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REVIEW

Epidemiology and clinical course of Crohn's disease: Results from observational studies

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Abstract

The authors review the clinical outcome in patients with Crohn's disease (CD) based on studies describing the natural course of the disease. Population-based studies have demonstrated that the incidence rates and prevalence rates for CD have increased since the mid-1970s. The authors search for English language articles from 1980 until 2011. Geographical variations, incidence, prevalence, smoking habits, sex, mortality and medications are investigated. An increasing incidence and prevalence of CD have been found over the last three decades. The disease seems to be most common in northern Europe and North America, but is probably increasing also in Asia and Africa. Smoking is associated with an increased risk of developing CD. Age < 40 at diagnosis, penetrating/stricturing complications, need for systemic steroids, and disease location in terminal ileum are factors associated with higher relapse rates. A slight predominance of women diagnosed with CD has been found. Ileocecal resection is the most commonly performed surgical procedure, and within the first five years after the diagnosis about one third of the patients have had intestinal surgery. Smoking is associated with a worse clinical course and with increased risk of flare-ups. In most studies the overall mortality is comparable to the background population. To date, the most effective treatment options in acute flares are glucocorticosteroids and tumor necrosis factor (TNF)-α- blockers. Azathioprine/methotrexate and TNF-α-blockers are effective in maintaining remission.

Key words: Crohn's disease; Epidemiology; Diagnosis; Smoking; Extra-intestinal manifestations; Therapy

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INTRODUCTION

The incidence rates for Crohn's disease (CD) and ulcerative colitis (UC) in Western countries have increased since the mid-1970s. The same trend, although less pronounced, is also seen in the developing world[1-3]. The reported geographical variations in incidence may in part be due to differences in diagnostic tools and study design, and many of the epidemiological studies have been retrospective and hospital-based[4]. CD is a disease with a broad spectrum of clinical manifestations, and the initial presentation is seldom a good predictor of the clinical course[5-7]. Patients with newly diagnosed CD often ask about expectations related to the course of the disease. To answer this question, information on the natural course of CD based on observational, population-based

cohort studies is crucial. The "natural course" in CD might be different in 2011 compared to the situation for instance in the 1980s, and there are at least two reasons for this: we now have better tools to diagnose the condition in an earlier phase, and we have new therapeutic agents that hopefully will alter the course of the disease.

The primary aim of this article is to review the clinical outcome in patients with CD based on population-based studies conducted over the last thirty years, focusing predominantly on studies describing the natural clinical course in representative cohorts of patients with CD.

The factors investigated include incidence, prevalence, age, sex, smoking, geographical differences, surgical aspects, extra-intestinal manifestations, mortality, medication, clinical course with focus on relapse and surgery, the location and behavior of the disease, and finally, the need for sick leave/unemployment. A Medline search (1980 to 2011) for English language articles was conducted.

The MESH term "Crohn disease" was combined with free text search for "population based" and "clinical". This search yielded sixty-seven articles. All potential relevant articles were evaluated.

EPIDEMIOLOGICAL ASPECTS OF CROHN'S DISEASE

Incidence, prevalence and time-trends

The incidence of CD differs depending on the region studied. The United Kingdom, North America and the northern part of Europe are the areas with the highest incidence[8-10]. A Danish study from 1997 found that the mean incidence rate for men per 100 000 person years increased from 3.3 in 1981-1984 to 4.1 in 1989-1992[11]. For women in the same area and in the same time intervals, the incidence rate increased from 4.6 to 6.2. A peak incidence rate was found among 15-29-year-olds, with an incidence rate among men and women of 5.3 and 9.1, respectively. A recent study in which all new CD cases in Finland between 2000 and 2007 were included revealed an overall incidence rate of 9.2 per 100 000 inhabitants[12]. The incidence rate in Olmsted County, Minnesota, United States was 5.7 cases per 100 000 person years between 1940 and 1993[10]. During the study period, a marked increase in incidence was found: in 1940-1943 the incidence rate was 1.0, while the rate in 1984-1993 was 6.9. Traditionally, the incidence has been low in Asia and Africa. Studies from these areas suggest that the incidence of CD is increasing[2,13].

The prevalence of CD in Europe varies from less than 10 to about 150 per 100 000 inhabitants[9,14]. An adjusted prevalence of 133 per 100 000 was found in Minnesota, United States in 1991[10]. One study from South Korea indicated prevalence of 11.2[15]. From the existing data, one can conclude that the incidence and prevalence rates of CD have increased over last decades.

Sex and age at diagnosis and smoking

In a retrospective study from the United Kingdom on patients diagnosed with CD[16], the patient population was divided in three groups by year of diagnosis: 1986-1991, 1992-1997 and 1998-2003. Of a total of 341 subjects diagnosed with CD, 62% were females. In all time intervals, the median age at diagnosis was 30 years. In a prospective study from Denmark, all patients in Copenhagen County diagnosed with UC and CD from 2003 to 2005 were followed for 11.3 mo (median); 54% of the CD patients were females, and median age at diagnosis was 31 years[8]. A retrospective study from Olmsted County, Minnesota, United States showed that 54% of the patients were females, and the median age at diagnosis was 29.5 years[10].

In Norway, the Inflammatory Bowel South-Eastern Norway (IBSEN) group, in a prospective study, has followed patients with inflammatory bowel disease (IBD) since the beginning of the 1990s[17]. This study reported a slight predominance of women diagnosed with CD, with a male/female-ratio of 0.95. The median age at diagnosis was 30 years. In Finland, no significant difference between the genders was found[12]. A population-based Canadian study[18] found a female predominance: 58% of the patients were women. Cigarette smoking is associated with increased risk of developing CD[19]. Smoking negatively influences the clinical course of CD and is also associated with the clinical recurrence of CD after surgical resection in CD patients[20]. Cosnes *et al*[21] found that smoking, particularly heavy smoking, markedly increased the risk of flare-ups of the disease.

Based on these studies, the conclusion is that there is a slight predominance of women diagnosed with CD, that the age at diagnosis is approximately 30, and that cigarette smoking is harmful in patients with CD.

Appendectomy

The relationship between appendectomy and the risk of developing CD has been debated, and in 2009, a systematic review of the literature was performed[22]. The authors found that the relative risk (RR) for having CD diagnosed following an appendectomy was significantly elevated. Within the first year after the surgery, the RR was 6.69 (95% CI: 5.42-8.25). An increase in the risk of developing CD also was found 1-4 years after the appendectomy, but thereafter the risk was not increased. Another study confirmed these results, but no increased risk of developing CD was found in patients who underwent appendectomy before the age of ten[23]. It seems that there was an inverse relationship between appendectomy and the development of UC, at least in patients who underwent appendectomy before the age of 20[24].

Geographical differences

The occurrence of CD seems to vary according to geographical location. A north-south axis has been found in both Europe and in the United States, with higher incidence and prevalence in the northern regions. In a study from 1996[25] on the incidence of IBD across Europe, incidence rates were found to be 80% higher in northern centers than in southern. A French study from 2006[26] also demonstrated a north-south gradient within France. Data from Columbia support the clinical experience that

CD is rare in South America[27]. Based on a prospective European population-based inception cohort of 380 CD patients, a difference in management was observed between northern and southern centers, indicating that CD patients in the north had a more severe disease course than did those in the south[28]. One problem is that there are still huge differences in diagnostic facilities. South Asians who live in Europe are more likely to develop IBD than South Asians who do not. In some regions of the world, there are diagnostic challenges due to overlap with intestinal tuberculosis[1]. In Brazil, Argentina, Puerto Rica and Panama, the prevalence of CD and UC together is between 20-100/100 000 inhabitants, but very few reports exist, and the ratio between CD and UC is uncertain. This is in marked contrast to the numbers from the United States and Canada, where the prevalence numbers vary between 320/100 000 and 511/100 000 inhabitants[27]. The reasons for these differences are not fully elucidated.

Hispanics in the United States are less prone to develop IBD than the non-Hispanic population. It is known that the *NOD2* gene on chromosome 16 is a marker for the susceptibility to CD. A recent study showed that 4.4% of Hispanics and 9.1% of the white population have NOD2[29]. This indicates that there are real differences in incidence/prevalence between North and South America.

Clinical important risk factors

In many studies, risk factors predicting a disabling course of CD are described. The IBSEN group[30] has described the relapse rates and need for surgery one, five, and ten years after the diagnosis. Age < 40 at diagnosis and the need for systemic steroids to treat the first flare-up were factors associated with higher relapse rates. Age < 40 at diagnosis, disease location in terminal ileum and penetrating/stricturing complications were associated with higher risk for surgery (Tables 1 and 2). Beaugerie *et al*[31] also found that age < 40 at diagnosis of CD, presence of perianal disease, and initial requirement for steroids were independent factors predicting disabling disease during the first five years after the diagnosis. Henriksen *et al*[32] did not find any association between CRP levels and a risk of surgery for the CD group as a whole, but a significant linear association between CRP levels and a risk of surgery was found with L1 localization (disease localization in terminal ileum).

SURGERY

Bowel resection

Stenoses, fistulas and abscesses are the main reasons for bowel resection in patients with CD.

In a Danish study from 2003-2005, 12% of CD patients underwent bowel resection performed within one year after the diagnosis, and the median time from diagnosis to resection was one month (range 0-8 mo)[8]. The authors compared the results to what was seen in patients diagnosed with CD in the same area between 1962 and 1987. In the earlier period, as many as 35% of the CD patients underwent bowel resection performed within the first year of diagnosis. A shorter delay from the onset of symptoms to diagnosis and the introduction of more intensive immunosuppressive therapy might be among the explanations for this decreased risk of surgical resection.

The Montreal classification of CD includes the location (L) of the disease, where L1 is location in the terminal ileum, L2 is in the colon, L3 is an ileocolonic location, and L4 is an upper GI location[33]. In one study, patients with L1 location at diagnosis had increased likelihood of intestinal surgery[5]. Oral corticosteroid use within three months of diagnosis, stricturing disease and low age at diagnosis were also associated with increased likelihood of resection. In the IBSEN study, the cumulative probability of surgery was 13.6%, 27.0% and 37.9% at one, five, and ten years after diagnosis[30], respectively. In this cohort, L1 location was strongly associated with surgery compared to L2 and L3 locations (Table 1).

A United Kingdom study of changes in medical treatment and surgical resection rates from 1986 to 2003 found a marked reduction in the proportion of patients needing intestinal surgery[16]. Within five years of diagnosis of CD, 59% of the patients diagnosed from 1986-1991 had intestinal surgery. In patients diagnosed between 1992-1997 and 1998-2003, 37% and 35%, respectively, had intestinal surgery within five years of diagnosis. In addition, there was a significant reduction in patients undergoing any surgical procedure (surgery for perianal disease or intestinal surgery) during an advanced stage of disease. Ileocecal resection was the most commonly performed procedure. The most striking reductions were seen in the numbers of ileocecal resections and in the numbers of panproctocolectomies.

A French retrospective study with 2573 CD patients[34] divided the cohort in five groups according to the year of diagnosis (1978-1982, 1983-1987, 1988-1992, 1993-1997 and 1998-2002). The main outcome criterion was the time to first intestinal resection. The cumulative probability to receive immunosuppressants [azathioprine (AZA), methotrexate (MTX)] increased from 0 in the 1978-1982 cohort to 0.56 in the 1998-2002 cohort. Interestingly, in contrast to the study from the United Kingdom[16], one found that the year of diagnosis did not have any significant effect upon the need for surgery.

Extra-intestinal manifestations

Extra-intestinal manifestations of CD include musculoskeletal, dermatologic, ocular, hepatobiliary, vascular and renal complications[35]. About 25%-46% of the patients with CD will experience extra-intestinal manifestations[36,37]. Primary sclerosing cholangitis (PSC) is in many ways the most serious, and the most serious complication from this condition is cholangiocellular carcinoma (CCC)[37]; 7% to 15% of the patients with PSC eventually develop CCC[38,39], 60%-70% of the PSC patients are male, and the age at diagnosis is about 40 years. There is a close relationship between UC and PSC. The relationship

Table 1 Cumulative rate (Cum %) of CD patients with relapsing disease during the first year and in the periods 1-5 and 5-10 years after diagnosis (Solberg *et al*[30], with permission)

Variables at diagnosis	Total in each subgroup	Relapse during the 1st year		Relapse between 1-5 yr		Relapse between 5-10 yr	
		cum% (CI)	*P* value	cum% (CI)	*P* value	cum% (CI)	*P* value
Age groups							
A1 < 40 yr	148	54 (50-58)	0.7	80 (77-83)	0.6	61 (57-65)	0.03
A2 ⩾ 40 yr	49	51 (44-58)		76 (70-82)		43 (36-50)	
Gender							
Female	95	54 (49-59)	0.9	76 (72-80)	0.4	56 (51-61)	0.9
Male	102	53 (48-58)		81 (77-85)		57 (52-62)	
Location							
L1: Terminal ileum	51	54 (47-61)	0.4	78 (72-84)	0.8	57 (50-64)	0.1
L2: Colon	94	57 (52-64)		76 (72-80)		49 (44-54)	
L3: Ileocolon	48	44 (37-51)		81 (75-87)		69 (62-76)	
L4: Upper GI	4	75 (53-97)		100 (-)		75 (53-97)	
Behavior							
B1: Inflammatory	127	56 (52-60)	0.7	79 (75-83)	0.6	54 (50-58)	0.4
B2: Stricturing	50	49 (42-56)		74 (68-78)		64 (57-71)	
B3: Penetrating	20	50 (39-61)		85 (77-93)		55 (44-66)	
Systemic steroids							
No	86	47 (42-52)	0.08	69 (64-74)	0.008	47 (42-52)	0.02
Yes	109	59 (54-64)		85 (82-88)		63 (58-68)	
Missing	2	-		-		-	
Smoking status							
Never	82	52 (47-57)	0.5	79 (75-84)	0.9	59 (54-64)	0.09
Current smoker	82	57 (52-62)		79 (75-84)		61 (56-66)	
Ex-smoker	29	45 (36-54)		76 (68-84)		38 (29-47)	
Missing	4	-		-		-	
Total	197	54 (50-57)		79 (76-82)		56 (53-60)	

χ^2 comparisons within each subgroup; CI: Confidence interval; GI: Gastrointestinal.

Table 2 Risk factors at diagnosis associated with surgery during follow-up analyzed by Cox regression (Solberg *et al*[30], with permission)

Variables at diagnosis	Number in analysis	Number with surgery (%)	Unadjusted			Adjusted		
			HR	95% CI	*P* value	HR	95% CI	*P* value
Age								
A1: < 40 yr	165	69 (42)	1	[Ref]	0.03	1	[Ref]	0.03
A2: ⩾ 40 yr	72	16 (22)	0.5	0.3-0.9		0.5	0.3-0.9	
Gender								
Female	118	40 (34)	1	[Ref]	0.9	Not included		
Male	119	45 (38)	1	0.7-1.6				
Location								
L1: Terminal ileum	64	38 (59)	1	[Ref]	< 0.001	1	[Ref]	
L2: Isolated colonic	115	26 (23)	0.2	0.1-0.4		0.3	0.2-0.6	0.001
L3: Ileocolon	54	17 (32)	0.3	0.2-0.6		0.3	0.2-0.5	< 0.001
L4: Upper GI[1]	4	4 (100)	1.4	0.5-3.8		1.6	0.5-4.4	0.4
Behavior								
B1: Inflammatory	147	32 (22)	1	[Ref]	< 0.001	1	[Ref]	
B2: Stricturing	64	36 (56)	3.5	2.1-5.6		2.3	1.3-4.1	0.004
B3: Penetrating	26	17 (65)	4.9	2.7-8.8		5.4	3.0-9.9	< 0.001
Smoking status[2]								
Never	103	38 (37)	1	[Ref]	0.2	Not included		
Current < 10 cigarettes/d	57	18 (32)	0.8	0.4-1.4				
Current > 10 cigarettes/d	36	18 (50)	1.9	0.8-2.6				
Ex-smoker	35	11 (31)	0.8	0.4-1.6				
Systemic steroids[3]								
No	106	36 (34)	1	[Ref]	0.8	Not included		
Yes	129	48 (37)	1.1	0.7-1.6				

[1]Difficult to conclude because of an insufficient number of patients; [2]data unknown in 6 cases. There were none in the operated group; [3]data unknown in 2 cases; There was one in the operated group. Ref: Reference variable; HR: Hazard ratio; CI: Confidence interval.

between CD and PSC is less pronounced but marked. Studies form Sweden and Holland showed that 72% and 73%, respectively, of the PSC patients with IBD had UC, and 7% and 25%, respectively, of the PSC patients with IBD had CD[40,41].

In both studies, a certain proportion of patients with PSC did not have a diagnosis of IBD. To date, no medical treatment has been established to be effective. A hydrophilic dihydroxy bile acid, ursodeoxycholic acid, is used in the treatment of PSC, but the efficacy of the treatment is not well established. A recent study even concluded that serious adverse events were more common in the drug-treated group than in the placebo group[42].

Five-year follow up data from the IBSEN study showed that the cumulative occurrence of peripheral arthritis related to CD is 14%; 6% had ankylosing spondylitis; 1% had psoriatic arthritis; and 19% had undifferentiated spondyloarthropathy[43-45]. In Canada, one study following the patients from 1984 to 1997 showed that 6027 patients suffering from IBD had a 40% increased risk of fractures compared to the control group[46]. The incidence rate ratio (IRR) for fracture at the hip was 1.59 (95% CI: 1.27-2.00, $P < 0.001$); the IRR for fracture of the spine was 1.74 (95% CI: 1.34 -2.24, $P < 0.001$); while the IRR for rib fracture was 1.25 (95% CI: 1.02-1.52, $P = 0.03$). No differences were found in the IRR between CD and UC patients. A study from Olmsted County, United States, showed that the relative risk for osteoporotic fractures in CD patients was 1.4 (95% CI: 0.7-2.7), and the risk ratio for thoracolumbar vertebral fracture was 2.2 (95% CI: 0.9-5.5)[47].

Mortality

During the decades from 1970 to 1990, population-based studies have shown a slightly decreased life expectancy in CD patients[48-50]. Because these studies are from the era before the introduction of the immunomodulating agents, the applicability might be of limited value.

A meta-analysis from 2007[51] identified 13 papers that reported standardized mortality ratios (SMR). Most of these papers included patients diagnosed in the 1950s to the 1970s, although four of them included patients diagnosed from 1980 to 1985. In this study, an age-adjusted mortality risk in CD patients was more than 50% greater than in the general population, but three of the studies actually reported an SMR below 1.0. A meta-analysis from 2010[52] also confirmed slightly increased mortality in CD patients (SMR 1.39, 95% CI: 1.30-1.50). In a recent report, a complete 10-year follow-up was achieved in 197 of 237 patients[30]. Two deaths during follow-up were probably CD-related. Another study did not show any decrease in survival curves for the total group of 373 CD patients followed for five years compared to the background population, although a small subgroup of patients diagnosed at the age of 20-29 and a subgroup with extensive small bowel disease displayed slightly increased mortality[53]. In the Netherlands, 1187 patients diagnosed with IBD during a 12-year period from 1991 were included[54]. The mortality in CD, UC, and indeterminate colitis was comparable to the background population, but the disease-specific mortality risk was significantly increased for gastrointestinal causes in both CD and UC patients. Overall, a slight increase in mortality was found in CD patients. This is mainly caused by malignant diseases in the gastrointestinal tract and in the lungs[52].

Medication

CD is a chronic disorder that, at least so far, is not curable. The induction and maintenance of symptom improvement and, at best, the induction and maintenance of mucosal healing are the goals of treatment[55]. Disease location, disease severity and complications should be taken into consideration when therapy is to be decided.

Even at high doses and prolonged administration, glucocorticosteroids (GCSs) induce endoscopic remission in less than one third of the patients with colonic CD[56]. Use of GCSs has a favorable effect on the symptoms of Crohn´s disease of the small intestine but will not achieve a significant reduction in endoscopically observed inflammation[57].

A few decades ago, a large clinical trial[58] showed that CD patients with colonic involvement were especially responsive to sulfasalazine, but a European multicenter double-blind study from the 1980s did not show any beneficial effects from sulfasalazine as compared to 6-methylprednisolone[59]. Oral mesalamine has been, and still is, widely used in the treatment of CD. A meta-analysis of three large, double-blind, randomized studies in the treatment of active CD showed that mesalamine 4 g/d was better than placebo in reducing the Crohn's Disease Activity Index, but the clinical significance was unclear[60]. The recently published European evidence-based consensus on the diagnosis and management of CD[61] concluded that active colonic CD may be treated with sulfasalazine if only mildly active, and that mesalazine should be considered no more effective than placebo in the treatment for active ileal or colonic CD.

The rationale for the use of antibiotics in the treatment of mild to moderate CD is the hypothesis that bacteria may cause or exacerbate CD. Metronidazole, 10 or 20 mg/kg per day, compared to placebo, did not show any difference in the ability to induce remission in patients with mild/moderate disease[62]. Comparison of ciprofloxacin and mesalamine did not reveal any consistent pattern[63]. About 50% in each group achieved clinical remission. A recent meta-analysis[64] concludes that long-term treatment with nitroimidazoles or clofazimine appeared to be effective in CD patients.

A recent review on the effect of AZA or 6-mercaptopurine for the maintenance of remission in CD[65] concluded that both AZA and 6-mercaptopurine had a positive effect on maintaining remission. The study reported weak evidence for a steroid-sparing effect of AZA. In a recent single-center study[66], the authors found that MTX is efficient as a second-line immunomodulator in chronic active CD. In steroid-dependent CD patients, complete remission and steroid withdrawal were seen in 77% of the cases after 22.9 mo of treatment. After six months,

one, two, and three years on MTX, 95.3%, 89.5%, 70.6% and 62.8%, respectively, were in remission[67]. However, a high proportion of the patients developed side-effects (79% and 39%, respectively), including hepatotoxicity and hair loss[66,67]. Side effects associated with the use of AZA and 6-mercaptupurine include leucopenia, thrombocytopenia, pancreatitis and an increased risk of developing lymphoma[65]. The introduction of anti-tumor necrosis factor (TNF) agents has changed the treatment of refractory CD. Although the causes of CD are not known, many of the molecules involved in the disease process have been identified and can act as targets of biological treatment. TNF is a cytokine that promotes inflammatory responses in many diseases, including CD[68]. Infliximab is effective in both luminal and fistulizing CD[69,70] and is highly effective and safe in children[71]. The combination of infliximab and AZA is more effective in moderate-to-severe CD than infliximab alone[72]. One problem is that, each year, about 10% of patients, for different reasons, drop out of treatment[73]. Adalimumab is a human monoclonal antibody against TNF. It is administered subcutaneously and has proven effective in the treatment of luminal CD[74]. Certolizumab pegol is approved in the United States for the treatment of CD[68]. No trials exist that compare the three different anti-TNF agents, but it seems that infliximab, adalimumab and certolizumab pegol are comparable in efficacy. Anti-TNF agents definitely deserve to be considered as a treatment option for patients with CD; it is therefore widely discussed when patients should be introduced to these agents, and further studies are needed to establish this aspect of the approach to treatment.

In a review article, Vermeire *et al*[75] summarized the therapies that have been shown to alter the natural history of CD. Mucosal healing, the need for hospitalizations/surgery together with decreased recurrence after surgery, are surrogate markers of changes in the natural course of the disease. Anti-TNF agents have shown the ability to induce mucosal healing and to reduce the need for surgery in randomized, placebo-controlled studies. It is not known, however, if they can reduce the risk of recurrence after surgery.

CLINICAL COURSE

Markov models will show the probability of changes in state from one time-point to another. This model was used in a Danish study from 1995[6]. One found that the disease activity course in CD is not dependent on age, sex, or localization of the disease. The United Kingdom study and the French study[16,31] showed conflicting results, at least in the proportion of patients requiring surgery. The IBSEN study showed that ten years after the diagnosis was made, the course was generally better than in earlier reports[30]. The need for immunosuppressives and GCSs declined from the first five-year period to the second five-year period. The probability of surgery was 37.9%, and fewer patients than expected developed complicated disease behavior; however, the cumulative relapse rate was as high as 90% (Table 2). Because we have had the opportunity for biological treatment for some years now, we are looking forward to evaluating new epidemiological studies on the clinical course of the disease.

Sick leave/unemployment

There are just a few reports on sick leave/unemployment in patients with CD. In 2006, Bernklev *et al*[76] found that 24.6% of women with CD were on a disability pension (DP) five years after the diagnosis was established, which was a three-fold increase compared to the background population (8.8%). Five years after the diagnosis, 53% of the CD patients reported taking sick leave during the prior six months; 23% of the sick leaves were CD-related. A Dutch study from 2002 also concluded that CD patients had a significantly higher frequency of sick leave than the controls (odds ratio 1.7, 95% CI: 1.2-2.6)[77]. Both studies concluded that having CD is correlated to an increased unemployment rate. An earlier Danish study did not find any differences in the state of employment between CD patients nine years after the diagnosis compared to a control group, and as few as 3% were on DP[78].

CONCLUSION

Population-based studies have demonstrated that the incidence and prevalence of CD have increased over the last three decades. CD is most common in northern Europe and North America, and there is a slight predominance of women diagnosed with the disease. The majority of patients experience progression from inflammatory disease to the development of strictures and fistulas. Within the first five years of the disease, at least one third of the patients have had intestinal surgery, where ileocecal resection is the most commonly performed procedure. Appendectomy is associated with an increased risk of having CD diagnosed within the first four years after the surgery. A rising incidence and a slight female predominance is found in CD. The diagnosis is made when the patients are approximately thirty years old. Smoking is associated with an increased risk of developing CD, with a negative clinical course in patients with CD, and with increased risk of flare-ups of the disease in both operated and non-operated patients.

The overall mortality in most studies is comparable to the background population, although subgroups of CD patients seem to have slightly increased mortality. New therapeutic approaches are promising. To date, the most effective treatment options in acute disease are GCSs and TNF-α-blockers. TNF-α-blockers and AZA/MTX are effective in maintaining remission.

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