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INFLAMMATORY BOWEL DISEASE AND ASTHMA: A POPULATION-BASED CASE-CONTROL STUDY

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Abstract

Background & Aims—A few cross-sectional studies reported an increased risk of inflammatory bowel disease (IBD) among asthmatics. We conducted a population-based case-control study that applied predetermined criteria for asthma and IBD to determine whether asthma, as a T-helper 2 (Th2) condition, reduces the risk of IBD a Th1 condition.

Methods—This was a population-based case-control study using criteria-based ascertainment for IBD and asthma. Subjects were all Rochester, Minnesota, residents who had developed IBD between 1964 and 1983 and their age-and gender-matched controls, using 1:1 matching. Controls were randomly selected from the community using the Rochester Epidemiology Project database and confirmed not to have IBD. All cases and controls were merged with the database comprising all Rochester residents with or without asthma between 1964 and 1983.

Results—Of the 231 IBD cases, 55% had ulcerative colitis and the remainder had Crohn's disease. Of these, 50.4% were male and 98.1% were Caucasians. The mean age at the time of IBD diagnosis was 33.8 years. Four cases (1.7%) had asthma prior to index date of IBD, whereas two controls (0.9%) had asthma (unadjusted odds ratio: 3.0, 95% CI: 0.31–28.84, P=0.34). Similarly, 16 IBD cases (6.9%) had asthma ever while 12 controls (5.2%) had asthma ever (unadjusted odds ratio: 1.4, 95% CI: 0.62–3.38, p=0.40).

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Conclusions—Asthma as a Th2 condition does not reduce the risk of IBD as a Th1 condition. Because of the limitations of our study and others, the association between asthma and IBD needs to be further studied.

Keywords

Asthma; inflammatory bowel disease; epidemiology; risk; ulcerative colitis; Crohn's disease; Rochester Epidemiology Project; case-control study

INTRODUCTION

Inflammatory bowel disease (IBD) is estimated to affect as many as 1.4 million persons in the United States1 and 10% of them are children.2 The prevalence of both ulcerative colitis and Crohn's disease has been reported to increase over the past few decades.3 Indeed, the rising trends of IBD incidence and prevalence are also evident in Rochester, Minnesota.1, 4

The etiology of inflammatory bowel disease is unknown, but the condition seems to be the result of a combination of environmental and immunogenic.5, 6 Luminal antigens are believed to activate T helper 1 (Th1) cells producing tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 that polarize immune activity toward a pro-inflammatory response.7, 8 Although risk factors associated with IBD have been extensively studied,1, 9–12 little is known about whether individuals with certain chronic conditions such as asthma that have a Th2-predominant immune milieu have a reduced risk of developing IBD given the reciprocal inhibition of Th1 immune response by Th2 cytokines (e.g., IL-4, IL-5, and IL-13) or response.13–15 This concern becomes significant considering that asthma is the most common chronic illness in childhood and a major cause of morbidity in adults, affecting 4–17% of children and 7.3–10.1% of adults in the US.16–18 The incidence and prevalence of asthma has increased over the past decades both in the US and globally.16, 19, 20 These same trends were seen in Rochester, Minnesota.21, 22 The impact of these rising trends in asthma prevalence and incidence on the risk of IBD is not well studied. There are a few studies which have addressed this issue but also have important limitations, such as lack of case (IBD) and exposure (asthma status) ascertainment by predetermined criteria, and the cross-sectional nature of the studies, making these studies susceptible to detection bias23–25. For example, these studies used ICD codes for asthma ascertainment, and ICD code-based ascertainment for asthma may not be suitable for testing the hypothesis because a delay in the diagnosis of asthma for those who met the criteria for asthma in health care setting has been well documented.21, 26 This delay in the diagnosis of asthma might be more common among controls than cases (i.e., detection bias) leading to a positive association between asthma and IBD.

We hypothesized that individuals with asthma might have a lower risk of IBD compared to those without asthma. Our primary aim was to test this hypothesis and we addressed the limitations of previous studies by conducting a population-based case-control study using criteria-based ascertainment for asthma and IBD.

METHODS

The study was approved by the Institutional Review Boards at both Mayo Clinic and Olmsted Medical Center. We conducted a population-based case-control study that assessed the relationship between asthma and IBD using the existing data sets for IBD cases and asthma status among the residents of Rochester, Minnesota between 1964 and 1983.

Study Design

The study was designed as a population-based case-control study. Disease status was IBD cases and their 1: 1 age and gender-matched controls without IBD. Exposure was asthma status. The frequency of asthma was compared between cases and controls to determine the association between asthma and IBD.

Study Setting

Rochester, Minnesota has unique epidemiologic advantages to conduct a population-based epidemiologic study such as this. Our study setting has a virtually self-contained health care environment and unified medical record system. All medical records for the residents of Olmsted County, Minnesota are available for epidemiologic investigation through the NIH-funded Rochester Epidemiology Project.27 All diagnostic information has been indexed since 1935 using Berkson codes even before ICD codes were available.27

Case Ascertainment

Previous studies identified 286 IBD (129 Crohn's disease and 157 ulcerative -colitis) cases between 1964 and 1983 and their index date of IBD from the Olmsted County, Minnesota, residents. The details of identification of individuals with IBD were previously reported.28, 29 Briefly, IBD cases were Olmsted county residents who had developed IBD between January 1, 1964 and December 31, 1983. Cases were ascertained by predetermined criteria for IBD which are delineated in Table 1. Previous studies used these criteria for epidemiologic investigation of IBD.30–35 Briefly, cases were required to have features consistent with IBD, after review of all available clinical, radiological, endoscopic and histologic findings. All medical records were reviewed by a gastroenterologist to confirm the diagnosis of Crohn's disease (CD) and ulcerative colitis (UC). The index date of IBD was the time when one met criteria for IBD. For the present study, additional exclusion criteria were: 1) non-residents of Rochester because our original asthma epidemiology study identified only asthmatics from the residents of the City of Rochester, Minnesota, 2) no research authorization for medical record review, and 3) medical records without sufficient information for our study. Rochester residency was defined by living in Rochester, Minnesota, for at least one year prior to index date of IBD, to avoid patients who were seeking tertiary care from outside of Rochester. The IBD epidemiological studies done previously28, 29, 31, 34, 35 included residents of Olmsted County, not Rochester alone, and some of these studies did not require one year of residency prior to diagnosis to be included as a case.31, 35 Thus, our study excluded some of the original study cohort for IBD.

Identification of Controls

The eligible controls were randomly selected from the residents of Rochester, Minnesota who had never developed IBD during the study period (1964–1983) and after the study period until the end of 2007. Therefore, controls had never had IBD as of the end of 2007. After a list of potential controls was generated through the Rochester Epidemiology Project database, controls were matched to cases with regard to age (within six months for children younger than 18 years of age and within one year for adults), gender, registration year (within one year), and visit day (within one year of index date of IBD). Therefore, because IBD cases and their matched controls had similar clinic registration date (beginning point of follow-up) and visit day within one year of index date of case (end point of follow-up), we ensured that cases and controls had a similar length of follow-up period. Controls had the same exclusion criteria as cases.

Exposure (Asthma Status) Ascertainment

Once we identified confirmed IBD cases and their controls, we determined asthma status by merging the list of cases and controls with a previous study database that included all Rochester residents with asthma between 1964 and 1983. A previous study determined asthma status of all Rochester, Minnesota, residents between 1964 and 1983 based on predetermined criteria for asthma delineated in Table 2, and identified 2,499 Rochester, Minnesota, residents with asthma.21 The original study assessed the reliability of the criteria. Random samples of records were reviewed by different nurse abstractors and analyzed for inter-observer reliability and agreement rates between abstractors and a high degree of concordance was found.17 The asthma criteria have been extensively used in previous epidemiologic investigations.17, 36, 37 Determining the temporal relationship between asthma and IBD was feasible since the original study included the incidence dates for asthma in all confirmed asthma cases.

Other Variables

We collected data pertinent to this study from medical records. These included sociodemographic variables, cigarette smoking history, history of atopic conditions other than asthma, family history of asthma, family history of atopic conditions other than asthma, medications, family history of IBD, and comorbid conditions. The co-morbid conditions examined in this study include pro-inflammatory conditions (e.g., rheumatoid arthritis, type I diabetes, psoriasis, systemic lupus erythematosus), alcohol abuse, and chronic obstructive lung disease, and immunosuppressive therapy at or prior to the index date of IBD. Atopic conditions other than asthma were defined as the physician diagnosis of atopic dermatitis/eczema or allergic rhinitis/hay fever documented in medical records.

Data Analysis

Because previous studies reported the incidence of IBD,34 we did not calculate the incidence of IBD for our study subjects. We compared the frequency of sociodemographic and other pertinent variables between cases and controls. To test the hypothesis, the primary analysis was to compare the frequency of asthma prior to the index date of IBD between IBD cases and controls and the secondary analysis was to compare the frequency of asthma ever regardless of the index date of IBD between cases and controls. To determine the association between IBD and asthma, data were fitted to a conditional logistic regression for matched analysis. The odds ratio for asthma was calculated, with 95% confidence interval, and tested for statistical significance using a two-sided alpha error of 0.05.

RESULTS

Study Subjects

The characteristics of the study subjects are shown in Table 3. There were 286 IBD cases among the Olmsted County, Minnesota, residents who met the criteria for IBD. Of these 286 IBD cases identified, 55 cases were excluded due to non-Rochester residency (n=43), no research authorization for medical record review (n=7), and no sufficient information in medical records (n=5). Of the 231 enrolled cases 50.4% were male and 98.1% were Caucasians. Fifty-five percent of them had ulcerative colitis and the rest were cases of Crohn's disease. The median and mean age at the index date of IBD was 28.5 and 33.8 years, respectively.

Asthma and Inflammatory Bowel Disease

The mean age of patients at index date of asthma was 48.5 (SD 15.31) and 44.8 years (SD 9.07), with median of 45.5 and 45.0 in cases and controls respectively, and the mean

duration between the diagnosis of asthma and that of IBD was 20.2 years (SD 19.16), with median of 16.1 years. The results on the relationship between asthma and IBD are summarized in Table 4. The results showed that asthma did not reduce the risk of IBD. Rather there might be a potentially increased risk of IBD among individuals with asthma, compared to non-asthmatics, but the results did not reach statistical significance. This was true for asthma ever (development of asthma regardless of index date of asthma). Given the small number of asthma frequency in both cases and controls and no association between asthma and IBD, we did not assess the relationship between asthma and Crohn's disease and ulcerative colitis separately.

Influences of Atopic-Related Variables on the Risk of IBD

We also assessed the association of IBD with atopic conditions other than asthma (atopic dermatitis/eczema or allergic rhinitis/hay fever), family history of asthma, and family history of atopic conditions other than asthma. The results are summarized in Table 5. IBD was associated with none of these variables.

Other Variables and IBD

Of the 231 IBD cases, there were 121 cases (52.4%) with a history of smoking and 84 (36.4%) without such history. In 26 cases (11.2%), smoking history was unknown. The smoking history was not associated with risk of IBD (OR: 1.11, 95% CI 0.71 –1.76, p=0.64). Also, immunosuppressive therapy prior to the index date of IBD (p = 0.34), family history of IBD (p=0.22), and alcohol abuse (p=0.2), were not associated with the risk of IBD. None of the co-morbid conditions were associated with the risk of IBD, which could be because of our small sample size of study population.

DISCUSSION

Our study findings show that a diagnosis of asthma did not reduce the risk of subsequent IBD, and individuals with asthma had a risk of IBD that was not significantly different than that of non-asthmatic individuals. Also, there was no significant relationship between atopic conditions other than asthma and IBD. Furthermore, other atopy-related variables such as family history of asthma or other atopic conditions were not associated with the risk of IBD.

In our study results, the frequency of asthma in all IBD cases prior to index date of IBD was 1.7%, compared to 0.9% in controls (OR: 3.0: 95% CI 0.31–28.84, p=0.34). The frequency of asthma ever (regardless of index date of IBD) in all IBD cases was 6.9% whereas that in controls was 5.2% (OR 1.4: 95 % CI 0.62–3.38). Similarly, this was true for other atopic conditions (15.6% vs. 11.7%, respectively, p=0.22). Therefore, in contrast with our hypothesis, even if asthma and other atopic conditions are Th2-predominant immune conditions and IBD is a Th1 or proinflammatory condition, this did not translate into an inverse relationship between asthma or other atopic condition and IBD. Rather the frequency of asthma or other atopic conditions in IBD cases tended to be higher than that in controls, suggesting a potentially increased risk of IBD among individuals with asthma or other atopic conditions. Along these lines, the family history of asthma or atopic conditions was not related to the risk of IBD either. Our post-hoc power calculation suggests that we had 80% power to detect an odds ratio of 2.65 as an effect size. Thus, our study may have had limited statistical power to address the study aim given the reported effect sizes on the association between asthma and IBD in the literature. Overall, our data suggest that neither asthma nor other atopic conditions reduces the risk of IBD, but the potential possibility of increasing the risk of IBD by asthma status needs to be carefully examined in a larger study with similar study design to ours.

There is no study with which we can directly compare our results due to differences in study design and ascertainment criteria for asthma and IBD. A few studies investigated the epidemiologic relationship between IBD and asthma. Bernstein et al reported that the prevalence of asthma in ulcerative colitis cases and their controls were 21.2% and 15.1%, respectively (prevalence ratio for asthma:1.53, 95% CI: 1.41–1.66).23 They also found a similar trend in the relationship between Crohn's disease and asthma, with prevalence of 19.9% and 15.7% in cases and controls, respectively (prevalence ratio for asthma: 1.34, 95% CI: 1.24–1.46). Their study was designed as a population-based cross-sectional study and utilized the Manitoba Health administrative database and ascertained IBD and asthma status based on ICD-9 code. Weng et al conducted another population-based cross-sectional study in the United Stated and found that IBD patients were more likely to have asthma, compared to controls (OR for asthma: 1.5, 95% CI 1.5–2.3).25 This study also utilized administrative data and ICD code for determining for IBD and asthma status. Cohen et al examined the relationship between atopic dermatitis and IBD by conducting a population based cross-sectional study which utilized ICD codes for atopic dermatitis and IBD.24 They found an increased risk of IBD among individuals with atopic dermatitis (OR:1.5, 95%CI: 1.29–1.78). These cross-sectional studies are susceptible to detection bias, a bias that arises from differential identification of outcome events by patients, clinicians or examiners. In these studies, individuals with asthma might have sought medical care more frequently or earlier than those without asthma, and thus, asthmatics might be more likely to reveal symptoms of IBD to clinicians and reach the diagnosis of IBD than non-asthmatics. Likewise, asthma symptoms in individuals with IBD might be more likely to be detected compared to those without IBD due to the potential IBD-related pulmonary symptoms or increased access to medical cares. Specifically, ICD code-based ascertainment of asthma may not be suitable for addressing the study aim because a significant proportion of individuals who met the criteria for asthma (15–65%) have been reported to have a delay in the diagnosis of asthma.21، 26 Detection bias can arise if this delay in the diagnosis of asthma (i.e., ICD code) occurs disproportionately more among controls than cases. In other words, asthma frequency by ICD code is likely to be lower in controls than cases and it might result in a positive association between IBD and asthma. Therefore, the degree of detection bias cannot be assessed in a cross-sectional study and none of these studies adequately addressed this concern. The epidemiologic relationship between asthma and IBD, particularly a possibility of an increased risk of IBD among individuals with asthma, needs to be further studied in a large-scale population-based study with similar study design to ours.

The main strengths of our study include the population-based study design, ascertainment of IBD and asthma by predetermined criteria rather than ICD code or self-report and epidemiologic advantages of our study setting with self-contained health care environment and unified medical record systems among health care providers in the community. The limitations of our study include the inherent limitations of retrospective study, predominantly Caucasian population, and a relatively smaller sample size compared to previous studies.

In conclusion, given the burgeoning literature on the potential reciprocal relationship between Th1 vs Th2 immune responses, our study results reassure patients that neither asthma nor other atopic conditions influence the future risk of developing IBD. Our study results also mitigate the public health community's concern about the impact of the rising trend of asthma over the past decades on the risk of other chronic conditions such as IBD. However, because of the limitations of our study and others, the epidemiologic association between asthma and IBD needs to be further studied in the future.

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Abbreviations

IBD	Inflammatory bowel disease
OR	Odds ratios
95% CI	95% confidence interval

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Table 1

The Criteria for Inflammatory Bowel Disease.

The diagnosis of Crohn's disease required at least two of the following:	
1	History of abdominal pain, weight loss rectal bleeding or diarrhea
2	Compatible endoscopic findings such as skip lesions, cobblestoning, fistulas, or perianal disease
3	Characteristic radiologic findings such as mucosal ulcerations, fistulas or strictures
4	Characteristic gross features noted at laparotomy and surgical pathology, such as bowel wall induration, mesenteric lymphadenopathy, or serosal creeping fat / inflammation
5	Histopathologic features of transmural inflammation or epithelial granuloma with no evidence of infectious organisms
The diagnosis of ulcerative colitis required one of the following:	
1	Evidence of mucosal inflammation and ulceration based on endoscopic, radiologic, surgical, or histologic findings
2	Findings of diffusely granular or friable mucosa on endoscopy, continuous involvement of the colon by endoscopy, radiographic or pathologic examination, and none of the features of Crohn's disease.
Patients suspected to have an infectious, antibiotic-associated, or ischemic etiology were excluded	

Table 2

The Criteria for Asthma

Patients were considered to have ***definite*** asthma if a physician had made a diagnosis of asthma or if each of the following 3 conditions were present. Patients were considered to have ***probable*** asthma if the first 2 of the following 3 conditions were present:

1 History of cough and /or dyspnea, plus wheezing, OR history of cough and / Or dyspnea plus wheezing on examination.

2 Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and

3 Two or more of the following

- Nocturnal cough
- Non smoker (14 years or older)
- Nasal polyps
- Blood eosinophilia
- Positive wheal and flare skin tests or elevated IgE
- History of atopy (atopic conditions)
- Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted or methacholine challenge test showing greater than 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator

Table 3

Sociodemographic Characteristics of Study Subjects

	IBD Cases (n=231)	Controls (n=231)
Age (years)	33.8 ± 16.36	33.5 ± 16.26
Gender (%)		
Male	50.4	50.4
Female	49.6	49.6
Ethnicity (%)		
White	98.1	98.1
non-white	1.9	1.9
Education levels (%)		
Less than high school	0.6	5.1
High school graduate	30.8	36.4
Some college education	27.3	22.7
College graduate	23.8	27.8
Graduate school	17.4	13.1

Table 4

The Relationship between IBD and Asthma

Asthma status	IBD (n=231)	Control (n=231)	OR (95% CI)	p-value
Asthma prior to index date of IBD (%)				
Yes	1.7	0.9	3.0 (0.31 – 28.84)	0.34
No	98.3	99.1	Referent	
Asthma ever (%)				
Yes	6.9	5.2	1.4 (0.62 – 3.38)	0.40
No	93.1	94.8	Referent	

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Table 5

The Relationship between IBD and Other Atopy-related Variables

Other atopy-related variables	IBD (n=231)	Control (n=231)	OR (95% CI)	p-value
Atopy before IBD (%)				
Yes	15.5	11.7	1.4 (0.81–2.38)	0.22
No	84.5	88.3	Referent	
Atopy ever (%)				
Yes	27.7	28.5	1.0 (0.60–1.57)	0.90
No	72.3	71.5	Referent	
Family history of asthma (%)				
Yes	2.5	2.5	1.0 (0.32–3.10)	1.00
No	87.5	87.5	Referent	
Family history of atopic conditions other than asthma (%)				
Yes	2.1	3.0	0.7 (0.23–2.25)	0.56
No	87.9	97.0	Referent	