Geographic Distributions of Microscopic Colitis and Inflammatory Bowel Disease in the United States

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Background: Crohn's disease (CD) and ulcerative colitis (UC) are characterized by similar geographic distributions. We used a large database of pathology reports to analyze the geographic distribution of microscopic colitis (MC) and compare it with those of UC and CD.

Methods: A population of 671,176 individual patients with colonic biopsies was studied stratified by gender and state of residence. The occurrence of each diagnosis MC, UC, or CD, was expressed as proportional rate per 1000 colonoscopies with biopsies from each individual state.

Results: UC and CD tended to be common in states in the Northeast or North Central regions of the U.S. and relatively rare among several southern states. MC appeared to follow a somewhat inverse pattern, as it was most common among some states from the Southwest (Colorado, New Mexico, Arizona, Nevada) and other states of southern latitude, such as Florida, Georgia, California, but relatively uncommon among states in the Northeast. The geographic distributions of UC and CD were significantly correlated with each other ($R = 0.60$ and $P = 0.0004$). No significant correlation was observed between MC and UC or CD.

Conclusions: The differences in epidemiologic behavior point at a dissimilar set of risk factors that shape the occurrence of MC as opposed to UC or CD.

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Key Words: collagenous colitis, Crohn's disease, epidemiology of inflammatory bowel disease, geographic distribution, microscopic colitis, ulcerative colitis

The occurrence of inflammatory bowel disease (IBD) is characterized by a marked geographic variation.[1,2] In general, IBD is more common in the affluent societies of Westernized countries. In Europe and North America, IBD is more common among populations living in northern than southern latitudes.[1–5] Within the U.S., several previous studies, using statistics of mortality, hospitalizations, physician visits, and colonoscopy, have confirmed a similar pattern of more frequent occurrence in northern than southern states.[6–8] In these studies, ulcerative colitis (UC) and Crohn's disease (CD) were generally characterized by similar geographic distributions. Microscopic colitis (MC) is a condition that includes a spectrum of histological abnormalities of the colonic mucosa, ranging from an increase in the number of intraepithelial lymphocytes ("lymphocytic colitis") to a diffuse lymphoplasmacytic infiltrate of the lamina propria, prominent intraepithelial lymphocytosis, and the formation of a thick subepithelial collagen band ("collagenous colitis").[9,10] Clinically, MC is associated with watery diarrhea that responds to similar medications as CD and UC. Its epidemiologic and clinical relationships with other forms of IBD are still unknown. Overall, the epidemiology of MC is less well characterized than that of UC or CD. The clinical terms microscopic, lymphocytic, and collagenous colitis have been missing from the 9th and 10th revisions of the International Classification of Diseases (ICD). The diagnosis of MC relies primarily on the histological appraisal of its characteristic features in patients with chronic or intermittent diarrhea. Because the diagnosis cannot be made based on clinical criteria alone, it is less likely to enter disease registries, be recorded by health surveys, or become listed on death certificates. Caris Life Sciences, a specialized gastrointestinal laboratory, has maintained a large database of pathology reports from endoscopy patients distributed throughout the U.S. In the present study, we used this unique database to study the geographic distribution of MC and compare it with the geographic distributions of UC and CD.

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MATERIALS AND METHODS

Data Source

The present study was conducted at Caris Life Sciences, a specialized gastrointestinal laboratory, operating with private

outpatient endoscopy centers distributed throughout the United States. The results of all surgical pathology were stored in a single electronic database. Besides demographic characteristics, each patient record also contained the clinical and endoscopic diagnoses, as well as a detailed list of all results of surgical pathology. If individual patients appeared in the database with multiple colonoscopy reports, only the results of the index endoscopy were included, when the colitis was first diagnosed. For controls, only the results of their first colonoscopy were considered. Surgical pathology diagnoses were coded in a predefined, standardized, and searchable fashion. The study was approved by the Caris Life Sciences Institutional Review Board. All data of the study were collected exclusively by reviewing preexisting records, and no direct contact with either patients or providers was made. No individual patient information was revealed and patient records were deidentified before being included in the present analysis. For these reasons the study protocol was exempted from the need for informed consent from its participants.

Biopsy Specimens

Patients included in this study were referred to gastroenterologists by primary care providers or other specialists from almost every U.S. state, comprising a broad sampling of primary gastroenterology practice in the U.S. Approximately 1500 individual gastroenterologists distributed throughout the U.S. contributed to the database. The endoscopies were performed at private, community-based endoscopy centers, or multispecialty surgery centers. All patients in the database who underwent colonoscopy with mucosal biopsies between January 2008 and December 2010 were included in the analysis. The presence of colon biopsy specimens was the sole criterion for inclusion.

Biopsy specimens were processed centrally in three laboratories located in Irving (Dallas), Texas, Phoenix, Arizona, and Boston, Massachusetts. Identical sectioning and staining procedures were followed in each laboratory. Slides were reviewed and interpreted by an experienced group of dedicated subspecialty-trained gastrointestinal pathologists, who have shared a common approach to biopsy evaluation. Uniformity among the pathologists was achieved through a standardized approach to specimen handling and a predetermined set of diagnostic criteria and terminology for biopsy interpretation. Consensus has been maintained and updated through daily multiheaded microscope conferences, monthly didactic conferences, journal club, terminology and criteria review committee, and ongoing comprehensive quality assurance review. All three centers participated simultaneously in these activities through teleconferencing. Over 350,000 tissue specimens were examined per year.

UC, CD, or indeterminate colitis were diagnosed when a set of biopsies from a colonoscopy met the histopathological criteria for IBD as defined by the Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the Crohn's and Colitis Foundation of America.[11] Caris pathologists correlated the histological findings with the clinical and endoscopic information provided to generate the diagnoses of UC, CD or, when the histopathology was unequivocally suggestive of IBD but the clinical, endoscopic, and topographic information was insufficient, indeterminate colitis.

Caris pathologists diagnose lymphocytic and collagenous colitis according to the criteria they have outlined in Carmack et al.[12] Briefly, the criteria for lymphocytic colitis include increased intraepithelial lymphocytes (>20 lymphocytes per 100 enterocytes) in an architecturally normal colonic mucosa, accompanied by surface epithelial disarray and a mixed inflammatory infiltrate in the lamina propria.[12,13] The infiltrate contains superficial lymphoplasmacytosis, typically with eosinophilia in the lamina propria. Variable epithelial disarray and damage is usually seen at least focally. Collagenous colitis is distinguished by an increase in the thickness of the subepithelial collagen band (sometimes referred to as the "collagen table") in a setting otherwise typical of lymphocytic colitis.[14] Because of the essentially identical clinical aspects and associations of these two histopathological entities and the consensus that they are parts of the spectrum of a single nosologic entity, for the purpose of this study we amalgamated them under the umbrella term "microscopic colitis."

Statistical Analysis

The statistical analysis was carried out using Access and Excel (Microsoft, Redmond, WA), as well as the statistical software of SAS (Cary, NC). The analysis was focused on the geographic distributions of MC, UC, CD, and all IBD, comprised of UC, CD, and indefinite colitis combined. The data were stratified by male and female gender. The occurrence of each diagnosis was expressed as proportional rate per 1000 colonoscopies with biopsies from each individual state. Two rates were considered statistically different if their 95% Poisson confidence intervals did not overlap. The geographic distributions of each two diagnoses were compared using least-square linear regression analyses. The disease distributions among different gender groups were compared calculating odds ratios (OR) and their 95% confidence intervals (CI). Differences in age between two diagnostic groups or U.S. census regions were compared using Student's *t*-test.

RESULTS

Over 670,000 individual patients were included in the present study, of whom 17,000 were diagnosed with UC or CD and 9,900 with MC. Besides UC and CD, the overall group of IBD also included 754 patients with indefinite colitis. Table 1 contains a stratification of the patient population by gender and histological diagnosis. MC was 3-fold more common among women than men: OR: 2.98, 95% CI: 2.84–3.12. By comparison, CD was only slightly more common in women (OR: 1.14, 95% CI: 1.07–1.21) and UC was slightly less common in women than men (OR: 0.93,

TABLE 1. Patient Population Stratified by Histological Diagnosis and Gender

	Microscopic Colitis	Crohn's Disease	Ulcerative Colitis	All IBD	All Colonoscopies
Age (SD)	62.6 (15.0)	46.6 (16.6)	49.4 (16.4)	48.7 (16.4)	59.2 (13.6)
Females	7,438 (2.19%)	2,050 (0.60%)	5,647 (1.66%)	7,697 (2.27%)	339,200 (100%)
Males	2,475 (0.75%)	1,758 (0.53%)	5,941 (1.79%)	7,699 (2.32%)	331,222 (100%)
Sex ns	6 (0.80%)	2 (0.27%)	11 (1.46%)	13 (1.72%)	754 (100%)
Total	9,919 (1.48%)	3,810 (0.57%)	11,599 (1.73%)	15,409 (2.30%)	671,176 (100%)

ns, not specified.

95% CI: 0.89–0.96). Patients with MC were significantly older ($P < 0.0001$) than CD or UC patients.

Table 2 shows the patient population stratified by geographic region, gender, and histological diagnosis. Except for minor differences, the age and gender distributions were similar across patient populations from different census regions of the U.S. MC was significantly more common in the West than any other region, whereas CD was significantly less common in the West than any other region. UC was lowest in the South compared with other regions.

Besides analyzing the geographic distribution on a regional level, the data also provided the opportunity to study them by individual states. Based on state size and referral patterns, the total number of colonoscopies per state in the database varied between 1 and 62,476. Overall similar statistical results were obtained using the entire dataset or subsets restricted to larger states. To assure statistically reliable data for individual states, the final analysis was limited to the 30 largest states with populations greater than 3600 individual patients. Among these states, the number of patients with MC or IBD varied between 39 and 1090 or 68 and 1276, respectively. Table 3 shows the geographic distributions of the three diagnoses and all IBD combined among the 30 states with the largest numbers of colonic biopsy reports. Similar to previous studies, IBD tended to be common in states of the Northeast or North Central division of the Midwest and relatively rare among several Southern states. MC appeared to follow a somewhat inverse pattern, as it was most common among some states from the Southwest (Colorado, New Mexico, Arizona, Nevada) and other states of southern latitude, such as Florida, Georgia, California, but relatively uncommon among states in the Northeast.

Within each diagnostic category, there was a strong correlation between disease frequency among women and men ($P < 0.0001$ for all diagnoses) (Fig. 1). UC and CD were also significantly correlated with each other, with $R = 0.60$ and $P = 0.0004$ (Fig. 2). Significant correlation coefficients were found if gender subgroups were compared with each other, that is, female UC with female or male CD, and male UC with female or male CD. However, no significant correlations were observed between MC and all IBD combined or between MC and UC or CD analyzed separately.

DISCUSSION

Little is known about the epidemiology of MC and possible environmental risk factors, which influence its occurrence. In using a large database of pathology reports, we analyzed the geographic distribution of MC within the U.S. and compared it with those of UC and CD. Whereas

TABLE 2. Patient Population Stratified by Region, Gender, and Histological Diagnosis

	Northeast	Midwest	South	West	Region ns	Grand Total
Age (SD)	58.5 (13.6)	59.4 (13.7)	59.1 (13.7)	59.9 (13.3)	59.4 (13.3)	59.2 (13.6)
Females	61,121 (49%)	48,387 (50%)	144,882 (52%)	83,021 (50%)	1,789 (51%)	339,200 (51%)
Males	64,628 (51%)	47,271 (49%)	134,844 (48%)	82,795 (50%)	1,684 (48%)	331,222 (49%)
Sex ns	230 (0%)	213 (0%)	190 (0%)	118 (0%)	3 (0%)	754 (0%)
Microscopic colitis	1,476 (1.17%)	1,172 (1.22%)	3,946 (1.41%)	3,303 (1.99%)	22 (0.63%)	9,919 (1.48%)
Crohn's disease	764 (0.61%)	590 (0.62%)	1,716 (0.61%)	727 (0.44%)	13 (0.37%)	3,810 (0.57%)
Ulcerative colitis	2,621 (2.08%)	1,649 (1.72%)	4,358 (1.56%)	2,940 (1.77%)	31 (0.89%)	11,599 (1.73%)
All IBD	3,763 (2.99%)	2,444 (2.55%)	6,798 (2.43%)	4,033 (2.43%)	47 (1.35%)	17,085 (2.55%)
Total	125,979 (100%)	95,871 (100%)	279,916 (100%)	165,934 (100%)	3,476 (100%)	671,176 (100%)

ns, not specified.

TABLE 3. Geographic Distribution of Microscopic Colitis, and IBD Among 30 US States

	Microscopic Colitis	Crohn's Disease	Ulcerative Colitis	All IBD
Northeast				
Connecticut	11.0	6.0	18.8	27.2
Massachusetts	10.2	6.5	15.5	25.4
New Jersey	9.6	7.4	24.3	34.3
New York	6.5	4.3	18.4	26.5
Pennsylvania	12.8	7.5	25.6	35.4
Midwest				
Illinois	13.3	9.3	21.8	34.8
Indiana	14.9	3.9	11.3	16.5
Kansas	13.5	4.7	13.5	18.7
Michigan	14.3	4.5	16.2	22.8
Missouri	17.7	6.3	17.7	26.5
Ohio	15.6	6.8	18.7	27.4
South				
Florida	17.2	4.9	12.8	19.5
Georgia	15.8	8.4	19.0	30.3
Kentucky	22.7	9.6	17.8	30.6
Louisiana	11.1	4.2	13.4	20.2
Maryland	12.7	8.5	17.6	29.9
North Carolina	10.4	6.0	14.6	23.8
Oklahoma	14.0	3.1	14.3	20.0
South Carolina	10.4	2.9	15.9	21.8
Texas	12.5	5.4	15.3	22.6
Tennessee	16.4	6.8	12.8	22.4
Virginia	11.6	8.2	21.3	33.3
West				
Alaska	19.2	8.1	24.2	35.1
Arizona	22.6	4.2	16.1	22.2
California	15.6	3.5	18.9	24.3
Colorado	26.5	2.8	16.3	20.7
Nevada	19.8	8.3	20.8	33.4
New Mexico	24.3	2.7	14.1	18.3
Oregon	17.2	5.1	16.3	24.7
Utah	19.1	6.3	20.1	28.0

Data expressed as proportional rates per 1000 colonoscopies with biopsies.

UC and CD showed similar geographic variations, no resemblance was found to that of MC.

There are several potential limitations of the present analysis. Because our study used a nonpopulation-based dataset, we had to calculate proportional rates (per colonoscopies with biopsies) rather than prevalence rates per living population. The numbers of case and control subjects available for individual states were influenced not only by state size but also by geographic referral patterns to the Caris pathology laboratory. Our reliance on pathology reports prevented us from considering IBD cases with small bowel involvement only or diagnosed based on other criteria besides colonic biopsy. This limitation may have contributed to the relative dominance of UC over CD patients in our patient population, whereas most epidemiologic studies from North America have found ratios closer to 1 when comparing the two diagnoses.

These limitations need to be contrasted with some obvious advantages in using the Caris database to carry out epidemiologic analyses. With its three main laboratories located in Dallas, Boston, and Phoenix, Caris Life Sciences handles gastrointestinal biopsy specimens submitted from endoscopists distributed throughout the U.S. All diagnoses in the database are based exclusively on histological evaluation by board-certified pathologists specialized in gastrointestinal surgical pathology. These characteristics are especially important for MC, the diagnosis of which rests primarily on the microscopic appearance of colonic biopsy specimens. Since all patients of the present study underwent colonoscopy with endoscopic biopsies, it is unlikely that patients with a diagnosis of MC or IBD were missed or erroneously assigned to the comparison group. There is a possibility, however, that diligence and expertise in managing patients with chronic diarrhea varies among practices and that such variations contributed to the observed geographic patterns. Gastroenterologists specializing in IBD may be unevenly distributed throughout the U.S. and some of the observed patterns may be influenced by an underlying selection bias in the recruitment of endoscopy practices. One would expect such selection bias to affect MC and IBD alike rather than being restricted to one or the other disease entity alone. Moreover, expertise and specialization in colorectal diseases and IBD tends to parallel exposure to large patient populations harboring these diagnoses. The geographic distribution of IBD is validated by similar geographic patterns that have been reported by previous investigators relying on different types of epidemiologic data.[1–8]

Besides varying practice patterns among gastroenterologists, the observed geographic distributions could have been also influenced by underlying variations among pathologists in establishing the various diagnoses. The methods section lists multiple measures of quality assurance implemented among the three Caris laboratories. However, no amount of joint training, criteria touting, joint sessions, or conferences will ever be able to completely eliminate all interobserver variability in surgical pathology, or, for that matter, in any other specialty. Caris pathologists use all the above methods, including a criteria committee that prepares and attempts to enforce their use through a widespread quality control program. Besides Dallas, pathologists from the other two locations in Boston and Phoenix read 10%

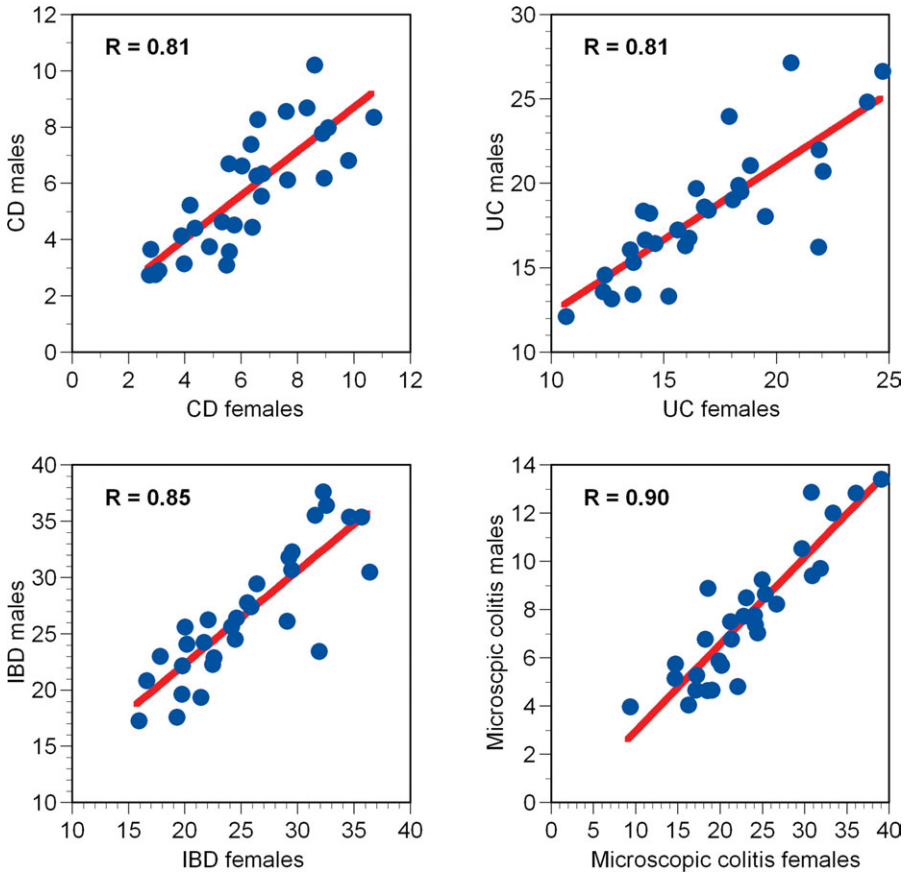

FIGURE 1. Correlations among the geographic distributions of male and female patients with UC, CD, IBD, and MC. Data expressed as proportional rates per 1000 colonoscopies with biopsies; each point represents a separate U.S. state. $P < 0.0001$ for all R-values.

and 25% of all colon biopsies, respectively, and join conferences through video links that include telepathology, that is, high-quality live images delivered to each site. In addition, cases from various states are constantly shifted from one laboratory to another, depending on pathologists' availability, daily volume, and other factors. Therefore, the influence that any single site or individual pathologists can exert on the prevalence of a specific condition is likely to be negligible.

The distinct north–south gradient and the similarity among UC and CD are striking features in the geographic

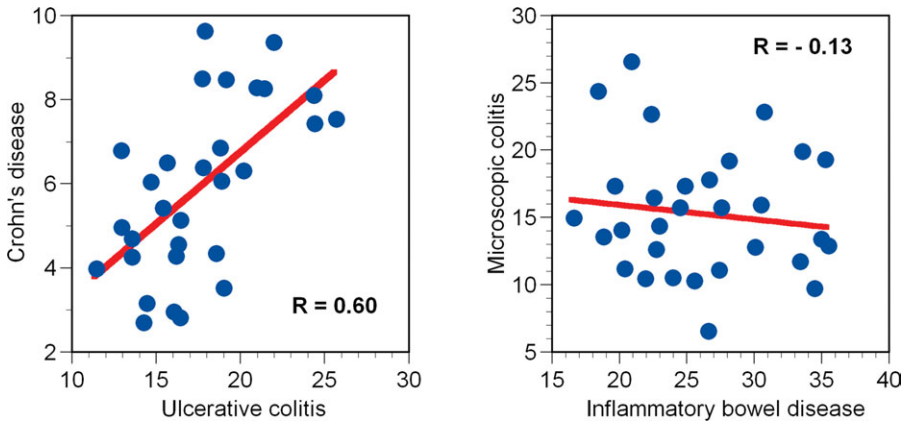

FIGURE 2. Correlations between the geographic distributions of UC and CD (left graph), and between IBD and MC (right graph). Data expressed as proportional rates per 1000 colonoscopies with biopsies; each point represents a separate U.S. state. $P = 0.0004$ for $R = 0.60$ and $P = 0.5014$ for $R = -0.13$.

distribution of IBD.[1–8] The reasons for this behavior are unknown. There is a significant correlation between amount of exposure to ultraviolet radiation and the occurrence of IBD. However, it is presently unclear whether such association reflects a causal relationship or represents a mere ecologic bias. The epidemiology of IBD is characterized by many striking features, such as large temporal, ethnic, occupational, and socioeconomic variations.[1–3] Like its other epidemiologic features, the geographic distribution strongly suggests that environmental factors must play a role in the etiology of IBD. The similarity in the geography of UC and CD also suggests that the two diseases must share one or several identical risk factors. The dissimilar geographic distribution of MC alludes to a set of environmental risk factors that are different from those of UC or CD. The dissimilar age and gender distributions also point in the same direction.

In conclusion, the present analysis of a large pathology database confirms a similar geographic distribution of UC and CD across the U.S., as previously observed with respect to other morbidity parameters. UC and CD both appear to be generally more common in northern than southern U.S. states. MC does not share a similar geographic distribution with UC or CD. This difference in epidemiologic behavior points at a dissimilar set of risk factors that shape the occurrence of MC as opposed to UC or CD.

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