A Population-based Ecologic Study of Inflammatory Bowel Disease: Searching for Etiologic Clues

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The authors’ objective in this study was to determine geographic variations in the incidence of inflammatory bowel disease (IBD), specifically Crohn’s disease and ulcerative colitis, in the Canadian province of Manitoba and its association with the sociodemographic, geographic, and disease-related characteristics of the study population. Using the University of Manitoba IBD Epidemiology Database, the authors applied spatial and ecologic techniques to visualize, explore, and model the incidence of Crohn’s disease and ulcerative colitis for the period 1990–2001. The study demonstrated marked, statistically significant geographic variability in rates of both Crohn’s disease and ulcerative colitis associated with the characteristics of the study population. Incidences of Crohn’s disease and ulcerative colitis were observed to be highest among non-Aboriginal persons, persons of high socioeconomic status, persons with the lowest rates of enteric infection, and persons with the highest rates of multiple sclerosis. The observation of an inverse association between IBD incidence and rates of reportable enteric infection at the population level is consistent with the “hygiene hypothesis,” which suggests that early exposure to enteric agents affords protection against eventual development of IBD. The positive association between IBD incidence rates and multiple sclerosis suggests that these two chronic, immunologically mediated diseases may have a common environmental etiology. This study underscores the importance of environment in IBD causation.

colitis, ulcerative; Crohn’s disease; inflammatory bowel disease; multiple sclerosis

Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease; IRR, incidence rate ratio.

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While the causes of inflammatory bowel disease (IBD) are unknown, there is evidence that the condition is immunologically mediated and that genetic factors may play an important role in its etiology. Significant temporal and geographic variation in IBD incidence suggests that extrinsic environmental factors acting at the population level may be involved in its pathogenesis. Since the mid-1900s, the incidence of IBD has been observed to be rapidly increasing in Northern European and North American populations (1, 2). In addition, significant geographic variations in IBD incidence have been observed in the United States, Norway, and Canada.

Older studies have suggested that IBD occurs more frequently in populations of high socioeconomic status (3, 4). Recently, in Manitoba, Canada, using different
population-based approaches, Blanchard et al. (5) found IBD to be associated with a slightly higher socioeconomic status (5), and using other analysis strategies, Bernstein et al. (6) found no difference in socioeconomic status compared with controls. As the prevalence of IBD increases, it will be important to reassess its association with socioeconomic status in the context of other possibly related variables. Previously, IBD has been associated with Jewish ethnicity and has been observed less frequently in minority populations and in populations exposed to high levels of enteric infection in early childhood (1, 5, 7). It is important to try to better understand how variations in population-level characteristics across time and space may be affecting the trajectory of IBD.

In this report, we build upon recent work undertaken to document and model rates of IBD in the Canadian province of Manitoba. Employing updated data and more advanced geographic methods, we used the University of Manitoba IBD Epidemiology Database to refine initial descriptions of population-level variations in IBD in Manitoba and the sociodemographic, ethnic, and environmental factors associated with these variations. Additionally, we examined whether IBD incidence covaries at the population level with the incidence of multiple sclerosis, a chronic, immunologically mediated disease that shares temporal phenotypic and immunopathogenetic similarities with IBD.

MATERIALS AND METHODS

Study setting

The study was conducted in the central Canadian province of Manitoba. Manitoba has a population of 1.1 million people, and more than 50 percent (n = 645,000) reside in the City of Winnipeg, the provincial capital (8). The majority of Manitobans are of European descent, whereas 10 percent of the population is self-identified as having Aboriginal ancestry. Manitoba has a universal health insurance plan, and all residents of the province are eligible to receive health-care services with no payment required at the time of service.

Data sources

The IBD data used for this study were obtained from the University of Manitoba IBD Epidemiology Database, which has been described in detail previously (9). For the purposes of this study, only incident and prevalent cases of IBD for the years 1990–2001 inclusive were used.

The ecologic measure of socioeconomic status used in the study was created by combining small-area estimates from the 2001 Census Canada micro-data files (8) for average family income, unemployment rate, and percentage of the adult population with some postsecondary education. The resulting composite index, known as the Socio-Economic Status Index, was generated using the SIG-EPI program (10), version 1.030, with standardized z scores and equal weights attributed to each variable. Three ecologic measures of ethnicity—the percentage of the population reporting Jewish ethnicity, the percentage of the population reporting Aboriginal ancestry, and the percentage of the population reporting “visible minority” status—were also obtained from the 2001 Census Canada micro-data files (“visible minorities” are defined as persons, other than Aboriginal peoples, who are non-Caucasian in race or non-White in color). Small-area estimates of the age-standardized enteric infection incidence rate (the combined incidence of all cases of reportable enteric disease, the most frequent being campylobacteriosis, salmonellosis, shigellosis, and giardiasis) from 1996–2001 were obtained from the Public Health Branch of Manitoba Health, and small-area estimates of multiple sclerosis incidence rates for 1989–1998 were obtained from a multiple sclerosis surveillance database recently developed at the Public Health Branch of Manitoba Health (11).

The “urban residence” designation was assigned to persons living in the City of Winnipeg, the only urban center in Manitoba with a population greater than 50,000 (8). The “on-reserve” designation was assigned to persons living in one of the 61 First Nations reserve communities scattered throughout rural Manitoba.

Assessment of time trends

For assessment of temporal trends in IBD, age-standardized annual incidence and prevalence rates were calculated for the years 1990–2001. Annual incidence rates were calculated using the midyear population at risk based on the Manitoba population registry. Annual prevalence rates were calculated on June 15 of each year using the midyear population at risk. Directly age-adjusted rates were calculated using the 1996 Manitoba population as the standard.

Spatial methods

Records in the University of Manitoba IBD Epidemiology Database were geocoded to neighborhoods in the City of Winnipeg (n = 230) using postal codes and to health municipalities in rural areas of Manitoba (n = 268) using the Manitoba Health municipal code recorded in the health record. The resulting set of 498 geographic areas had an average population size of 2,000. Spatial analysis of the data was undertaken in three steps according to the three-component framework proposed by Gatrell and Bailey (12).

In the first step, data visualization, directly age-standardized Crohn’s disease and ulcerative colitis incidence rates for 1990–2001 combined were estimated for each of 498 geographic areas. To control for unstable rate estimates resulting from small case counts, stable rate estimates were generated by means of an adaptive mean nearest-neighbor smoothing algorithm, using a program written in Epi Info, version 6.04d (13). This program uses a spatial weights table calibrated to the population size of each geographic area and its first-, second-, and third-order neighbors. Data for geographic areas with a population under 10,000 were smoothed by adaptively borrowing both numerator and denominator data from neighboring geographic areas to the degree required to generate a denominator of approximately constant size (10,000 persons). Directly standardized rates using the 1996 general Manitoba population at risk as the standard were calculated using the borrowed data. Thematic

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maps of standardized rates were produced for both Crohn’s disease and ulcerative colitis.

In the second step, data exploration, the spatial scan statistic was used to confirm that disease patterns identified at the data visualization stage were not due to random spatial variation. This statistic, which identifies high- and low-rate cluster areas through the aggregation of contiguous geographic regions, was calculated using SaTScan, version 2.1 (14). The software was set to find age-adjusted clusters with a maximum size of 50 percent of the study population, and detected clusters were tested for significance using 999 Monte Carlo random simulations. The program assumes a Poisson distribution and calculates indirectly standardized rates (expressed as the relative risk, which is the observed rate divided by the expected rate) for each identified geographic cluster. Only clusters significant at the \[ p < 0.05 \] level were retained for mapping. The specifics of the spatial scan statistic have been described elsewhere (15).

In the third step, data modeling, the composite measure of socioeconomic status (Socio-Economic Status Index) and the ethnicity- and disease-related characteristics (enteric infections, multiple sclerosis) associated with each of the 498 geographic study areas were classified into tertiles. These were assigned to the individual IBD records in the database. Using the Poisson regression functionality in NCSS 2001 (16), incidence rate ratios adjusted for age and gender were then calculated for each predictor variable. Ninety-five percent confidence intervals were calculated and corrected for model overdispersion using the phi multiplier function in NCSS.

**RESULTS**

**Temporal trends**

The age-adjusted incidence of Crohn’s disease remained relatively constant between 1990 and 2001, decreasing slightly from 15.24 cases/100,000 population in 1990 to 13.65 cases/100,000 population in 2001 (figure 1, top). The average incidence rate during the study period was 14.8 cases/100,000 population. In 1990, there were 176 incident cases of Crohn’s disease, a number which decreased to 157 by 2001. The age-adjusted prevalence of Crohn’s disease increased significantly during the study period, from 164.6 cases/100,000 population in 1990 to 269.7 cases/100,000 population in 2001 (figure 1, top). The average cumulative prevalence rate during the study period was 222.2 cases/100,000 population. In 1990, there were 1,848
prevalent cases of Crohn’s disease; the number had increased to 3,140 by 2001.

The age-adjusted incidence of ulcerative colitis decreased between 1990 and 2001, from 16.19 cases/100,000 population in 1990 to 10.52 cases/100,000 population in 2001 (figure 1, bottom). The average incidence rate during the study period was 14.6 cases/100,000 population. In 1990, there were 181 incident cases of ulcerative colitis, a number which decreased to 123 by 2001. The age-adjusted prevalence of ulcerative colitis increased significantly during the study period, from 143.3 cases/100,000 population in 1990 to 240.9 cases/100,000 population in 2001 (figure 1, bottom). The average cumulative prevalence rate during the study period was 197.9 cases/100,000 population. In 1990, there were 1,581 prevalent cases of ulcerative colitis; the number had increased to 2,846 by 2001.

Data visualization

The thematic maps of Crohn’s disease and ulcerative colitis incidence (figure 2) show that there is marked geographic variability in the rates of both diseases across the province of Manitoba. Regionally, Crohn’s disease incidence rates range from <7.6 cases/100,000 population in the northern regions of the province and in the central core of the City of Winnipeg to as high as 28.07 cases/100,000 population in the outer suburbs of Winnipeg and in the southwestern corner of the province. Regional ulcerative colitis incidence shows similar patterns, with rates ranging from <9.9 cases/100,000 population in the north of the province and in the Winnipeg core to as high as 29.47 cases/100,000 population in the southwestern suburbs of Winnipeg and southwestern Manitoba.

Data exploration

The spatial scan statistic identified statistically significant high- and low-rate clusters of Crohn’s disease and ulcerative colitis incidence in most of the same geographic areas as those identified as high- and low-risk areas on the thematic maps (figure 3). High-rate clusters of both Crohn’s disease and ulcerative colitis incidence with relative risks greater than 1 were identified in Winnipeg suburbs and southwestern Manitoba (relative risks ranged from 1.3 to 2.9); low-rate clusters of Crohn’s disease and ulcerative colitis incidence with relative risks less than 1 were observed in the central core of Winnipeg and in southern Manitoba (relative risks ranged from 0.37 to 0.54). A low-rate cluster in northern Manitoba was identified only for Crohn’s disease (relative risk = 0.645). This confirms that there is nonrandom clustering of Crohn’s disease and ulcerative colitis events across the province and suggests that the marked spatial patterns in incidence observed in the thematic maps are unlikely to have occurred by chance alone.

Data modeling

Table 1 shows that for both Crohn’s disease and ulcerative colitis, age- and gender-adjusted incidence rates are strongly graded by the individual, geographic, socioeconomic, and disease-related variables used in this study. Compared with the lowest reference quantile, the incidence of Crohn’s disease was observed to be highest in females (incidence rate ratio (IRR) = 1.37, 95 percent confidence interval (CI): 1.24, 1.50) and in the age group 20–29 years (IRR = 3.78, 95 percent CI: 3.27, 4.37). After adjustment for age and sex, Crohn’s disease incidence was also observed to be highest in urban areas (IRR = 1.29, 95 percent CI: 1.17, 1.41), off-reserve locations (IRR = 11.07, 95 percent CI: 4.81, 25.45), populations with the highest level of socioeconomic status (IRR = 1.77, 95 percent CI: 1.55, 2.02), the lowest percentage of the population reporting an Aboriginal background (IRR = 5.47, 95 percent CI: 3.37, 8.87), the highest percentage of the population reporting Jewish ethnicity (IRR = 1.52, 95 percent CI: 1.22, 1.89), persons with the lowest rates of enteric infection (IRR = 1.52, 95 percent CI: 1.31, 1.78), and persons with the highest rates of multiple sclerosis (IRR = 2.90, 95 percent CI: 2.19, 3.85). The relation of Crohn’s disease incidence to visible minority status was ambiguous, with the highest rate being observed in the middle tertile (IRR = 1.26, 95 percent CI: 1.08, 1.46). The relations between ulcerative colitis incidence and predictor variables were similar in direction to those observed with Crohn’s disease and were all statistically significant at the p < 0.05 level. The relation between ulcerative colitis and predictor variables tended to be weaker, however, as evidenced by smaller incidence rate ratios.

DISCUSSION

In this paper, we have described the temporal and spatial variation in Crohn’s disease and ulcerative colitis in Manitoba, Canada, for 1990–2001. Despite a constant or slightly decreasing incidence rate, the prevalences of both Crohn’s disease and ulcerative colitis in Manitoba are continuing to increase, since new cases continue to arise, particularly among young adults.

Thematic maps have shown a pronounced geographic concentration of both Crohn’s disease and ulcerative colitis incidence in the outer suburbs of Winnipeg and in southwestern Manitoba. The spatial scan statistic results suggest that these observed spatial patterns are real and are unlikely to have occurred by chance alone. The existence of true population-level variability in Crohn’s disease and ulcerative colitis incidence is further confirmed by the observation of a strong and significant grading of both Crohn’s disease and ulcerative colitis incidence rates by a number of geographic, individual, sociodemographic, ethnic, and disease-related predictor variables. We also found that there appears to be a high degree of spatial covariation between Crohn’s disease and ulcerative colitis. This covariation is not surprising, given that when IBD (either Crohn’s disease or ulcerative colitis) occurs in families, first-degree relatives of the proband with IBD are increasingly likely to contract either Crohn’s disease or ulcerative colitis (17).

We found a positive association of both Crohn’s disease and ulcerative colitis with higher socioeconomic status, paralleling our findings in a previous ecologic study (5). This observation is consistent with the “hygiene hypothesis.”
which suggests that persons with higher living standards may be protected from childhood infections because of cleaner environments and smaller households but are more susceptible to chronic intestinal inflammation in adulthood as a result of responding to infectious agents later in life (18, 19).

FIGURE 2. Incidence (number of cases per 100,000 population) of Crohn’s disease (top) and ulcerative colitis (bottom) in the province of Manitoba and the City of Winnipeg, Manitoba, Canada, 1990–2001. Results were age-standardized to the 1996 Manitoba population.
The hygiene hypothesis is further supported by the observation in this study of an inverse relation between IBD and rates of reportable enteric infection at the ecologic level. This observation conflicts with other studies, which have shown at the individual level a higher frequency of gastroenteritis or diarrheal illness during infancy or perinatal infections among future IBD patients (20, 21). Recall bias may be a limitation of these studies (20). However, these studies raise the possibility that there may be important differences as to the timing of infection in childhood when

FIGURE 3. Incidence analysis of Crohn’s disease (top) and ulcerative colitis (bottom) in the province of Manitoba and the City of Winnipeg carried out using the spatial scan statistic, Manitoba, Canada, 1990–2001. The maximum cluster was set at 50% of the study population.
infections are contracted. Infections acquired during the immediate perinatal period or early infancy may establish aberrant immune responses to microbes encountered at a later time, while early- to mid-childhood infections may promote tolerance to like organisms. The nature of our study did not allow assessment of the relation between age of enteric infection and development of IBD, but this could be important prospective, population-based research to pursue.

A First Nations community in Manitoba has been found to be ubiquitously infected with Helicobacter pylori, even at very young ages (22, 23). H. pylori infection has been associated with poorer domestic hygiene. The Manitoba Aboriginal population, even when living in the major urban area of the province, retains low rates of IBD. It is possible that the low rates of IBD observed in the core of Winnipeg may be the result of the high concentration of Aboriginal people living in that area who migrated there from remote reserve communities, bringing with them decreased susceptibility to IBD. For the Aboriginal population, there may be a genetic inability to mount an aberrant immune response to the microbe(s) that may cause IBD. Alternatively, earlier infections or contact with microbes through less-hygienic living conditions might promote tolerance to offending microbes later in life.

The most novel finding of interest is the significant association between areas with a high incidence of IBD and areas with a high incidence of multiple sclerosis. We have recently found that rates of multiple sclerosis are significantly higher among subjects with ulcerative colitis than among controls (24). Multiple sclerosis, like IBD, is thought to possibly be a complex T-cell-mediated disorder (25). Perhaps multiple sclerosis and IBD share similar etiologies, with persons genetically programmed to respond with either gut inflammation or neural inflammation. Multiple sclerosis,
like IBD, is associated with a high rate of affected first-degree relatives (26). Regions of overlap upon chromosomal analysis of susceptibility loci have been found for a number of autoimmune diseases, including multiple sclerosis and Crohn’s disease (27). This nonrandom clustering supports the notion that susceptibility to clinically distinct autoimmune diseases may be influenced by a common set of genes (28). Much as the NOD-2 gene, which encodes for a protein in gut antigen-presenting cells that triggers a cellular response to bacteria, is associated with Crohn’s disease (29, 30), perhaps genetic mutations in multiple sclerosis will be proven to be associated with myelin antigen-presenting cells, which might be proven to respond to the same microbes that trigger Crohn’s disease.

Previous epidemiologic reviews of IBD have suggested a gradient reflecting higher rates in northern climates than in southern ones (31–34), although the emergence of higher incidence rates in Southern Europe has led to questioning of this gradient (35). The high Manitoba incidence rates, which are the highest incidence rates yet reported for Crohn’s disease, may fit with a northern predilection for this disease. Recently, it was proposed that refrigeration and proliferation of psychrotrophic bacteria might be responsible for the upswing in Crohn’s disease in developed nations during the latter half of the 20th century (36). Perhaps these high rates, well spread out across Manitoba, suggest that organisms that survive cold well should be studied further.

This study had a number of methodological limitations that must be kept in mind when interpreting its results. First, the incidence rates were generated from data derived from administrative databases. However, a previous study evaluated the accuracy of this approach and found high specificity in comparison with detailed chart review (9). Secondly, we used an ecologic analysis. Indicators of socioeconomic status, ethnicity, and disease exposure were measured for one time period at the geographic level, since data on these factors were not available longitudinally in individual health records. The ecologic design has been considered weak for applying characteristics of a geographic area to individuals living within that area (37). However, recent work by Rose (38), Krieger et al. (39, 40), and Mustard et al. (41) has highlighted the important and independent effect that population-level factors have on the health of individuals. In our study, the ecologic predictor estimates that were applied to individual cases of Crohn’s disease were generated from a set of spatial units with an average population size of only 2,000 persons, minimizing the possibility of significant heterogeneity within those geographic areas.

In conclusion, this study has illustrated the power of having accurate population-based information on the epidemiology of IBD in Manitoba. Through the application of spatial and ecologic methods, we have demonstrated substantial clustering and small-area variations in the incidence of IBD and have shown that these variations are associated with the socioeconomic, ethnic, geographic, and disease-related characteristics of the study population. The results of this study provide strong evidence that the causes of IBD are environmental in nature and suggest that further work in modeling the relation of IBD to environmental determinants is warranted.

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REFERENCES


