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Risk Factors Associated With Progression to Intestinal Complications of Crohn's Disease in a Population-Based Cohort

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Abstract

Background and Aims—We sought to assess the evolution of Crohn's disease behavior in an American population-based cohort.

Methods—The medical records of all Olmsted County, Minnesota residents who were diagnosed with Crohn's disease from 1970 to 2004 were evaluated for their initial clinical phenotype, based on the Montreal classification. The cumulative probabilities of developing structuring and/or penetrating complications were estimated using the Kaplan-Meier method. Proportional hazards regression was used to assess associations between baseline risk factors and changes in behavior.

Results—Among 306 patients, 56.2% were diagnosed between the ages of 17 and 40 years. Disease extent was ileal in 45.1%, colonic in 32.0%, and ileocolonic in 18.6%. At baseline, 81.4% had non-stricturing non-penetrating disease, 4.6% had stricturing disease, and 14.0% had penetrating disease. The cumulative risk of developing either complication was 18.6% at 90 days, 22.0% at 1 year, 33.7% at 5 years, and 50.8% at 20 years after diagnosis. Among 249 patients with non-stricturing, non-penetrating disease at baseline, 66 changed their behavior after the first 90 days from diagnosis. Relative to colonic extent, ileal, ileocolonic, and upper gastrointestinal extent were significantly

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associated with changes in behavior, whereas the association with perianal disease was barely significant.

Conclusions—In a population-based cohort study, 18.6% of patients with Crohn's disease experienced penetrating or stricturing complications within 90 days after diagnosis; 50% experienced intestinal complications 20 years after diagnosis. Factors associated with development of complications were the presence of ileal involvement and perianal disease.

Keywords

Crohn's disease; complications; stricture; fistula; abscess; natural history

INTRODUCTION

Crohn's disease is a chronic inflammatory bowel disease (IBD) with variable clinical features and disease course. The phenotype of Crohn's disease has been categorized according to age at diagnosis, location of disease and disease behavior by the Vienna classification¹. Disease behavior is based on the presence or absence of intestinal complications such as stricture, fistula, and abscess, and can be sub-divided into 'non-stricturing and non-penetrating', 'stricturing' and 'penetrating'¹. There have been many reports, albeit primarily from referral center-based cohorts, indicating a change in behavior over time (i.e., disease progression) from a non-stricturing, non-penetrating type (disease complications absent) into stricturing and/or penetrating disease (disease complications present)²⁻⁶. There have been few population-based studies documenting the evolution of Crohn's disease phenotype^{7,8}. A recent population-based study from southeastern Norway reported that 36% of the Crohn's cohort were already noted to have had an intestinal complication at diagnosis, but only an additional 17% experienced an intestinal complication over 10 years of follow-up⁷.

The ultimate goal of medical therapy in Crohn's disease beyond achieving clinical response and sustained remission would be to alter the natural history of the disease; that is, to prevent the stricturing and/or penetrating complications that lead to surgery. Despite increasing usage of azathioprine and 6-mercaptopurine in a referral center-based cohort from Paris, these medications did not appear to decrease intestinal complication or surgical resection rates over a 25-year period⁹. However, there is accumulating evidence that anti-tumor necrosis factor (anti-TNF) agents with superior mucosal healing capabilities¹⁰ may have the ability to decrease hospitalization and surgery rates^{11,12}. It will therefore be important to identify clinical features of Crohn's disease that predict a higher risk for progression to intestinal complications, so that early therapy with biologic agents might be considered as a potential strategy to prevent complications from occurring¹³.

The natural history of fistulizing Crohn's disease and steroid-treated IBD patients in a population-based cohort from Olmsted County, Minnesota have been previously described^{14,15}. However, we have not previously described the change in behavior of Crohn's disease from non-stricturing, non-penetrating into stricturing and/or penetrating types. We sought to assess the evolution of Crohn's disease behavior in this cohort applying the Montreal classification, which is a modification to the Vienna classification¹⁶, and to determine baseline risk factors which would predict either fistulizing or stricturing complications over the disease course.

METHODS

Study Setting and Patients

Olmsted County, situated in southeastern Minnesota, had a population of 124,277 inhabitants in the 2000 U.S. Census. The majority of people reside in Rochester, the urban center of an otherwise rural county. In the 2000 census, 89% of residents were non-Hispanic white, and a substantial portion was of northern European heritage. Although 25% of county residents are employed in health care services (versus 8% nationwide), and the level of education is consequently higher (30% of adults have completed college versus 21% nationwide), the residents of Olmsted County are otherwise socioeconomically similar to the U.S. white population¹⁷.

Since medical care is practically self-contained within Olmsted County and provided by Mayo Medical Center, the Olmsted Medical Center, and their affiliated clinics and hospitals, it is possible to trace all IBD patients in the common medical record linkage system known as the Rochester Epidemiology Project¹⁷. Diagnoses are generated from all hospitalizations, outpatient episodes of care, emergency room visits, and endoscopic and surgical procedures. Medical records for each patient who has not denied research authorization to review records are available for review in paper or electronic format. Thus, true population-based studies of disease, even those which do not result in hospitalization, are possible. This medical records linkage system has resulted in the publication of over 1,600 population-based studies since the mid-1960s.

In previous studies, we have identified all Olmsted County residents who were diagnosed with Crohn's disease between 1940 and 2004¹⁸⁻²². A subset of this cohort, those diagnosed with Crohn's disease between 1970 and 2004, served as the study group. The institutional review boards of Mayo Clinic and Olmsted Medical Center approved the study. Five patients who were diagnosed with Crohn's disease after ileal pouch-anal anastomosis for presumed ulcerative or indeterminate colitis were excluded from this analysis, and one patient withdrew research authorization, leaving 306 patients with complete inpatient and outpatient medical records available for chart review. This group was followed through their medical records from date of Crohn's disease diagnosis until date of death, last follow-up, or date of last medical record abstraction (approximately April 2008).

Data Abstraction

Specific information was abstracted for age of diagnosis, behavior and location of disease based on the Montreal classification (Appendix 1). Stricturing disease was defined by the occurrence of constant luminal narrowing demonstrated on radiologic, endoscopic or surgical-pathologic methods with pre-stenotic dilatation and/or obstructive signs and symptoms, without the presence of penetrating disease¹. Penetrating disease was based on the occurrence of intra-abdominal inflammatory masses, abscesses and/or fistula³. Development of perianal disease (fistula or abscess) was not considered a change in behavior, but the presence of perianal fistula or abscess was considered a modifier of disease behavior as per the Montreal classification. If stricturing and penetrating complications were discovered at the same time or within 1 year of either event, the case was classified as penetrating³. Patients who progressed from stricturing then to penetrating disease beyond the one year time-frame were recorded as events in the stricturing analysis but censored at the time of development of stricture in the penetrating analysis, to prevent counting of too many events. Location of disease was defined by the maximal extent before the first bowel resection. Upper gastrointestinal disease (proximal to ileum, classified as L4 in Vienna classification) was added as a modifier if present together with more distal disease¹⁶.

Information on baseline putative risk factors at and within 90 days of diagnosis such as location of disease, age, gender, smoking, family history, extraintestinal manifestation, perianal disease, type of medical therapy and smoking status at diagnosis (non-smoker, ex-smoker and current smoker) were documented.

Statistical Analysis

The data were summarized with percentages, medians and ranges. Upper gastrointestinal disease whether isolated involvement or with concomitant sites of bowel involvement was placed under one location category. The Kaplan-Meier method was used to estimate the cumulative probability (1 minus survival-free) of an initial complication, separately for stricturing disease, penetrating disease, and a combination of these complications. It is important to note that for time to initial development of a complication (stricturing or penetrating), one complication was not used as a censoring event for another. Among the 306 Crohn's disease patients, the overall cumulative probability of change in behavior was assessed from date of diagnosis. Among the 249 patients with non-stricturing non-penetrating disease at baseline, the cumulative probability of change in behavior was assessed starting at 90 days after diagnosis. The 90-day run-in period was imposed to account for a possible time lapse between diagnosis and completion of investigations to fully determine the location of involvement and type of behavior.

Cox proportional hazards regression models were used to assess univariate associations between risk factors (known either at diagnosis or through the first 90 days post-diagnosis) and time to initial complication (either stricturing or penetrating). A multivariate Cox model was developed using a backward elimination approach starting with 8 primary predictor variables. Results are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). The association of perianal disease with a subsequent change to stricturing or penetrating behavior was assessed using a Cox proportional hazards regression model, considering perianal disease diagnosis as a time-dependent covariate. We checked the proportional hazards assumption for specific predictor variables, and a departure from this assumption was not detected for any of the primary predictor variables, except smoking status. However, smoking status did not have a clinically important impact on overall rates of intestinal complications (data not shown).

RESULTS

Baseline Characteristics

Three hundred six Crohn's disease patients were followed for a total of 3,013 person-years, with a median follow-up duration of 8.4 years (range, 2 days – 35.9 years). One hundred fifty patients (49%) were males (Table 1). The median age at Crohn's disease diagnosis was 30.2 years (range, 8.4-91.4). Perianal disease had been identified prior to Crohn's disease diagnosis in 15 patients (4.9%), and within the first 90 days of diagnosis in an additional 36 (11.8%). Among the 15 patients with perianal disease prior to Crohn's disease diagnosis, the median interval between perianal disease and Crohn's disease was 38 months (range, 3-142). Eighteen patients with perianal involvement at baseline also had colonic extent (5.9%). Extraintestinal manifestations were identified in 46 patients (15%), including 24 patients with arthritis (7.8%), 15 patients with erythema nodosum or pyoderma gangrenosum (4.9%), 10 patients with eye involvement (3.3%) and 4 patients (1.3%) with primary sclerosing cholangitis. Ten of these patients (3.3%) had multiple extraintestinal sites of involvement.

When the Montreal classification was applied to baseline characteristics (i.e., within the first 90 days), 249 patients (81.4%) had no intestinal complications. Fourteen patients (4.6%) were noted to have an intestinal stricture within the first 90 days of diagnosis, and 43 (14.1%) had

developed a penetrating complication. Using the Vienna classification, 206 patients (67.3%) had non-penetrating and non-stricturing disease, 14 patients had stricturing (4.6%) and 86 patients (28.1%) had either intestinal or perianal penetrating complications.

Change in Maximal Extent During Follow-up

The maximal extent of disease was ileal in 130 (42.5%), colonic in 88 (28.8%), and ileocolonic in 71 (23.2%). A total of seventeen patients had documented upper gastrointestinal involvement, and all but one had disease elsewhere. Altogether, only 20 patients (6.5%) had a change in disease extent between baseline and observation of their maximal extent.

Cumulative Risk of Stricturing or Penetrating Disease

Based on the Montreal classification, the cumulative risk of developing intestinal complications was assessed two ways. Starting from day of diagnosis, and assuming that complications occurring before or at diagnosis occurred on day 0, among a total of 306 patients, 123 patients experienced a stricturing or penetrating complication, with a median survival free of complication of 19.7 years. The cumulative incidence of either stricturing or penetrating disease in the entire cohort was 11.8% (95% CI, 8.1-15.3) at day 0, 18.6% (14.1-22.9) at 90 days, 22% (17.2-26.5) at 1 year, 33.7% (28.0-38.9) at 5 years, 38.7% (32.5-44.3) at 10 years, 50.8% (42.1-58.1) at 20 years and 54.4% (44.7-62.4) at 30 years after diagnosis (Figure 1a). The cumulative probability of stricturing disease was 2.9% (95% CI, 1.0-4.8) at day 0, 4.8% (2.3-7.2) at day 90, 7.2% (4.1-10.1) at 1 year, 12.4% (8.1-16.4) at 5 years, 15.2% (10.2-20.0) at 10 years, 21.6% (13.4-29.0) at 20 years, and 21.6% (13.4-29.0) at 30 years (Figure 1b). The cumulative risk of penetrating disease was 8.8% (5.6-11.9) at day 0, 14.3% (10.2-18.1) at day 90, 15.7% (11.5-19.7) at 1 year, 24.1% (18.9-29.0) at 5 years, 27.5% (21.8-32.8) at 10 years, 37.1% (28.5-44.6) at 20 years, and 41.7% (31.2-50.5) at 30 years (Figure 1c).

Starting the observation period at 90 days after diagnosis, a total of 66 patients among 249 patients who still had B1 disease at the 90-day baseline experienced a stricturing or penetrating complication. The cumulative incidence of developing either a stricturing or penetrating complication was 4.1% (95% CI, 6.6-11.6) at 1 year, 18.5% (13.2-23.4) at 5 years, 24.7% (18.4-30.5) at 10 years, 39.5% (29.5-48.1) at 20 years and 43.9% (32.5-53.4) at 30 years (Figure 2a). The median (range) length of follow-up in the 183 patients who had not experienced a stricturing or penetrating complication was 8.6 years (3 months – 36.1 years). Twenty-five patients (10.1%) experienced a stricturing complication. At 1, 5, 10, 20, and 30 years, the cumulative risk of developing stricturing disease among those with non-stricturing, non-penetrating disease was 2.5% (95% CI, 0.5-4.4), 8.0% (4.2-11.6), 11.0% (6.2-15.5), 17.6% (9.3-25.1) and 17.6% (19.3-25.1), respectively (Figure 2b). Forty-one patients (16.5%) experienced a penetrating complication. The cumulative risk of developing penetrating disease was 1.7% (95% CI, 0-3.3) at 1 year, 11.4% (5.6-7.1) at 5 years, 15.4% (10.1-20.4) at 10 years, 26.6% (17.3-34.8) at 20 years, and 31.9% (20.2-41.9) at 30 years (Figure 2c).

In the cohort of 306 patients, a total of 123 had a change (either stricturing or penetrating) in behavior. The 6 month cumulative risk (1 minus survival free) of surgery subsequent to this change was 81.6% (95% CI, 73.2-87.4), with 99 patients undergoing surgery within 6 months of the behavior change. In the cohort of 249 patients who had B1 disease at the 90-day baseline, a total of 66 had a change (either stricturing or penetrating) in behavior. The 6 month cumulative risk of surgery subsequent to this change was 76.7% (95% CI, 63.7-85.0), with 50 patients undergoing surgery within 6 months of the behavior change.

As mentioned previously, a total of 51 patients had developed perianal complications either prior to or within 90 days after diagnosis of Crohn's disease. An additional 35 patients (11.4%)

developed perianal disease during follow-up; thus, a total of 86 patients (28.1%) had perianal disease at some point in their disease course.

Using the Vienna classification, the cumulative risk of developing either penetrating or stricturing complication among the entire cohort of 306 patients was 39.7% (95% CI, 33.9-44.9) at 1 year, 50.5% (44.4-55.9) at 5 years, 56.4% (50.0-62.0) at 10 years, 60.6% (53.2-66.8) at 20 years and 64.1% (55.5-71.1) at 30 years. Among the 206 patients with B1 disease at the 90-day baseline, the cumulative probabilities of subsequently developing either stricturing or penetrating disease were 10.4% (95% CI, 6.1-14.5) at 1 year, 26.4% (19.9-32.4) at 5 years, 35.2% (27.5-42.1) at 10 years, 41.5% (31.7-49.8) at 20 years and 46.7% (34.8-56.4) at 30 years.

Factors Associated with Stricturing or Penetrating Complications

The association of baseline factors and time to intestinal complication was assessed in the patients who had B1 disease at the 90-day baseline using univariate proportional hazards regression (Table 2). A patient diagnosed between the ages of 17 and 40 years, relative to a patient diagnosed at or younger than 16 years, had an increased though non-significant risk of complication (HR, 2.07; 95% CI, 0.85 - 5.22). The disease extent noted at baseline was significantly associated with the occurrence of intestinal complications ($p < 0.001$). Relative to a patient with colonic extent, a patient with isolated terminal ileal disease was at seven-fold increased risk of a change in behavior (HR, 7.76; 95% CI, 3.47 - 17.4) while a patient with ileocolonic extent was at a five-fold increased risk (HR, 5.63; 95% CI, 2.29 - 13.9). Cigarette smoking status at baseline was not significantly associated with an increased risk for complication, nor was baseline medication use. The calendar year of diagnosis was not significantly associated with complication (HR per 5 years, 0.94; 95% CI, 0.83 - 1.06). The association of perianal disease with a subsequent stricturing or penetrating complication was found to be borderline significant when it was examined as a time-dependent covariate (HR, 1.69; 95% CI, 1.00 - 2.86, $p = 0.051$), and non-significant when it was examined at baseline (see Table 2).

In the multivariate proportional hazards regression model, disease location at baseline and 5-ASA/sulfasalazine use at baseline were significantly associated with time to complication (Table 3). Those with ileal disease alone had a 9-fold increased risk (HR, 9.25; 95% CI, 4.10 - 20.87, $p < 0.001$) to develop an intestinal complication relative to those with colonic disease, while ileocolonic Crohn's disease patients had a 6-fold increased risk (HR, 5.74; 95% CI, 2.33 - 14.13, $p < 0.001$) to develop a complication. Use of 5-ASA or sulfasalazine in the first 90 days was associated with a two-fold increased risk (HR, 2.25; 95% CI, 1.25 - 4.06, $p < 0.007$) of an intestinal complication.

DISCUSSION

In this population-based study on the evolution of Crohn's disease, almost 19% of patients had already experienced penetrating or stricturing complications within the first 90 days of diagnosis, and fully half of all patients had experienced an intestinal complication 20 years after diagnosis. Among those with non-stricturing and non-penetrating disease at baseline with progression to an intestinal complication, 76.7% of patients required bowel resection surgery within 6 months of the event. Disease location (ileal, ileocolonic and upper gastrointestinal involvement) and the use of 5-ASA or sulfasalazine at baseline were found to be significantly associated with disease progression.

To date, only a few population-based studies^{7, 8} had described the progression of Crohn's disease behavior. A New Zealand population-based study using the Montreal classification to phenotype their Crohn's cohort reported 27% of their patients to have experienced either a

stricturing or penetrating complication at diagnosis⁸. In a prospective European population-based inception cohort²³ study, 26.2% were classified as stricturing and/or penetrating behavior at diagnosis based on the Vienna classification. Similarly, in the study from Norway, 37.9% were found to have as either stricturing or penetrating disease at diagnosis⁷. Our lower rate of complication at diagnosis (18.6%, 95% CI, 14.1-22.9) maybe related to an earlier presentation of disease, secondary to better awareness and accessibility to healthcare services among our patients, a situation unique to the Olmsted County population given the higher proportion of residents involved in the healthcare industry.

Earlier hospital-based cohort studies had consistently described the tendency towards complications in the natural history of Crohn's disease³⁻⁶. In the largest referral-based cohort³ study, the cumulative risk of developing either stricturing or penetrating complication was 88% at 20 years, which is higher compared to 60.6% (95% CI, 53.2-66.8) in our cohort, using the Vienna classification. This disparity can be reasonably explained by a referral pattern bias for which patients with more severe disease and greater propensity for complications are more frequently seen in a tertiary institution.

Using the Montreal classification, the cumulative risk of developing a complication for the entire cohort in our study was 50.8% (95% CI, 42.1-58.1) at 20 years, which is lower owing to the re-classification of perianal disease as a modifier, and not as an inclusion within the penetrating disease category. The 10-year cumulative incidence rate of 38.7% (95% CI, 32.5-44.3) for complications seen in our cohort is lower than the 56% reported in another population-based cohort⁸, despite a longer period of follow-up (median 8.5 versus 6.5 years). Differential rates of cigarette smoking in both cohorts could not account for the lower cumulative risk of complication in our cohort, as the proportion of current smokers at diagnosis in both studies were fairly similar (37% versus 32.8%). Other yet to be identified environmental or genetic factors unique to geographical differences could explain the disparity in complication rates observed in both studies²⁴.

Among 249 patients with uncomplicated disease at baseline, the progression towards an intestinal complication occurred in 66 patients (26.6%). The morbidity associated with a change in disease behavior was substantial in this group of patients, with three out of every 4 patients requiring an intestinal resection within 6 months of the event. The risk of surgery associated with stricturing or penetrating disease behavior had also been well-established in several other studies^{7, 25-27}, suggesting that once bowel complication occurred, medical therapy may have a limited role in preventing surgery.

Among the baseline risk factors studied, disease location was found to be most strongly predictive of subsequent intestinal complication. The presence of ileal as well as upper gastrointestinal involvement were strongly associated with the progression towards strictures or penetrating disease, consistent with findings from other studies^{26, 28}. Possible explanations for this observation suggested by Louis *et al*²⁹ for the higher rate of intestinal complications seen in small bowel compared to colonic disease included differences in gut lumen diameter and the intensity of mucosal inflammatory reactions leading to permanent bowel damage.

We observed that the use of 5-ASA or sulfasalazine at baseline was associated with the risk of disease progression. This interesting finding is consistent with the overall weak efficacy data of 5-ASA/sulfasalazine, particularly for the treatment of small bowel Crohn's disease³⁰. In a randomized controlled trial comparing mesalamine to budesonide, there was a higher rate of hospitalization and severe adverse events among those treated with mesalamine³¹. At this point, we cannot be certain that 5-ASA/sulfasalazine truly increases the risk of intestinal complications among Crohn's patients, as our study was not designed to specifically assess its

effectiveness for the prevention of disease progression, and residual confounding cannot be excluded.

The issue of whether perianal disease is associated with intestinal fistulization is still controversial. A population-based study³² demonstrated a strong association between perianal and intestinal fistulization (odds ratio 5.0), although they often occurred exclusively of each other. Other studies^{26, 27} have supported the observation that perianal and intestinal penetrating disease manifested different clinical phenotypes. In our study, perianal disease was of borderline significance in predicting change in behavior with a HR of 1.69 (95% CI, 0.99-2.86). This is likely due to a type II error, when compared to a significant study by Tarrant *et al*⁸ with a HR of 1.62 (95% CI, 1.28-2.05) in a larger cohort of 715 Crohn's patients. In keeping with their clinical relevance as markers of disease progression and severity, perianal complications have also been associated with greater need for immunosuppressive therapy²⁷ and have been predictive of a disabling disease course³³.

Cigarette smoking is a well-known aggravating risk factor for disease progression as evidenced by an increased need for immunosuppressive therapy, surgery and higher post-operative recurrence rates^{34,35}. Our study did not demonstrate an association of baseline smoking status with a change in disease behavior, similar to another study specifically designed to explore the influence of smoking on clinical phenotype²⁸. In their study, disease location was the only critical factor in predicting disease progression and was independent of smoking status. Furthermore, our study only examined the effect of baseline smoking status on subsequent complication rates, and therefore did not evaluate the impact of smoking cessation, or the possibility of a dose and time-dependent effect of smoking on disease course.

To our knowledge, this is the first North American study describing the evolution of Crohn's disease behavior in a well-defined population-based cohort. Therefore, our study is devoid of referral center bias which tends to include the more severe spectrum of Crohn's disease patients. Our results strengthen existing reports that Crohn's disease is a chronic progressive destructive disease, with progression to intestinal complications in many patients. Our results also provide clinicians with the tools to prognosticate their patients with regards to intestinal complications, based on the presence of simple baseline clinical factors. Using the Montreal classification, we were able to demonstrate that ileal and upper gastrointestinal involvement, and perianal disease (of borderline significance statistically) were important risk factors for strictures and penetrating complications, consistent with other studies^{3, 8, 23, 33}. At diagnosis, 68% of patients had upper gastrointestinal, ileal, or ileocolonic disease and an additional 5.9 % of patients had colonic disease with perianal involvement. Thus, 73.9% of patients had clinical risk factors for disease progression at diagnosis, and a large percentage of patients who ultimately develop disease progression, progress within 1 year of diagnosis. We believe it would be important to further evaluate if early aggressive medical therapy for patients with such baseline risk factors would alter the natural history of the disease and lower the risk of intestinal complications.

There are several limitations to our study. Our study population was relatively small and perhaps underpowered to detect significant associations for some of the baseline factors which may be predictive of complications. Further studies should confirm if upper gastrointestinal involvement, ileal involvement and perianal disease are independent predictors of complications. While we were able to accurately phenotype our patients using the comprehensive Olmsted County medical records linkage system, we did not correlate clinical phenotypes with serotypes or genotypes, as they were not systematically evaluated in our cohort. Future studies would be helpful to determine the influence of serological markers and the role of genotyping in predicting the risk of disease progression³⁶. Furthermore, although we evaluated baseline clinical features associated with the development of intestinal stricturing

and/or penetrating event, our study did not evaluate the impact of modifiable factors such as on-going medical therapies and smoking.

In conclusion, almost 19% of patients had already experienced penetrating or structuring complications within the first 90 days of diagnosis, and fully half of all patients had experienced an intestinal complication 20 years after diagnosis in our population-based cohort study. Factors associated with disease progression (i.e., the presence of ileal, upper gastrointestinal involvement and perianal disease) were present in almost 75% of patients at or shortly after diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix 1

Montreal modification of the Vienna classification of Crohn's disease (adapted from Silverberg MS, et al¹⁶)

Age at diagnosis (A)			
A1	16 years or younger		
A2	17-40 years		
A3	Over 40 years		

Location (L)		Upper GI modifier (L4)	
L1	Terminal Ileum	L1 + L4	Terminal ileum + Upper GI
L2	Colon	L2 + L4	Colon + Upper GI
L3	Ileocolonic	L3 + L4	Ileocolonic + Upper GI
L4	Upper GI		

Behavior (B)		Perianal disease modifier (p)	
B1	Non-stricturing, non-penetrating	B1p	Non-stricturing, non-penetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

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Figure 1.

Cumulative probability of intestinal complications from date of diagnosis among 306 Olmsted County residents diagnosed with Crohn's disease between 1970 and 2004. a. Penetrating or stricturing complications; b. Stricturing complications; and c. Penetrating complications.

a. Penetrating or stricturing complications b. Stricturing complications

Figure 2. Cumulative probability of intestinal complications among 249 patients with non-stricturing, non-penetrating Crohn's disease after the 90-day baseline. a. Penetrating or stricturing complications; b. Stricturing complications; c. Penetrating complications.

Table 1

Baseline demographic and clinical characteristics of 306 Olmsted County, Minnesota, residents diagnosed with Crohn's disease between 1970 and 2004.

Factors at diagnosis	Disease Behavior at diagnosis			
	Overall 306 (100)	B1 249 (81.4)	B2 14 (4.6)	B3 43 (14.0)
Gender				
Male	150 (49.0)	123 (49.4)	7 (50.0)	20 (46.5)
Female	156 (51.0)	126 (50.6)	7 (50.0)	23 (53.5)
Age				
A1	35 (11.4)	32 (12.9)	2 (14.3)	1 (2.3)
A2	172 (56.2)	134 (53.8)	9 (64.3)	29 (67.4)
A3	99 (32.4)	83 (33.3)	3 (21.4)	13 (30.2)
Disease Location				
L1	138 (45.1)	93 (37.4)	11 (78.6)	34 (79.1)
L2	98 (32.0)	96 (38.6)	0 (0.0)	2 (4.6)
L3	57 (18.6)	49 (19.7)	2 (14.3)	6 (14.0)
L4	1 (0.3)	0 (0.0)	1 (7.1)	0 (0.0)
L1 + L4	7 (2.3)	6 (2.4)	0 (0.0)	1 (2.3)
L2 + L4	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)
L3 + L4	4 (1.3)	4 (1.6)	0 (0.0)	0 (0.0)
Disease behavior		--	--	--
B1	249 (81.4)			
B2	14 (4.6)			
B3	43 (14.0)			
Perianal Disease prior to or within 90 days of CD diagnosis				
Yes	51 (16.7)	43 (17.3)	0 (0.0)	8 (18.6)
No	255 (83.3)	206 (82.7)	14 (100.0)	35 (81.4)
Smoking history Not documented	7	5	1	1
Current smokers	98 (32.8)	81 (33.2)	3 (23.1)	14 (33.3)
Former smokers	45 (15.0)	41 (16.8)	0 (0.0)	4 (9.5)
Non-smokers	156 (52.2)	122 (50.0)	10 (76.9)	24 (57.1)
Family History Not documented	7	5	1	1
Yes	43 (14.4)	33 (13.5)	1 (7.7)	9 (21.4)
No	256 (85.6)	211 (86.5)	12 (92.3)	33 (78.6)
Extra-intestinal manifestation				
Yes	46 (15.0)	44 (17.7)	0 (0.0)	2 (4.6)
No	260 (85.0)	205 (82.3)	14 (100.0)	41 (95.4)

Values are expressed as number of patients; Values in parentheses (%); A1, age at diagnosis <17 years; A2, age at diagnosis 17-40 years; age at diagnosis >40 years; B1, non-stricturing, non-penetrating disease; B2, stricturing disease; B3, penetrating disease; L1, terminal ileum; L2 colon; L3 ileocolonic; L4 upper gastrointestinal tract

Table 2

Univariate associations between baseline factors and time to change in Crohn's disease behavior in 248 patients from Olmsted County, Minnesota who did not experience an intestinal complication at the 90-day baseline.

Factors at diagnosis	Patients, n (Total, 248*)	Events, n (Total, 66)	Hazard Ratio	95% CI	p-value
Age					
<16 years	32	5	1.0	Ref.	
16-40 years	133	45	2.07	0.82 – 5.22	0.12
>40 years	83	16	1.29	0.47 – 3.52	0.62
Disease Location					
Colon	96	7	1.0	Ref.	
Terminal ileum	92	39	7.76	3.47 – 17.4	<0.001
Ileocolonic	49	15	5.63	2.29 – 13.9	<0.001
Upper GI tract	11	5	9.48	2.99 – 30.1	<0.001
Gender					
Female	125	29	1.0	Ref.	
Male	123	37	1.46	0.90 – 2.37	0.13
Smoking status					
Non-smoker	121	26	1.0	Ref.	
Current smoker	81	32	1.49	0.88 – 2.52	0.13
Ex-smoker	41	7	0.83	0.36 – 1.90	0.65
Family history of IBD					
No	210	57	1.0	Ref.	
Yes	33	8	0.77	0.37 – 1.61	0.49
Extra-intestinal manifestation					
No	204	56	1.0	Ref.	
Yes	44	10	0.80	0.41 – 1.56	0.51
Perianal disease					
No	205	54	1.0	Ref.	
Yes	43	12	1.21	0.64 – 2.26	0.56
Any form of medication					
Yes	218	60	1.0	Ref.	
No	30	6	0.63	0.27 – 1.46	0.28

Factors at diagnosis	Patients, n (Total, 248 [*])	Events, n (Total, 66)	Hazard Ratio	95% CI	p-value
Corticosteroids					
No	139	36	1.0	Ref.	
Yes	109	30	1.30	0.80 – 2.12	0.29
5-aminosalicylates or sulfasalazine					
No	72	15	1.0	Ref.	
Yes	176	51	1.49	0.84 – 2.64	0.18
Azathioprine/6-mercaptopurine					
No	226	62	1.0	Ref.	0.78
Yes	22	4	0.87	0.31 – 2.40	
Antibiotics (>4 weeks)					
No	225	60	1.0	Ref.	
Yes	23	6	1.13	0.49 – 2.62	0.78

CI, confidence interval; IBD, inflammatory bowel disease.

^{*} One patients with <90 days follow-up from diagnosis was excluded from analysis

Table 3

Multivariate model of baseline factors and time to change in Crohn's disease behavior in 248 patients from Olmsted County, Minnesota who did not experience an intestinal complication at the 90-day baseline.

Factors at diagnosis	Hazard Ratio	95% CI	p-value
Disease Location			
Colon	1.0	Ref.	
Terminal ileum	9.25	4.10 – 20.87	<0.001
Ileocolonic	5.74	2.33 – 14.13	<0.001
Upper GI tract	12.65	3.93 – 40.73	0.007
5-aminosalicylates or sulfasalazine			
No	1.0	Ref.	
Yes	2.25	1.25 – 4.06	0.007