IBD epidemiology: Ongoing issues and new ideas. The Canadian perspective

ABR THOMSON, MD, PhD, FRCPC, FACP, FRS, FACG

ABR THOMSON. Inflammatory bowel disease epidemiology: Ongoing issues and new ideas. The Canadian perspective. Can J Gastroenterol 1993;7(2):142-148. The prevalence of inflammatory bowel disease (IBD) in Canada is increasing, especially for patients with Crohn's disease and for young women living in urban areas. The number of IBD patients varies widely across Canada, especially for Crohn's disease. Epidemiological studies have suggested that there may be an environmental, as well as a familial, factor in the pathogenesis of IBD, but it is not clear where the next breakthrough will occur. The cost to the patient is high, and the cost to society is alarming and increasing. Thankfully, medical and surgical therapy is improving, but when do we break the code, where do we get that lucky break, that long-awaited breakthrough?

Key Words: Canadian perspective, Epidemiology, Inflammatory bowel disease

Questions épidémiologiques et diagnostiques dans la maladie intestinale inflammatoire: perspective canadienne

RÉSUMÉ: La prévalence de la maladie intestinale inflammatoire augmente au Canada, particulièrement chez les jeunes femmes des régions urbaines. Le nombre de malades atteints de maladie intestinale inflammatoire varie considérablement au Canada, particulièrement pour ce qui est de la maladie de Crohn. Des études épidémiologiques ont suggéré le rôle possible de facteurs environnementaux et familiaux dans la pathogénèse de la maladie intestinale inflammatoire, mais on ignore dans quel domaine s'accomplira la prochaine percée. Le coût est très élevé pour le patient, et ne cesse de croître pour la société, atteignant des taux alarmants. Heureusement, le traitement médical et chirurgical s'améliore, mais la clef du mystère nous échappe encore.

CHRONIC IDIOPATHIC ULCERATIVE colitis and Crohn's disease are serious and perplexing chronic intestinal disorders. In the past 10 years much work has been done to identify new therapeutic modalities, surgical techniques have been advanced, the importance and role of nutritional therapy has been emphasized, and immunological and microbiological work has been undertaken in an attempt to determine the etiology of inflammatory bowel disease (IBD). Why then does there continue to be interest in the epidemiology of IBD (1)? Such work helps one to determine the size of the clinical problem and the potential impact on community health care delivery, the hospital-based impact, the training required for physicians and other health professionals, and the development of a rational funding base for continued research efforts. Epidemiological studies have also been used in an effort to determine clues of the possible etiology and cure of IBD. Considered possible etiological factors include contagion, childhood factors, smoking, medications, diet, genetic aspects and factors associated with relapses. Time-space clustering studies do not support the concept that there is an infectious agent responsible for the development of IBD (2,3) but, of course, careful microbiological work continues to attempt to identify a possible contagion.

POSSIBLE PATHOGENESIS

Exogenous factors in Crohn's disease have been critically reviewed (4). Three of six studies have suggested that persons with Crohn's disease were breastfed for shorter periods than usual, if at all (5-10). Increased consumption of refined carbohydrates (5,11-14),
cigarette smoking (14-18) and the use of oral contraceptive agents (OCA) (17-19) may be associated with IBD occurrence, although the association between OCA use and ulcerative colitis has been challenged (20-22). Methodological problems were inherent in some studies looking at the question of sugar consumption in patients with Crohn's disease. When these potential problems were addressed, one carefully conducted study found an insignificant, while another a significant, increase in sugar use (23,24). While a number of reports have suggested an association between the use of OCA and IBD, this has not been confirmed for Crohn's disease (21) or ulcerative colitis (20,22).

Cigarette smoking is associated with an increased incidence of disease by factors ranging from 1.8 (14) to 4.8 (25). Smokers have a higher incidence of Crohn's disease in a dose-dependent fashion (26), and smoking is associated with an increased risk of recurrence (27), including after surgery (28). Curiously, in 18 monozygotic twins who had at least one sibling with Crohn's disease, smoking was not found to be associated with concordance of disease (29). The ulcerative colitis/non-smoking and the Crohn's disease/smoking association has been examined by meta-analysis and against causality criterion for chronic diseases (30). In northern Alberta, smokers more likely have Crohn's disease than ulcerative colitis (22,31). These environmental factors, however, seem to play only mediating roles rather than being directly involved in the etiology of IBD.

A variety of medications have been examined for their possible association with IBD, including analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), OCA and ethanol. The development of IBD is not associated with ethanol use (31). NSAIDs may produce inflammatory lesions of the small intestine which may be distinctive or may mimic IBD (32-34). Patients with known IBD may relapse during treatment with NSAIDs (35-37).

The importance of nutritional assessment and dietary correction of deficiencies is well recognized in IBD, and there is a growing use of diet therapy (38,39) and elemental diets (40) in IBD therapy. While there may be multiple nutrient deficiencies in patients with IBD (41-43), there does not appear to be a deficiency in the intake of fibre or sugar, and there does not appear to be any confirmed abnormal intake of toothpaste (44,45) or corn flake cereal (46).

There is a general suspicion that genetic factors may be involved in the pathogenesis of IBD. It is well-recognized that approximately one patient in six with IBD will have an affected family member, and this association tends to be higher in the daughters and sisters of index female patients (47). Spousal IBD is rare (48), including a Canadian example (49). There is a higher risk of IBD if both parents had already developed IBD at the child's conception (48). Twin studies (29) in monozygotic and dizygotic twins have shown disease concordance, with a higher proband concordance rate among monozygotic twins with Crohn's disease (58.3%) than in those with ulcerative colitis (6.3%).

Certain human lymphocyte antigen alleles may be more common in patients with IBD, such as A2 in Crohn's disease and Bw35 in ulcerative colitis. One colonic glycoprotein (HCM species IV) is reduced in patients with ulcerative colitis, independent of the inflammatory activity; this reduction also occurs in unaffected monozygotic twins (50). The composition of mucin in Crohn's disease patients and their unaffected twins was not significantly different from controls.

The initial suggestion of an increase in intestinal permeability in relatives of patients with IBD (51) may not be for all probes or for all studies of intestinal permeability (52-54).

WHO ARE AFFECTED?

What is the size of the problem of IBD? Who are the patients who are at risk of developing Crohn's disease and ulcerative colitis? The usual epidemiological considerations are of incidence and time trends, age and gender of the patient, urban versus rural distribution, assessment of geographic patterns, educational attainment and ethnic variation. In such studies there is the problem of case identification, with the possibility of overestimating IBD patients (eg, including persons with irritable bowel syndrome or acute colitis). Furthermore, there is the possibility of underestimating the incidence of IBD because of the (unfortunately) frequent long intervals between the onset of symptoms and clinical diagnosis.

Factors predicting relapse: What are some of the factors which predict a relapse of IBD? Recurrence is frequent after surgery for Crohn's disease (55) or following a recent upper respiratory tract infection in patients with previously diagnosed ulcerative colitis (36). In patients with ulcerative colitis, a recent diarrhea episode, antibiotic ingestion or stressful life events do not appear to predict a recurrence. Relapse does show a seasonal pattern: higher rates of recurrence from August to January than from January to July (56) are noted. Recent ingestion of analgesics such as NSAIDs or acetylsalicylic acid may predict a recurrence (35,37). For most patients, however, it is unknown why they have a symptomatic recurrence at any given point. In fact, sometimes the recurrent intestinal symptoms in a patient with known IBD may be not so much from IBD, but rather from a superimposed irritable bowel syndrome (57).

World trends in demography of IBD: There are a variety of methods which have been used to identify patients with IBD, including mortality and hospital admission rates, and outpatient visits. From a composite of the world literature, the total incidence of ulcerative proctitis, ulcerative colitis and Crohn's disease is six to 20 per 105 population, with a range of prevalences reported between 90 and 300 per 105 population (58). The incidence and prevalence of ulcerative colitis appears to be stable, whereas that of Crohn's disease is increasing. These differences are not due just to improved diagnostic methods, or methods used to better distinguish between Crohn's disease and ulcerative colitis. The increased incidence of ulcerative colitis between 1965 and 1980.
(59) was due to more patients being diagnosed with ulcerative proctitis, rather than extensive ulcerative colitis (Figure 1). The number of ulcerative colitis patients living in an urban or a rural setting remained stable, whereas there was an increase in the number of patients with Crohn's disease (which always is higher in an urban than in a rural setting), with the incidence peaking in 1980 and then declining (Figure 2)(59).

Other workers (60) have suggested that the incidence of Crohn's disease is not decreasing in Sweden. From 1963
The incidence of Crohn’s disease is higher than the incidence for ulcerative colitis in both males and females (63). In northern Alberta, the incidence of both Crohn’s disease and ulcerative colitis increased from the mid-1960s until 1981 (Figure 3)(22). The prevalence of ulcerative colitis was highest between the years of 20 and 60, but there was no difference between males and females nor between urban and rural dwellers (22). In contrast, the prevalence of Crohn’s disease is highest among young urban females, intermediate and equal among urban males and rural females, and lowest in rural males (Figure 4). The peak frequency of Crohn’s disease in the eastern townships of Quebec also peaks at about age 30 (64), but the prevalence appears to be higher in southern and northern Alberta than in Quebec.

Hospital discharge rates: Sonnenberg (65) demonstrated that hospital discharges for ulcerative colitis in England and Wales have remained stable between 1961 and 1986, whereas the rates have increased for both males and females with Crohn’s disease (Figure 5). Between 1970 and 1987 in the United States of America, the rates of hospital discharges of patients with Crohn’s disease increased in both males and females. Discharge rates for patients with ulcerative colitis remained unchanged in males, but showed a smooth rate of decline in females. The age-specific discharge rates for ulcerative colitis varied little between 1971 and 1987 in patients aged 20 and over, whereas for males and females with Crohn’s disease, the age-specific discharge rates increased markedly between 1971 and 1986, and were much higher in persons aged 20 to 24 and 25 to 34 than at other ages.

Discharge rates for males and females with ulcerative colitis were reasonably stable from age 20 to over 75 years from 1971 to 1986. (Reproduced with permission from Riley R. Health Reports 1990;2:343)
decreased by 17% from 1971-77, and then increased by 41% from 1977-86. For females, the rates decreased by 18% from 1971-76, then remained steady from 1976-86. The male and female ulcerative colitis discharge rates were similar over the study period, but were much higher for Crohn's disease than for ulcerative colitis, and for females than for males (Figure 6). The age-specific discharge rates for males and females with ulcerative colitis did not vary greatly for the age groups 20 to 75 and over, and did not change much between 1971 and 1986 (Figure 7). In contrast, age-specific discharge rates were highest for Crohn's disease in the age groups 20 to 24 and 25 to 34 (for males and females); these rates have increased progressively from 1971-86 (Figure 8) Sonnenberg and co-workers (67) noted geographic variations in the morbidity rates of IBD, with lowest values in Minnesota and highest in Massachusetts with a trend towards higher standardized morbidity ratios in the northern compared with the southern states but with no obvious difference between the western versus the eastern states (Figure 9). Discharge rates for females with ulcerative colitis were similar across Canada from 1971-86 (Figure 10). In sharp contrast, for females with Crohn's disease the discharge rate increased markedly over this period and were much higher in Alberta, Nova Scotia, Newfoundland, Saskatchewan and British Columbia than Ontario or Quebec (Figure 11). The reasons for these geographic variations are unknown, but unlikely are related to financial considerations because of Canada's universal access health care system.

**Mortality rates:** The results of these community-based surveys may be substantiated by an examination of mortality rates and hospital discharge rates. Mendeloff and Dunn (68) reported that the combined mortality rate from Crohn's disease and ulcerative colitis
was independent of race, age or gender, and was approximately one per 10^5 population. The mortality rate from ulcerative colitis in northeast Scotland (69) or from Copenhagen, Denmark, (70) was no different from the general population, a finding confirmed by others (71-75). In Canada, while most of the deaths due to Crohn's disease occur in persons over the age of 45, most deaths in ulcerative colitis occur in individuals over the age of 65 (Figures 12,13). Between 1971 and 1986 there was actually a decline in the number of deaths due to Crohn's disease and ulcerative colitis in persons aged 45 to 64, but an increase was observed in those who were older.

**SUMMARY**

Epidemiological studies have suggested that there may be an environmental, as well as a familial, factor in the pathogenesis of IBD, but it is unclear where the next breakthrough will occur. We know who the patients are - and there are many of them - we know how high the hospital discharge rates are, and the mortality rates. The cost to the patient is high, and the cost to society is alarming and increasing (76). Thankfully, medical and surgical therapy is improving, but when do we break the code, where do we get that lucky break, that long-awaited breakthrough?

**REFERENCES**


