Original Article

Association of Asthma with Rheumatoid Arthritis: A Population-Based Case-Control Study

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What is already known about this topic? Asthma is typically considered a chronic inflammatory airway disorder with significant heterogeneity. A link between asthma and risk of other chronic inflammatory diseases is poorly understood.

What does this article add to our knowledge? Because asthma poses a significantly increased risk for rheumatoid arthritis (RA), RA may be an underrecognized asthma-associated comorbidity in a subgroup of patients with asthma. Development of strategies to identify this subgroup of patients with asthma will be warranted.

How does this study impact current management guidelines? Because RA, a potential asthma-associated comorbidity, is relatively underrecognized by caregivers and clinicians, and poses a serious threat to the health of patients with asthma, the guidelines need to address asthma-associated comorbidity including RA to inform and guide clinicians for a timely diagnosis and management of RA.

BACKGROUND: T_H1 and T_H2 cells have counterregulatory relationships. However, the relationship between asthma, a T_H2-predominant condition, and risk of systemic inflammatory diseases such as rheumatoid arthritis (RA), a T_H1 condition, is poorly understood.

OBJECTIVE: We aimed to determine whether asthma was associated with increased risks of incident RA among adults.

METHODS: We conducted a retrospective population-based case-control study that examined existing incident RA cases and controls matched by age, sex, and registration year from the general population in Olmsted County, Minnesota, between January 2002 and December 2007. We performed comprehensive medical record reviews to ascertain asthma status using predetermined asthma criteria. The frequency of a history of asthma before the index date was compared between cases and controls. Logistic regression models were used to adjust for confounding factors.

RESULTS: We enrolled 221 RA cases and 218 controls. Of the 221 RA cases, 156 (70.6%) were females, 207 (93.7%) were white, the median age at the index date was 52.5 years, and 53 (24.0%) had a history of asthma. Controls had similar characteristics except that 35 of 218 controls (16.1%) had a history of asthma. After adjustment for sex, age, smoking, body mass index, socioeconomic status, and comorbidity, asthma was significantly associated with increased risks of RA (adjusted odds ratio, 1.74; 95% CI, 1.05-2.90; $P = .03$).

CONCLUSIONS: Despite the counterregulatory relationship between T_H1 and T_H2 cells, patients with asthma had a significantly higher risk of developing RA than healthy individuals. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Asthma; Rheumatoid arthritis; Risk; Adults; Epidemiology*

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and hyperplasia, autoantibody formation (ie, rheumatoid factor and anti–citrullinated protein antibody), and destruction of joint cartilage and bone.[1] RA develops as the result of a complex interplay among susceptibility genes (ie, HLA-DRB1 locus), environmental triggers (ie,

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Abbreviations used
aOR- Adjusted odds ratio
HOUSES- HOUsing-based index of SocioEconomic Status
MIC- Major histocompatibility complex
NK- Natural killer
OR- Odds ratio
NKG2D- Natural killer group 2D
RA- Rheumatoid arthritis
REP- Rochester Epidemiology Project

smoking and socioeconomic status), and epigenetic modification, which promote loss of tolerance to self-proteins containing a citrulline residue, which is produced by posttranslational alteration.[1] RA is considered a T_H1 disorder, as reported in experimental,[2] clinical,[3] and epidemiological studies.[4] For instance, an *in vitro* study demonstrated that T-cell clones from the synovium of patients with RA produced large amounts of IFN-γ, with dominant T_H1/T_H0 patterns.[2]

Atopic diseases such as asthma are considered a T_H2-predominant disease.[5] Asthma is a chronic inflammatory disorder of the airways with significant heterogeneity.[6] A recent review argues that the impact of asthma goes beyond the airways, suggesting that asthma may not be a mere airway disease, but a chronic disease causing systemic inflammatory dysfunctions.[7] Modena et al[8] characterized bronchial airway epithelial cell gene expression (genetic clusters) and phenotypes (subject clusters) of 155 patients with severe asthma and determined that although a subgroup of patients with asthma showed expected T_H2-high immune profiles, another subgroup demonstrated a gene expression of T_H1-predominant inflammatory pathway such as TNF-α. These data suggest that significant phenotypic heterogeneity of asthma can be correlated with genetic clusters underlying molecular pathways including coexisting T_H2 and T_H1 immune pathways or endotypes. Therefore, a subgroup of asthma may exhibit systemic inflammatory features and its associated molecular pathway gearing toward T_H1 immune responses (eg, TNF-α). Hence, it is worthwhile to determine whether there is an association between asthma and the risk of T_H1-predominant conditions such as RA and to characterize a subgroup of patients with asthma at an increased risk of developing RA.

Although several studies assessed relationships between asthma and the risk of RA, the results have been inconsistent primarily due to non—hypothesis-driven analysis, sampling bias, and/or measurement bias. Moreover, no population-based study has tested *a priori* the hypothesis that asthma is associated with an increased risk of RA using both predetermined criteria for asthma status and RA.

Delineating the relationship between asthma and the risk of RA has clinical and scientific significance because asthma affects a significant proportion of individuals worldwide. Thus, it may provide important scientific insights into relatively unexplored systemic effects of asthma on serious chronic inflammatory diseases such as RA as well as the effect of coexistent RA on asthma course and management.

To address the aforementioned question, we conducted a population-based case-control study using specific predetermined criteria for both asthma and RA. We hypothesized that asthma increases the risk of RA.

METHODS

Study setting

All subjects were residents of Olmsted County, Minnesota, which is located in southeastern Minnesota.[9] The Olmsted County population is similar to the US white population, with the exception of a higher proportion of the working population employed in the health care industry.[10] Medical records—based research using the geographically defined population of Olmsted County is possible through the Rochester Epidemiology Project (REP).[9] The REP record-linkage system links all inpatient and outpatient medical records, from the Mayo Clinic, the Olmsted Medical Center, and their affiliated hospitals, as well as private practitioners and other health care providers in Olmsted County.

Study design and subjects

This is a population-based, retrospective case-control study that used an existing population-based cohort of incident adult RA cases between January 1, 2002, and December 31, 2007, in Olmsted County, Minnesota.[11] Briefly, the original study included 237 incident RA cases who fulfilled the 1987 American College of Rheumatology classification criteria.[12] It also included 237 control subjects (1:1 matching) who had no history of RA matched to each case by sex, birth (± 3 years), and registration year and were randomly selected from the same source population using the REP medical records linkage system. Because the detection of asthma is a function of follow-up duration, we addressed this concern by matching cases and controls by registration and index years, resulting in a similar follow-up duration. The exclusion criteria for cases and controls were change of research authorization, insufficient medical records, and medical conditions making it difficult to ascertain asthma status (Table I). The study was approved by the institutional review boards of both Mayo Clinic and Olmsted Medical Center.

Exposure ascertainment (asthma status)

For determining a history of asthma, we conducted comprehensive medical record reviews to apply predetermined asthma criteria (Table I), which have been extensively used in research[10] and were found to have excellent construct validity and reliability.[13] We included both definite and probable asthma because most probable patients with asthma become definite over time.[10] We also obtained asthma status based on symptoms, health care services, and treatments within 1 year before the index date. *Active asthma (current asthma)* at the index date was defined as the occurrence of any asthma-related episodes including asthma symptoms (ie, cough with wheezing, shortness of breath, and chest tightness), asthma medications, or unscheduled office visits, emergency department visits, urgent care visits, or hospitalization for asthma within 1 year before the index date. *Inactive asthma* was defined as the absence of aforementioned asthma-related events within 1 year before the index date. To assess the impact of asthma medications on RA risk, we collected information on asthma medication use including inhaled and oral corticosteroids within 3 months of the index date.

Other variables

Demographic and clinical characteristics included sex, age, race, family history of asthma, and other atopic conditions. Atopy status defined by aero- or food allergen was collected through comprehensive review of medical charts and the REP. We collected data on other atopic conditions such as allergic rhinitis, atopic dermatitis, and food allergy on the basis of a physician diagnosis documented in medical records to examine whether coexistence of allergic diseases