Aliment Pharmacol Ther 2002; 16: 51–60.

The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review

E. V. LOFTUS, JR*, P. SCHOENFELD† & W. J. SANDBORN*

**Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA; †Division of Gastroenterology, University of Michigan School of Medicine and VA Center for Excellence in Health Services Research, Ann Arbor, MI, USA*

Accepted for publication 28 July 2001

SUMMARY

Aim: To quantify, through systematic review, the epidemiology and natural history of Crohn's disease in North America.

Methods: The selected articles contained: (i) population-based samples of patients followed from the time of diagnosis; and (ii) objective diagnostic criteria for disease. Studies on the natural history of Crohn's disease also contained sufficient follow-up.

Data collection and analysis: For prevalence studies, data on the incidence, prevalence, gender and age at diagnosis were extracted. For natural history studies, data on the disease activity, use of medications and surgery were extracted.

Main results: The prevalence of Crohn's disease in North America ranges from 26.0 to 198.5 cases per 100 000 persons. The incidence rates range from 3.1 to 14.6 cases per 100 000 person-years. Most patients have a chronic intermittent disease course, while 13% have an unremitting disease course and 10% have a prolonged remission. Less than half require corticosteroids at any point. During any given year, approximately 10% are treated with corticosteroids and 30% are treated with 5-aminosalicylates. Up to 57% of patients require at least one surgical resection.

Conclusions: Between 400 000 and 600 000 patients in North America have Crohn's disease, and the natural history is marked by frequent exacerbations requiring treatment with corticosteroids, 5-aminosalicylate products and surgery.

INTRODUCTION

Crohn's disease is an idiopathic, chronic, inflammatory disease of the gastrointestinal tract that primarily affects the small intestine and colon. Crohn's disease is associated with significant morbidity, the need for treatment with sulfasalazine, mesalamine, corticosteroids and other immunomodulating agents, surgical resection of the intestine and a slightly increased mortality.[1] Knowledge of the natural history of Crohn's disease (e.g. the likelihood of surgical intervention or the likelihood of experiencing a flare of Crohn's disease in a given year) guides physicians when counselling Crohn's disease patients and offering advice regarding treatment options. More importantly, Crohn's disease is an idiopathic disorder, which may be caused by a combination of environmental and genetic factors. Better understanding of the epidemiology of Crohn's disease (e.g. differences in prevalence of Crohn's disease based on gender or geographical region) may identify areas for further research.

Correspondence to: Dr E. V. Loftus, Jr, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: loftus.edward@mayo.edu

Multiple studies have reported the incidence, prevalence, gender distribution and age of onset of Crohn's disease in well-defined, population-based cohorts of patients in North America and Western Europe.[2] However, these trials have reported a wide variation in the prevalence and incidence of Crohn's disease. Some of these differences between studies may be due to different study methodologies, while some differences in trial results may be due to true differences in the genetic or environmental factors present in certain populations. Multiple studies have also reported wide variations in the natural history of Crohn's disease. Many of these studies utilized referral centre populations, which may create a 'referral centre' bias (i.e. patients referred to quaternary medical centres may have the most severe disease activity levels and be more likely to undergo surgery and use multiple medications). Therefore, studies of the natural history of Crohn's disease should be performed in well-defined, population-based patient cohorts.[3–9] The use of systematic reviews may facilitate the identification of appropriately designed studies and a comprehensive evaluation of divergent results, while delineating topics that require further research.

Systematic reviews utilize comprehensive literature searches, with pre-specified inclusion criteria for the selection of studies, and duplicate extraction of data by independent investigators. These techniques minimize bias in the identification of appropriately designed studies and in the extraction of study data. This systematic review quantifies the prevalence and incidence of Crohn's disease in North America and describes the gender distribution and the age at diagnosis among Crohn's disease patients. In order to better define the natural history of Crohn's disease, this systematic review also addresses: (i) the percentage of Crohn's disease patients with inactive or quiescent, mildly active, moderately active or severely active Crohn's disease in a given year; (ii) the percentage of Crohn's disease patients experiencing a flare of active Crohn's disease in a given year; (iii) the percentage of Crohn's disease patients treated with conventional steroids in a given year; (iv) the percentage of Crohn's disease patients treated with 5-aminosalicylate products in a given year; and (v) the percentage of Crohn's disease patients treated with surgery.

METHODS

Search strategy for the identification of studies

A search of the on-line bibliographic database MEDLINE was carried out to identify potentially relevant English language articles published between 1966 and September 2000. The Medical Subject Heading (MeSH) terms 'Crohn's disease [epidemiology]' or 'inflammatory bowel disease [epidemiology]', and 'Crohn's disease' or 'inflammatory bowel disease' and 'prognosis' were used to perform keyword searches of the database. However, recently published literature is not always included in the MEDLINE database. Therefore, the on-line bibliographic database Current Contents/Science Edition was also searched for articles published between 1996 and September 2000 using the keywords 'Crohn's disease' OR 'Crohn disease' AND 'incidence' or 'prevalence'. Manual searches of the reference lists from the potentially relevant papers were performed in order to identify additional studies that may have been missed using the computer-assisted search strategy.

Study selection criteria

Laupacis *et al.*[10] defined criteria for properly designed studies of natural history and prevalence, including the use of: (a) samples of patients followed from the time of initial diagnosis (i.e. inception cohort); (b) appropriate and objective diagnostic criteria for disease; and (c) sufficiently long and complete follow-up using objective definitions of disease activity.

For studies on the prevalence and incidence of Crohn's disease in North America, study selection criteria were: (i) samples of North American patients followed from the time of initial diagnosis (i.e. inception cohort); (ii) appropriate and objective diagnostic criteria for disease; (iii) quantification of the prevalence, incidence, gender distribution and age at diagnosis; and (iv) published in full manuscript form.

For studies about the natural history of Crohn's disease, study selection criteria were: (i) population-based samples of patients followed from the time of initial diagnosis (i.e. inception cohort); (ii) appropriate and objective diagnostic criteria for disease; (iii) sufficiently long and complete follow-up using objective definitions of disease activity; (iv) quantification of disease activity and use of corticosteroids, sulfasalazine/mesalamine, other immunomodulators and

surgery; and (v) published in full manuscript form. Various criteria for the diagnosis of Crohn's disease and variable definitions of disease activity were considered to be acceptable. Representative criteria are summarized in Tables 1 and 2.

Potentially relevant articles were reviewed independently by two authors (EVL, WJS) to determine if they met the criteria specified above. Reviewers rated each article as eligible, ineligible or as having insufficient information to make a judgement about eligibility. Any disagreement among reviewers was resolved by consensus.

Data extraction and analysis

Eligible articles were reviewed in a blind fashion by two different investigators (EVL, WJS) and the results of the primary research studies were abstracted onto specially designed data extraction forms. Agreement between investigators was greater than 95%, and disagreement in data extraction was resolved by consensus. For studies on the prevalence of Crohn's disease in North America, the rates of incidence and prevalence, gender distribution and mean and median age of onset were extracted. For studies on the natural history of Crohn's disease, the disease severity or activity, use of medical therapy with sulfasalazine/mesalamine or corticosteroids and rates of surgical resection for each study were derived from life tables, survival curves or, where possible, by calculating life tables from the data provided.

Data extracted from the original research articles were converted into individual tables (incidence, prevalence or gender distribution with 95% confidence intervals). Age at diagnosis was also converted into individual tables (sample size, median, range, mean, standard deviation). Disease activity and the rates of medical therapy with sulfasalazine/mesalamine or corticosteroids and surgical resection were converted into individual tables. The tables are presented in a descriptive form. Due to the significant variability in the methods of reporting data, no attempt was made to pool the incidence or prevalence rates, gender distribution data, age at diagnosis data or data regarding the disease activity or severity, course or medical and surgical therapy.

Table 1. Criteria for the diagnosis of Crohn's disease

Olmsted County, MN, criteria (at least two of the following criteria present)[13]
History of abdominal pain, weight loss, malaise, rectal bleeding or diarrhoea
Characteristic endoscopic findings of ulceration, cobblestoning, fistula or perianal disease
Radiological features of stricture, fistula or cobblestoning
Macroscopic evidence of typical bowel wall induration, lymphadenopathy or serosal involvement at laparoscopy
Histopathology consistent with Crohn's disease

Table 2. Criteria for definitions of disease activity in Crohn's disease

Olmsted County, MN, criteria
Disease severity defined by the type of therapy and by the patient's response to therapy[8]
Most intensive therapy (in descending order of intensity)
1 Surgery
2 Immune modifier or corticosteroid
3 Sulfasalazine, 5-aminosalicylate, antibiotics or topical therapy, including topical corticosteroids
4 No medication
Patients were then categorized into one of eight disease severity states at any given point in time
1 Remission or no medication state: no medication for Crohn's disease (excluding anti-diarrhoeals)
2 Mild disease: treatment with sulfasalazine, a 5-aminosalicylate (mesalamine or olsalazine), an antibiotic (metronidazole or ciprofloxacin) or topical therapy, including topical corticosteroids
3 Severe disease, drug-responsive: treatment with oral corticosteroids or immunosuppressive medications (6-mercaptopurine, azathioprine, methotrexate or ciclosporin A) with documented improvement
4 Severe disease, drug-dependent: treatment with oral steroids or immunosuppressive therapy lasting more than 6 months, with documented improvement
5 Severe disease, drug-refractory: treatment with oral steroids or immunosuppressive therapy with no documentation of clinical improvement within 2 months for corticosteroids or within 6 months for immunosuppressive medication (patients receiving corticosteroids for more than 6 months who had evidence of continuing high activity, as defined by stool pattern, abdominal pain, fever or weight loss, were classified as drug-refractory)
6 Surgery: in-patient surgical procedures for Crohn's disease (the surgery state included the entire hospital admission and 6 weeks of post-hospitalization convalescence; minor surgical procedures performed in the out-patient setting were excluded)
7 Post-surgical remission: no medication or treatment for Crohn's disease following surgical procedure for Crohn's disease
8 Death: death from any cause

RESULTS

Characteristics of selected studies

One thousand, one hundred and thirty-eight references were reviewed. Fifteen studies of 10 cohorts satisfied the inclusion criteria for incidence cohort studies to determine the prevalence, incidence, gender distribution and age of onset of Crohn's disease in North America.[11–25] In several instances, case ascertainment was hospital-based.[15–17, 22–24] In other studies, case ascertainment was population-based.[11–14, 19, 21, 25] In two studies, case ascertainment was both hospital- and population-based.[18, 20] All potential diagnoses were confirmed by medical record review in 12 studies[11–18, 20–25] or by the use of a validated database.[19] Three studies in one population-based cohort longitudinally satisfied the inclusion criteria for incidence cohort studies to determine the natural history of Crohn's disease.[7–9]

Prevalence of Crohn's disease in North America

Studies on the prevalence of Crohn's disease in North America have produced widely disparate estimates, which may represent the effect of environmental factors or genetic factors in the development of Crohn's disease. Four North American cohort studies[14, 19–21] reported adequately on the prevalence of Crohn's disease (Table 3). The prevalence rates ranged from 26.0 to 198.5 cases per 100 000 persons. Based on an estimate of 300 million people in North America and rates from the two most recent studies, there are approximately 400 000–600 000 patients with Crohn's disease in North America.

Generally, more recent studies demonstrate higher prevalence rates. This finding, in combination with recently stable incidence rates (see below), suggests that individuals may be living longer with Crohn's disease. In Olmsted County, MN, USA, the prevalence was assessed at three points in time. The prevalence rose from 91 to 144 cases per 100 000 persons between 1983 and 1991, an increase of 58% over 8 years.[14] The two studies with the highest prevalence rates were performed in the 1990s.[14, 19] The study with the lowest prevalence rate was performed in a staff-model health maintenance organization in southern California in the 1980s.[20] This low prevalence rate may reflect either the relatively large Hispanic population in this cohort or an effect from the specific geographical region.[20]

Hispanics may have a lower prevalence of Crohn's disease than Caucasians. The study with the lowest prevalence of Crohn's disease[20] examined a population that was 31% Hispanic. In this study, the prevalence of Crohn's disease among Hispanics was one-tenth that of Caucasians (4.1 vs. 43.6 cases per 100 000 persons). The other three study populations were predominantly Caucasian.[14, 19, 21] However, this finding may also be related to environmental exposures found in northern latitudes. The three study populations with the higher prevalence rates were all located in northern latitudes.[14, 19, 21] The two studies with the highest prevalence[14, 19] were performed within 3 years of each other in locations only 400 miles apart.

Incidence of Crohn's disease in North America

Studies on the incidence of Crohn's disease in North America have also produced widely disparate estimates. Incidence rates from the 10 most recent North American cohort studies are shown in Table 4. Incidence rates ranged from 3.1 to 14.6 cases per 100 000 person-years. Based on an estimate of 300 million people in North America, approximately 9000–44 000 people are diagnosed with Crohn's disease each year.

The analysis of the study results reinforces the demographic information obtained from the prevalence

Table 3. Prevalence of Crohn's disease in North America

Study (reference)	Setting	Case ascertainment	Source population size	Prevalence date	Prevalence*
Pinchbeck *et al.*[21]	Northern Alberta	Population-based	1295000	12/31/81	44.4
Kurata *et al.*[20]	Southern California	HMO, out-patient	627000	1988	26.0
Loftus *et al.*[14]	Olmsted County, MN	Population-based	106000	1/1/91	144.1†
Bernstein *et al.*[19]	Manitoba	Population-based	1140000	12/31/94	198.5†

HMO, health maintenance organization.
*Cases per 100 000 persons (most recent prevalence data for source population shown).
†Rates known to be age- and sex-adjusted.

Table 4. Incidence of Crohn's disease in North America

Study (reference)	Setting	Case ascertainment	Source population size	Incidence date	Incidence*
Garland *et al.*[24]	15 cities, USA	Hospital	1070000	1973	4.5†
Calkins *et al.*[16]	Baltimore, MD	Hospital	2174000	1977–79	3.1†
Nunes and Ahlquist[17]	Spokane, WA	Hospital	171000	1981	8.8
Pinchbeck *et al.*[21]	Northern Alberta	Population-based	1295000	1981	10†
Hiatt and Kaufman[18]	Northern California	HMO, out-patient	156000	1980–81	7.0
		HMO, hospital	1700000	1982	8.2
Stowe *et al.*[22]	Monroe County, NY	Hospital	700000	1980–89	3.9
Kurata *et al.*[20]	Southern California	HMO, out-patient	627000	1987–88	3.6
		HMO, hospital	1994000	1988	5.4
Loftus *et al.*[14]	Olmsted County, MN	Population-based	106000	1984–93	6.9†
Bernstein *et al.*[19]	Manitoba	Population-based	1140000	1989–94	14.6
Ogunbi *et al.*[25]	Georgia	African–American children only	748000	1986–95	8.8

HMO, health maintenance organization.
*Cases per 100 000 person-years (most recent incidence data for source population shown).
†Rates known to be age- and sex-adjusted.

data. The incidence of Crohn's disease appears to be increasing, appears to be more common in northern latitudes and appears to be more common in Caucasians.[14, 17, 19, 21, 25] A series of population-based studies from Olmsted County, MN, extending from 1935 to 1993, demonstrated that the incidence of Crohn's disease rapidly increased between the late 1950s and early 1970s and then stabilized at roughly 7 cases per 100 000 person-years.[12–14] The two highest incidence rates were noted in Canadian locales. However, a 'north–south gradient' of incidence was not universally observed.[18] One of the highest incidence rates noted was among African–American children in Georgia.[25] A series of hospital-based studies from Baltimore noted the different incidence rates between Caucasians and non-Caucasians: 3.4–3.5 cases per 100 000 person-years by 1977–79 in Caucasians vs. 1.3 cases per 100 000 person-years by 1977–79 in non-Caucasian men.[15, 16]

Gender distribution and age of onset of Crohn's disease

The gender distribution of Crohn's disease was available in all 10 cohorts (Table 5), and there appeared to be a slight female predominance, with the percentage of females ranging from 48% to 66%. In seven studies, the female prevalence ranged between 50% and 60%. The female predominance was over 60% in two studies,[18, 21] both performed 20 years ago. It was under 50% in only one study, performed three decades ago.[24]

Information on the age at diagnosis of Crohn's disease was explicitly presented in only two studies.[14, 20] The mean age at diagnosis could be estimated from tables showing the age distribution in five additional

Table 5. Sex distribution of Crohn's disease in North America

Study (reference)	Years	Type and number of cases	Female (%)
Garland *et al.*[24]	1973	44 incidence	48
Nunes and Ahlquist[17]	1971, 1981	41 incidence	60
Calkins *et al.*[16]	1977–79	183 incidence	55
Pinchbeck *et al.*[21]	1981	1011 prevalence	66
Hiatt and Kaufman[18]	1980–81	11 incidence	64
Stowe *et al.*[22]	1973–86	784 incidence	54
Kurata *et al.*[20]	1987–88	169 prevalence	58
Loftus *et al.*[14]	1940–93	225 incidence	54
	1991	145 prevalence	50
Ogunbi *et al.*[25]	1986–95	34 incidence	53
Bernstein *et al.*[19]	1994	2268 prevalence	59
	1989–94	997 incidence	59

Table 6. Age of onset of Crohn's disease in North America

Study (reference)	Years	Number and type of cases	Mean age at diagnosis (years)
Nunes and Ahlquist[17]	1971, 1981	41 incidence	45*
Calkins *et al.*[16]	1977–79	180 incidence	35.6*
Pinchbeck *et al.*[21]	1981	1101 prevalence	33.9*
Hiatt and Kaufman[18]	1980–81	11 incidence	38.2*
Kurata *et al.*[20]	1987–88	169 prevalence	35.9
Loftus *et al.*[14]	1940–93	225 incidence	33.4
Bernstein *et al.*[19]	1989–94	997 incidence	37.7*

*Not explicitly stated, but estimated based on available data.

Table 7. Projected lifetime clinical course for Crohn's disease (reprinted with permission from Silverstein *et al.*[8])

	Using median age		Using mean age	
Disease state	Course (year)	%	Course (year)	%
Remission	11.10	23.9	10.36	24.3
Mild	12.68	27.3	11.73	27.5
Severe, drug-responsive	0.41	0.9	0.38	0.9
Severe, drug-dependent	1.98	4.3	1.83	4.3
Severe, drug-refractory	0.82	1.8	0.76	1.8
Surgery	0.51	1.1	0.47	1.1
Post-surgery remission	18.88	40.7	17.11	40.1
Total	46.38	100	42.64	100

cohorts.[16–19, 21] The results are summarized in Table 6. In all but one of the studies, the mean age at diagnosis was between 33 and 39 years. The median age at diagnosis (29.5 years) was available in only one study.[14]

The so-called 'bimodal' distribution of age at diagnosis of Crohn's disease typically refers to a peak in incidence in the second or third decades of life, followed by a second (usually smaller) peak later in life, typically the sixth or seventh decades. Such a distribution was noted in four studies.[18, 20, 22, 24] However, a 'unimodal' distribution, with a peak incidence in the second or third decades, followed by a gradually diminishing incidence thereafter, was also seen in four studies.[14, 16, 19, 21] In a single study, the peak incidence was seen after 50 years.[17]

Natural history of Crohn's disease

Natural history data may quantify the likelihood that a patient with Crohn's disease will be in remission or will be experiencing mild or severe disease activity at a given point in time. These data suggest that most patients with Crohn's disease are in remission during any given year. A population-based study, performed in Olmsted County, MN, described the lifetime clinical course of Crohn's disease using disease states defined by medical and surgical therapy, as outlined in Table 2, and a Markov model analysis was used to calculate the time in each disease state.[8] In this study, a representative patient spent 24% of the lifetime disease course in medical remission, 27% with mild disease, 1% with severe drug-responsive disease, 4% with severe drug-dependent disease, 2% with severe drug-refractory disease, 1% in surgery and 41% in post-surgical remission (Table 7).

On the other hand, natural history data indicate that only a small minority of Crohn's disease patients will experience *prolonged* remission. An early study from Olmsted County reported that 13% of patients had an unremitting disease course, 73% had a chronic intermittent disease course and 10% were 'cured'.[13] A subsequent study from Olmsted County reported that, over time, a decreasing proportion of patients are in a medical remission state, and an increasing proportion of patients are in a post-surgical remission state, while the proportions of patients with mild disease, drug-responsive disease, drug-dependent disease or drug-refractory disease are relatively constant (Figure 1).[8] However, based on available data, it is impossible to determine

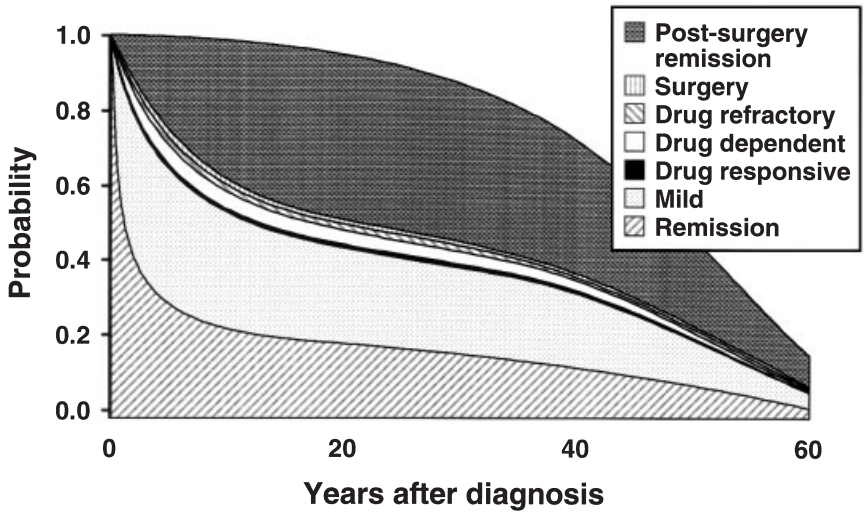

Figure 1. Proportion of Crohn's disease patients in each treatment state by year since the diagnosis of Crohn's disease (Reprinted with permission from Silverstein *et al.*[8]).

whether the age at diagnosis, gender, disease location, ethnicity or other possible prognostic factors will predict patients that are likely to have a prolonged remission.

Further natural history data estimate the use of medical therapy among patients with Crohn's disease. A population-based study from Olmsted County reported that 43% of patients with Crohn's disease received treatment with conventional corticosteroids at some point in their disease history.[9] During any given year, approximately 10% of patients in Olmsted County were treated with conventional corticosteroids or other immune modifier agents (Figure 1).[8] During any given year, approximately 30% of patients in Olmsted County were treated with 5-aminosalicylate products (Figure 1).[8]

Surgery also appears to be common in patients with Crohn's disease, based on population-based studies. An early study from Olmsted County reported that 41% of patients with Crohn's disease underwent at least one resection.[7] A subsequent study from the same area reported that 57% of patients underwent at least one operative procedure.[8]

DISCUSSION

This systematic review of the incidence and prevalence of Crohn's disease in North America identified several important pieces of demographic information. Firstly, the current prevalence of Crohn's disease in North America is 144–198 cases per 100 000 persons. Secondly, the incidence rate of Crohn's disease currently ranges between 3 and 14 new cases per 100 000 person-years. Thirdly, there is a very slight female predominance. Fourthly, the peak period for the onset of Crohn's disease is in the second and third decades of life.

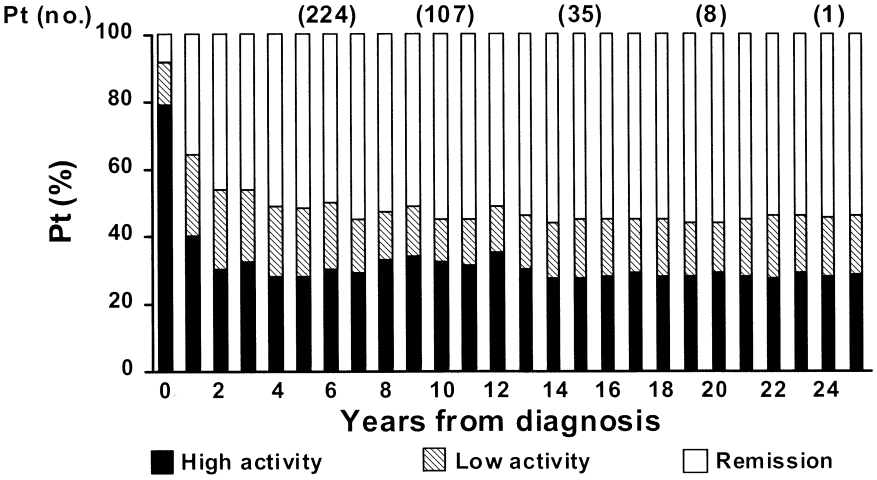

Figure 2. Disease activity distribution in the total patient group in each year from diagnosis and 25 years ahead. (From year 14 to year 25, the mean values are given, as no significant change upwards or downwards occurred.) Number of patients (Pt) in parentheses (Reprinted with permission from Munkholm *et al.*[6]).

If the incidence rates of Crohn's disease identified by this systematic review are extrapolated to the North American population as a whole, between 9000 and 44 000 new cases of Crohn's disease should be diagnosed in North America annually. If recent prevalence data (144–198 cases per 100 000 persons) are extrapolated to the entire North American population, the current prevalence of Crohn's disease may be between 400 000 and 600 000 cases. These estimates have several limitations. Because they assume a uniform prevalence both geographically and across ethnic groups, they may overestimate the prevalence. However, these figures may be an underestimate of the true prevalence, as the only longitudinal prevalence data available suggest that the prevalence of Crohn's disease is increasing, and the data available are already 6–9 years old. Regardless of the exact number, these data indicate that the burden of Crohn's disease in North America is significant.

The majority of patients with Crohn's disease are diagnosed in the second or third decade of life. There was a variation in the overall age distribution of cases, however, with half of the studies suggesting a bimodal distribution and half suggesting a unimodal distribution. The age distributions are likewise mixed in European studies. Perhaps this may be explained by misclassification or by varying diagnostic criteria; alternatively, the condition may be expressed heterogeneously under different environmental conditions.

Systematic reviews may be most helpful because they identify new areas for research. The data in this systematic review suggest that people in northern latitudes and Caucasians are more likely to develop Crohn's disease. The slight female predominance of Crohn's disease was a fairly consistent finding, but its cause and significance remain unclear. In several of these cohorts, a dramatic increase in incidence among females in the third decade of life explained much of the overall increase in incidence that occurred in the 1960s.[14, 22] Such occurrences have led to speculation about the role of female hormones in general, and oral contraceptives and hormone replacement therapy in particular, in the pathogenesis of Crohn's disease. Although cigarette smoking, a well-described risk factor for Crohn's disease, was not formally studied in these cohorts, it also became more prevalent among women in the 1960s, coincident with the rise in incidence and prevalence. Future research focused on these issues may better delineate the environmental, hormonal and genetic factors which predispose patients to Crohn's disease.

This systematic review also identified several important pieces of information about the natural history of Crohn's disease. At any given point in time following the first year of the disease, roughly 10% of Crohn's disease patients have high activity, 25% have low activity and 65% are in remission. However, a static view of disease activity is misleading, as disease activity often fluctuates. Approximately 13% of Crohn's disease patients have chronically active disease, 73% have a chronic intermittent course, while only 10% remain in remission over many years. This pattern of disease activity highlights the need for effective drug therapy, both for the control of active disease and for the maintenance of disease remission.

Approximately 43% of Crohn's disease patients required conventional corticosteroids at some point in their disease history, and roughly 10% required corticosteroids in any given year. About 30% of patients required sulfasalazine or 5-aminosalicylate products in any given year. Up to 57% of all patients required at least one surgical resection.

The above natural history data were extracted from several studies of a single population-based cohort in North America,[7–9] which may raise concern about the generalizability of these data. However, the natural history of Crohn's disease in Olmsted County is surprisingly similar to that in Copenhagen County, Denmark,[3–6] which to our knowledge is the best-characterized inception cohort of Crohn's disease in either Europe or North America. A study of disease activity performed in Copenhagen County reported that, in the first year after diagnosis, 80% of patients had high disease activity, 15% had low activity and 5% were in remission. After the first year, 30% had high activity, 15% had low activity and 55% were in remission during any given year (Figure 2).[6] The same study reported the clinical course over a continuous 5-year period (years 3–7); 25% of patients had active disease every year, 22% were in remission and 53% changed between years with remission and years with relapse (Figure 3).[6] Considering the first 7 years, 20% of patients had active disease every year, 13% had a relapse-free course and 67% fluctuated between years with relapse and years in remission. In Copenhagen County, 56% of patients with Crohn's disease received treatment with conventional corticosteroids at some point in their disease history.[5] During the first 3 years following the diagnosis of

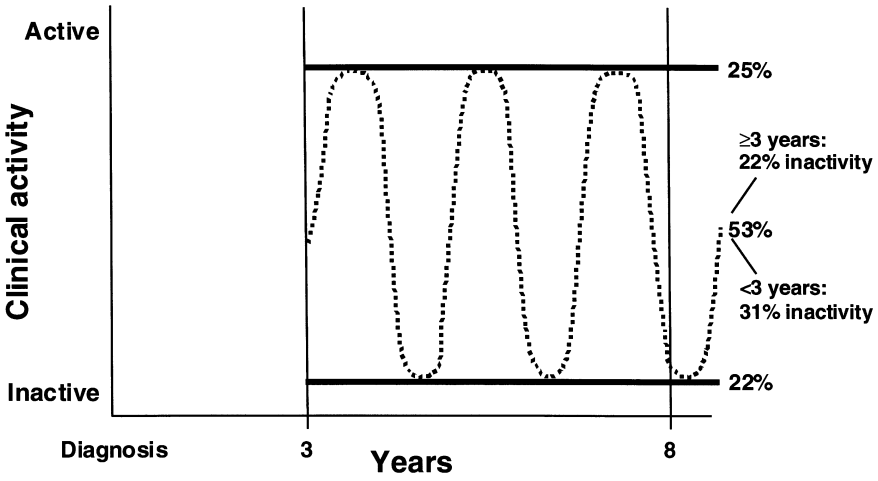

Figure 3. Graphical presentation of the prevalence figures of 5-year activity courses for 171 patients, 3–7 years after diagnosis (Reprinted with permission from Munkholm *et al.*[6]).

Crohn's disease, 58% of patients did not receive corticosteroid therapy, 19% received corticosteroids for 1 year and 22% received corticosteroids for two or more years.[6] During the first 3 years following the diagnosis of Crohn's disease, 20% of patients did not receive therapy with 5-aminosalicylate products, 16% received 5-aminosalicylate products for 1 year and 64% received 5-aminosalicylate products for two or more years.[6] An early study from Copenhagen County reported that 42% of patients with Crohn's disease had one operation within 10 years of diagnosis and an additional 13% had two or more operations within 10 years.[3] A subsequent study from Copenhagen County reported that the cumulative probability of operation 15 years after the diagnosis of Crohn's disease was 70%.[4]

The differences in the prevalence of use of medical and surgical therapy in these two cohorts may reflect differences in disease activity, but more likely reflect differences in medical practice between the two locales. The relatively high prevalence of conventional corticosteroid use highlights the burden of disease activity and again points to the need for more effective and less toxic drugs to control disease activity.

Overall, this review of the data has identified several areas that deserve attention in future research. The information about natural history is based on fairly limited data. Despite all that has been written about Crohn's disease, we found only two population-based cohorts in which medication usage, disease activity and surgical history were described in detail.[3–9] The natural history data discussed above come from Olmsted County, MN, USA and Copenhagen County, Denmark, limiting the generalizability of these data. The development of wider population-based networks of Crohn's disease patients would be ideal to develop more generalizable natural history data. The available data also do not provide enough information to determine whether age, gender, ethnicity, disease location or other possible prognostic factors may help to predict which patients are likely to be in remission for many years. Finally, future prevalence and incidence data must focus on environmental, hormonal and genetic factors which may predispose patients to Crohn's disease. All of these issues could be adequately addressed with the development of a nationwide longitudinal database of Crohn's disease patients.

ACKNOWLEDGEMENTS

This study was supported by an unrestricted grant from AstraZeneca LP.

The opinions and assertions contained herein are the sole views of the authors and should not be construed as official or as representing the views of the Department of Veteran Affairs or the US Government.

REFERENCES

1 Hanauer SB. Inflammatory bowel disease [published erratum appears in N Engl J Med 1996; 335 (2): 143]. N Engl J Med 1996; 334: 841–48.
2 Logan RF. Inflammatory bowel disease incidence: up, down or unchanged? Gut 1998; 42: 309–11.
3 Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease – based on results from a regional patient group from the county of Copenhagen. Gut 1985; 26: 146–50.

4 Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. Gastroenterology 1993; 105: 1716–23.
5 Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994; 35: 360–2.
6 Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995; 30: 699–706.
7 Agrez MV, Valente RM, Pierce W, Melton LJ III, van Heerden JA, Beart RW Jr. Surgical history of Crohn's disease in a well-defined population. Mayo Clin Proc 1982; 57: 747–52.
8 Silverstein MD, Loftus EV, Sandborn WJ, *et al.* Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology 1999; 117: 49–57.
9 Faubion WA, Loftus EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study of corticosteroid dependence. Gastroenterology 2001; 121: 255–260.
10 Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. J Am Med Assoc 1994; 272: 234–7.
11 Sedlack RE, Nobrega FT, Kurland LT, Sauer WG. Inflammatory colon disease in Rochester, Minnesota, 1935–1964. Gastroenterology 1972; 62: 935–41.
12 Sedlack RE, Whisnant J, Elveback LR, Kurland LT. Incidence of Crohn's disease in Olmsted County, Minnesota, 1935–1975. Am J Epidemiol 1980; 112: 759–63.
13 Gollop JH, Phillips SF, Melton LJ III, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943–1982. Gut 1988; 29: 49–56.
14 Loftus EV Jr, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival [published erratum appears in Gastroenterology 1999; 116 (6): 1507] [see comments]. Gastroenterology 1998; 114: 1161–68.
15 Monk M, Mendeloff AI, Siegel CI, Lilienfeld A. An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore I. Hospital incidence and prevalence 1960–1963. Gastroenterology 1967; 53: 198–210.
16 Calkins BM, Lilienfeld AM, Garland CF, Mendeloff AI. Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci 1984; 29: 913–20.
17 Nunes GC, Ahlquist RE Jr. Increasing incidence of Crohn's disease. Am J Surg 1983; 145: 578–81.
18 Hiatt RA, Kaufman L. Epidemiology of inflammatory bowel disease in a defined northern California population. West J Med 1988; 149: 541–6.
19 Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999; 149: 916–24.
20 Kurata JH, Kantor-Fish S, Frankl H, Godby P, Vadheim CM. Crohn's disease among ethnic groups in a large health maintenance organization. Gastroenterology 1992; 102: 1940–8.
21 Pinchbeck BR, Kirdeikis J, Thomson AB. Inflammatory bowel disease in northern Alberta. An epidemiologic study. J Clin Gastroenterol 1988; 10: 505–15.
22 Stowe SP, Redmond SR, Stormont JM, *et al.* An epidemiologic study of inflammatory bowel disease in Rochester, New York. Hospital incidence. Gastroenterology 1990; 98: 104–10.
23 Nordenholtz KE, Stowe SP, Stormont JM, *et al.* The cause of death in inflammatory bowel disease: a comparison of death certificates and hospital charts in Rochester, New York. Am J Gastroenterol 1995; 90: 927–32.
24 Garland CF, Lilienfeld AM, Mendeloff AI, Markowitz JA, Terrell KB, Garland FC. Incidence rates of ulcerative colitis and Crohn's disease in fifteen areas of the United States. Gastroenterology 1981; 81: 1115–24.
25 Ogunbi SO, Ransom JA, Sullivan K, Schoen BT, Gold BD. Inflammatory bowel disease in African–American children living in Georgia. J Pediatr 1998; 133: 103–7.