27(10):1261–1264.
6. Kim S, Marigowda G, Oren E, Israe E, Wechsle ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol*. 2010;125(6):1336–1343.

Inverse association of asthma and hay fever with cancer in the 2015 National Health Interview Survey database



Although immune hyperresponsiveness to common inhaled antigens is inherent to allergy and asthma, with allergens perceived as danger signals,¹ there is an active immune underreactivity promulgated by cancer cells,² which allows progression of this potentially fatal disease process. How one immunologic extreme relates to the clinical expression of the other immunologic extreme has not been established.

Previous studies have found an association among allergic disease, asthma, hay fever, and cancer; however, the nature of this association remains to be determined. Turner et al³ reviewed 148 epidemiologic studies between 1966 and 2005 for the association between allergy and cancer with mixed findings. Allergic disease was associated with a significant reduction in pancreatic cancer, non-Hodgkin lymphoma, glioma, and breast cancer.³ However, no conclusion could be reached about the overall association between allergy and cancer. In contrast, a meta-analysis by the International Lung Cancer Consortium of 16 studies⁴ concluded that there was an increased relative risk of lung cancer associated with asthma. However, this did not necessarily imply a causal effect of asthma on cancer risk.

We investigated the clinical coexistence of allergy and asthma with cancer using the 2015 National Health Interview Survey, a nationally representative database of patients, to examine associations between personal histories of hay fever, asthma, and cancer, as reported to be diagnosed by a physician. The National Health Interview Survey (NHIS) is an annual, nationally representative survey of patients with information on demographic, neighborhood-level, and medical condition variables. We investigated the data from 2015 and conducted bivariate analyses among demographic variables, allergy, asthma, and cancer. The primary independent variable was hay fever or asthma, with a dependent variable of cancer. Asthma and cancer were defined as ever been diagnosed with these conditions by a physician or health care professional, except hay fever, which was self-reported as being present in the past 12 months. Covariates for these analyses were identified a priori from the literature and included age, sex, race, obesity, smoking status, and socioeconomic factors, including insurance coverage and family income. Finally, nested multivariate logistic regression models were conducted. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc).

Data from 33,672 adults (15,071 [44.76%] male and 18,601 [55.24%] female) were eligible for inclusion in this study. The mean (SD) age of survey participation was 49.9 (18.3) years, ranging from 20 and 85 years. A total of 25,831 participants (76.71%) were non-Hispanic white, 4673 (13.88%) were black, and 1983 (5.89%) were Asian. Obesity was reported in 30.40% of the

participants. Asthma was found in 4343 patients (12.90%) and hay fever in 2957 (8.77%). A total of 302 patients (91.24%) reported a cancer diagnosis duration of longer than a year before the survey. A significantly greater proportion of females had cancer compared with males (5.66% vs 4.10%, $P = .009$). Fewer patients had asthma and cancer concurrently compared with those with cancer alone (1.47% vs 8.29%, $P < .001$), as did patients with hay fever and cancer, compared with those with cancer alone (1.1% vs 8.7%, $P < .001$).

Unadjusted logistic regression models of asthma predicted negative odds of cancer with an odds ratio of 0.73 (95% CI, 0.67–0.81). After adjustment for age, sex, race, obesity, smoking status, insurance coverage, and family income, the odds decreased to 0.60 (95% CI, 0.50–0.73) ($P < .001$). Similar negative associations were seen in univariate and multivariate regression of hay fever predicting cancer (ie, the odds of a cancer diagnosis in patients with a history of ever having hay fever after adjusting for the above variables was 0.57 [95% CI, 0.47–0.67] [$P < .001$]).

We found that a personal history of hay fever or asthma, which are markers of allergic disease, were significantly negatively associated with overall cancer diagnoses.

The confounding results in the literature may be attributable to methodologic flaws across studies³ vs focus on individual cancer types, some of which may be positively and others negatively associated with allergic disease. Our study found that across overall averaged cancer diagnoses, there is an association with a history of hay fever and asthma. One of the methodologic issues often reported is the accuracy of measurement and reporting of allergy and asthma. Most studies rely on self-reported allergies, which may be inaccurate or subject to bias.³ Although our study is also a survey report, it relies on “having ever been told by a doctor” if the patient has asthma. Nonetheless, all 3 variables are, in essence, self-reported, which is a limitation of the study.

Enhanced immune surveillance has been proposed as an explanation of the inverse association between allergy or asthma with cancer. This theory proposes that the immune system is continuously searching for tumor cells as they arise and destroys them⁵ and those with a history of allergic disorders may have enhanced or up-regulated immune surveillance.^{5,6}

Eosinophilia has also been associated with improved prognosis of certain cancers⁷ possibly by eosinophil degranulation-mediated tumor cytotoxicity. Peroxidase derived from eosinophils works with macrophage reactive oxygen species to target tumor cells⁷ and increase generation of cytotoxic free radicals.⁷ In addition, natural killer cells may be protected from reactive oxygen species by histamine,⁸ which may prevent reactive oxygen species generation in monocytes and macrophages and thus protect natural killer cells and T-cell subsets.⁸ Finally, it has been hypothesized that allergens may share

Disclosures: None.

Funding: None.

molecular epitope patterns with tumor antigens⁹; therefore, increased anti-tumor IgE antibodies may potentiate allergic responses.⁹

We found that allergy and asthma are negatively associated with cancer diagnoses before 50 years of age. Whether this association is attributable to confounding covariates that are not captured or an immunologically conferred cancer protection is not elucidated. We acknowledge that association is not proof of causation (or, in this case, protection). Further investigation of the cellular mechanisms, including IgE anticancer T_H2 responses, may be helpful in clarifying the underlying mechanism or pathway and potential clinical significance of this negative association. Prospective studies need to be performed to prove a truly causal association.

Niloofar Anooshiravani, MD^{*,†}

Sairaman Nagarajan, MD, MPH^{*,†}

Maria-Anna Vastardi, MD^{*,†}

Rauno Joks, MD^{*,†}

^{*}Center for Allergy and Asthma Research

State University of New York Downstate Medical Center

Brooklyn, New York

[†]Department of Allergy and Immunology

State University of New York Downstate Medical Center

Brooklyn, New York

Niloofar.anooshiravani@downstate.edu

References

1. Matzinger P. The evolution of the danger theory. *Expert Rev Clin Immunol*. 2012; 8(4):311–317.
2. Ribas A. Adaptive immune resistance: how cancer protects from immune attack. *Cancer Discov*. 2015;5(9):915–919.
3. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. *Int J Cancer*. 2006;118:3124–3132.
4. Rosenberger A, Bickeböller H, McCormack V, et al. Asthma and lung cancer risk: a systematic investigation by the international lung cancer consortium. *Carcinogenesis*. 2012;33(3):587–597.
5. McWhorter WP. Allergy and risk of cancer: a prospective study using NHANESI followup data. *Cancer*. 1988;62(2):451–455.
6. Eriksson NE, Holmén A, Högstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy*. 1995;50(9):718–722.
7. Munitz A, Levi-Schaffer F. Eosinophils: “new” roles for “old” cells. *Allergy*. 2004; 59:268–275.
8. Hellstrand K, Brune M, Naredi P, et al. Histamine: a novel approach to cancer immunotherapy. *Cancer Invest*. 2000;18(4):347–355.
9. Cotterchio M, Lowcock E, Hudson TJ, Greenwood C, Gallinger S. Association between allergies and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2014;23(3):469–480.

Seasonal trends in asthma exacerbations

Are they the same in asthma subgroups?



Asthma exacerbations have seasonal patterns that may differ by age group.^{1–3} The proposed underlying causes of these seasonal variations include viral upper respiratory tract infections, ambient air pollutants, and climate changes with an increase in aeroallergens.⁴ The recognition of seasonal patterns may help with identification and avoidance of asthma triggers.

There is emerging literature on phenotyping asthma to further understand its pathophysiology and appropriate management. Both smoking and obesity have been associated with corticosteroid insensitivity and severe asthma symptoms.^{5–8} Little is known, however, regarding seasonal variations in both of these asthma subgroups. The objective of this study was to evaluate whether the seasonal trends in asthma exacerbations persist in subgroups of smokers and morbidly obese individuals.

The number of asthma exacerbations for each month during a period of 3 years (2015–2017) was extracted from the electronic health record of an academic community health care system in Ohio. The search for asthma exacerbation included any of the *International Classification of Disease* (ICD) diagnoses: mild intermittent, mild persistent, moderate persistent, severe persistent, and unspecified asthma with acute exacerbation. Outpatient, emergency department, and hospital admission diagnoses were included. Institutional review board approval was obtained from MetroHealth Medical Center in Cleveland, Ohio. The number of asthma exacerbations was plotted over time to evaluate seasonal trends in 3 age groups (≤ 18 years, 19–64 years, and ≥ 65 years). Asthma exacerbations were also plotted over time in adults (> 18 years of age) and stratified by body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) (< 40 or ≥ 40) and current smoking status. The overall trend of asthma exacerbations over time was evaluated by linear regression. The

Edwards test was used to assess for seasonality ($\alpha = 0.05$). Prais-Winsten regression with autocorrelation adjustment was performed in the morbidly obese and smoker subgroups after logarithmic transformation of the outcome variable (number of asthma exacerbations) using Stata statistical software, version 12.0 (StataCorp).

A total of 19,603 cases of asthma exacerbations were analyzed during the 3-year period (2015–2017). The population was 61.5% female and 38.5% male. Ethnicity was 16.9% Hispanic and 83.0% non-Hispanic, further categorized into 39.6% white, 58.7% African American, and 1.7% other.

The number of asthma exacerbations per month was stratified by age as shown in Figure 1. There was a statistically significant positive association between the number of asthma exacerbations and time in months in all age subgroups ($P < 0.05$), indicating an upward trend over time. The test of seasonality was statistically significant in all age groups ($P < 0.001$ for ≤ 18 years of age, $P < 0.001$ for 19–64 years of age, and $P = 0.001$ for ≥ 65 years of age). The angles of maximum rate were -18° (late November) and -22° (late November) for the 18 years or younger group and 19 to 64 years of age groups, respectively. However, the angle of maximum rate was $+67^\circ$ (late February) in the 65 years or older group.

There were 7948 asthma exacerbations in adults with a BMI less than 40 and 2825 exacerbations in adults with a BMI of 40 or greater. Seasonality of asthma exacerbations appeared to persist in adults when stratified by BMI ($P < 0.001$ with BMI < 40 and ≥ 40), which was also evident graphically (Fig 1). The angles of maximum rate were -19.9° (late November) and -0.87° (middle December) for the BMI groups of less than 40 and 40 or greater, respectively.

There were 3139 and 9333 asthma exacerbations in adult smokers and adult nonsmokers, respectively. The angle of maximum rate was -12.67° (early December) in adult nonsmokers and -36.21° (middle November) in adult smokers. Although the