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The changing face of Crohn's disease: a population-based study of the natural history of Crohn's disease in Örebro, Sweden 1963-2005

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Short title: Crohn's disease in Örebro, Sweden 1963-2005

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Abstract

Objective

Changes in medical therapy and surgery might have influenced the natural history of Crohn's disease (CD). Our aim was to explore the short-term outcome of CD and to specifically assess trends in disease phenotype, medications and surgery in the first five years from diagnosis.

Material and Methods

A population-based cohort comprising 472 CD patients diagnosed within the primary catchment area of Örebro University Hospital 1963-2005 were identified retrospectively and described. Data on medication, surgery, progression in disease location and behaviour, were extracted from the medical records. Patients were divided into three cohorts based on year of diagnosis.

Results

The proportion of patients with complicated disease behaviour 5 years after diagnosis decreased from 54.4% (95%CI, 43.9-65.6) to 33.3% (27.4-40.0) in patients diagnosed 1963-1975 and 1991-2005, respectively ($p=0.002$), whereas the proportion of patients progressing to complicated disease behaviour was stable among those with non-stricturing, non-penetrating disease at diagnosis ($p=0.435$). The proportion of patients undergoing surgery decreased from 65.8% (55.4-76.0) to 34.6% (28.6-41.5) in patients diagnosed 1963-1975 and 1991-2005, respectively ($p<0.001$). The reduction in surgery preceded an increased use of immunomodulators and was explained by a decrease in surgery within three months from diagnosis ($p=0.001$).

Conclusions

We observed a striking decrease in complicated disease behaviour and surgery five years after CD diagnosis, the latter largely due to a decrease in early surgery. Our findings suggest that the introduction of new treatments alone does not explain the reduction in surgery rates, the

increasing proportion of patients with inflammatory disease at diagnosis also play an important role.

Keywords

Crohn's disease, natural history, surgery

Introduction and Aims

Crohn's disease is a chronic inflammatory bowel disease with a broad spectrum of clinical manifestations and variable outcome. Historically, Crohn's disease was believed to be an ileocaecal disorder, potentially cured by radical surgery. With time it became clear that the inflammation could affect the entire gastrointestinal tract and that recurrence of disease was common even after extensive surgery. Medical therapy advanced with the use of immunomodulators and the introduction of biologics. Changes in medical therapy and surgical practice over time might have influenced the natural history of the disease and possibly reduced surgery rates (1-7). However, epidemiological studies that have evaluated the effect of immunomodulators on surgery rates have yielded conflicting results (7-9). Recent clinical trials have also questioned the effect of immunomodulators as primary prophylaxis to reduce the need for surgical resections (10, 11).

The risk of progression towards complicated disease behaviour with strictures and/or fistulas and need of surgery might be influenced by factors other than medication. Time from onset of symptoms until diagnosis and initiation of treatment, that is diagnostic delay, has been associated with increased risk of stricturing disease and surgery (12). We have previously reported an increasing proportion of patients with non-stricturing, non-penetrating behaviour at diagnosis over time, pointing towards an earlier diagnosis or change in disease phenotype (13). Whether patients with non-stricturing, non-penetrating behaviour at diagnosis can avoid future disease complications necessitating surgery by adequate medical anti-inflammatory therapy is unknown. If so, this could possibly influence the rates of surgery in patients with Crohn's disease over time. However, whether the risk of disease progression to complicated disease behaviour depends on the time period of diagnosis is unknown.

Our aim was to explore changes in the short-term natural history of Crohn's disease over time. More specifically, we wanted to assess trends in disease phenotype, medication and

surgery in patients diagnosed with Crohn's disease within a well-defined population-based cohort in Sweden between 1963 and 2005, with patients followed for five years from diagnosis.

Materials and Methods

Study area and patient population

The primary catchment area of Örebro University Hospital includes a mix of urban and rural settings. The population increased from 150 177 in 1963 to 181 063 in 2005 and is served by Örebro University Hospital, 17 primary health care clinics and some private general practitioners but no private gastroenterologists. Since the 1970s all individuals with suspected or verified inflammatory bowel disease (IBD) have been referred to the hospital. All colonoscopy procedures and histopathological examinations within the catchment were performed at Örebro University Hospital.

The population-based inception cohort consisted of patients diagnosed with Crohn's disease within the primary catchment area of Örebro University Hospital, between 1st of January 1963 and 31st of December 2005 (n=472) and has been described previously in detail (13). In short, patients of all ages with a diagnosis of CD were identified retrospectively by evaluation of medical records of all current and previous patients at the colitis clinic, Örebro University Hospital, and amended by computerised search in the inpatient, outpatient, primary care and histopathological records. Patients who died or left the area were censored on the date of death or emigration. Patients were divided into three cohorts based on the year of diagnosis: 1963-1975; 1976-1990; and 1991-2005.

The Uppsala Regional Ethics Committee approved the study (2010/304).

Data collection

The medical records for all patients were reviewed by YZ and data on patient demographics, disease characteristics, drug treatments and any surgical procedures from diagnosis and during follow-up were collected using standardized questionnaires. Records for patients where clinical data were uncertain were jointly reviewed by YZ, CT and JH.

Description of variables

Patient demographics included age at diagnosis, date of diagnosis, sex, smoking status at diagnosis and date of death or emigration. Crohn's disease location and behaviour at diagnosis and during follow-up were classified according to the Montreal classification (14). Disease location was defined as occurrence of Crohn's disease lesions, demonstrated by the radiological, endoscopic, or surgical-pathologic methods. Progression in disease location was defined as change from ileal (L1) or colonic (L2) to ileocolonic (L3) disease. Development of upper gastrointestinal (L4) disease was regarded as a modifier of disease locations and was not considered as a progression in location. Progression in disease behaviour was defined as occurrence of stricturing (B2) or penetrating (B3) disease other than at diagnosis. Stricturing (B2) disease was defined by the presence 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 disease. Penetrating (B3) disease was defined by the occurrence of intraabdominal inflammatory masses, abscesses and/or fistula. Development of perianal disease was not considered as a change in behaviour. Dates of changes in disease location and disease behaviour were documented. Information on medication for Crohn's disease was collected, including type of medications, commencement and termination dates. Medications included: 5-aminosalicylic acid (oral; sulfasalazin,

mesalazin, olsalazin, balsalazid), corticosteroids (systemic; betamethason or prednisolon), budesonide (oral), immunomodulators (azathioprine, 6-thioguanine, 6-mercaptopurine or methotrexate) and anti-TNF therapy (infliximab, adalimumab or certolizumab). To specifically explore long-term treatment strategies, we assessed the use of long-term corticosteroid treatment, using the definition (any systemic corticosteroid therapy for ≥ 1 year during which there was no more than eight weeks break before restarting) published previously (7). Long-term corticosteroids use was calculated manually by extracting information about prescription of betamethason or prednisolon from the medical notes. Since the 1970s all patients with inflammatory bowel disease (IBD) have had appointments at the hospital and IBD related medication has almost exclusively been prescribed by physicians at the hospital. Surgery related to Crohn's disease included bowel resections (ileocecal resection, colectomy, other resection) and defunctioning stoma formation without concomitant resection. A stoma was considered permanent in patients having undergone a proctectomy or with severe refractory perianal disease with strictures or fistulas preventing stoma closure. The date of the first surgical procedure related to Crohn's disease was documented.

General treatment policy

Corticosteroids were available during the entire study period and primarily used for acute flares. Long-term corticosteroid use was avoided when possible. Sulfasalazin became available in Sweden in the 1970s, but was successively replaced by 5-aminosalicylic acid (5-ASA) drugs from the mid 1980s. Treatment with thiopurines, primarily azathioprine, was initiated in selected cases during the early/mid 1980s and has been increasingly used since then, primarily for steroid-dependent or refractory disease. Methotrexate was occasionally used for thiopurine intolerance or failure. In 1995 budesonide was introduced, primarily for

mild to moderate Crohn's disease involving the ileum and/or ascending colon. The first anti-TNF agent, infliximab, was approved for Crohn's disease in 1999. Initially anti-TNF therapies were used for refractory disease only.

Statistical analysis

Continuous variables are presented as median (range) or median (interquartile range [IQR]) where appropriate. Categorical variables are presented as frequencies (percentages) and comparison of distributions of categorical variables used the Chi squared test. In all analyses patients were followed from diagnosis of Crohn's disease until the outcome of interest, death, emigration, or end of follow-up (5-year from diagnosis), whichever occurred first. Life tables using a Kaplan-Meier approach were used to estimate cumulative probability of first progression in disease location, initial complication (stricturing or penetrating disease whichever came first), receiving 5-aminosalicylic acids, immunomodulators, anti-TNFs and of undergoing surgery. Kaplan-Meier curves were compared using the log-rank test, comparing rates within three months, one year and five years after diagnosis. A *P* value of <0.05 was considered statistically significant. Stata statistical software (Release 12. College Station, TX: StataCorp LP) was used.

Results

Demographic information

The study included 472 patients within the primary catchment area of Örebro University Hospital diagnosed with Crohn's disease from the 1st of January 1963 to the 31st of December 2005 (table 1). Information on disease location and behaviour at diagnosis and follow-up was available for 469 (99.4%) patients.

Table 1. Characteristics at diagnosis and at 5-year follow-up in patients with Crohn's disease diagnosed in the Örebro catchment area during 1963-2005 by year of diagnosis.

	1963-1975	1976-1990	1991-2005	Total 1963-2005
Number of patients	79	175	218	472
Patients with complete follow-up	79 (100%)	158 (90.3%)	196 (89.9%)	433 (91.7%)
Female	41 (51.9%)	92 (52.6%)	117 (53.7%)	250 (53.0%)
Age at diagnosis (median (range))	23 (3-66)	32 (6-79)	39.5 (5-87)	33 (3-87)
Smoker at diagnosis	37 (46.8%)	52 (29.7%)	62 (28.4%)	151 (32.0%)
Age at diagnosis				
A1 (<= 16 years)	12 (15.2%)	25 (14.3%)	29 (13.3%)	66 (14.0%)
A2 (17-40 years)	56 (70.9%)	86 (49.1%)	81 (37.2%)	223 (47.2%)
A3 (> 40 years)	11 (13.9%)	64 (36.6%)	108 (49.5%)	183 (38.8%)
Location at diagnosis^a				
L1 (Ileal)	32 (40.5%)	72 (41.1%)	87 (39.9%)	191 (40.5%)
L2 (Colonic)	21 (26.6%)	61 (34.9%)	78 (35.8%)	160 (33.9%)
L3 (Ileocolonic)	23 (29.1%)	41 (23.4%)	48 (22.0%)	112 (23.7%)
L4 (Isolated upper gastrointestinal)	2 (2.5%)	1 (0.6%)	5 (2.3%)	8 (1.7%)
Location at follow-up				
L1 (Ileal)	24 (30.4%)	70 (40.0%)	82 (37.6%)	176 (37.3%)
L2 (Colonic)	20 (25.3%)	58 (33.1%)	74 (33.9%)	152 (32.2%)
L3 (Ileocolonic)	33 (41.8%)	46 (26.3%)	58 (26.6%)	137 (29.0%)
L4 (Isolated upper gastrointestinal)	1 (1.3%)	1 (0.6%)	4 (1.8%)	6 (1.3%)
Behaviour at diagnosis^b				
B1 (Non-stricturing/non-penetrating)	35 (44.3%)	103 (58.9%)	160 (73.4%)	298 (63.5%)
B2 (Stricturing)	31 (39.2%)	33 (18.9%)	28 (12.8%)	92 (19.5%)
B3 (Penetrating)	10 (12.7%)	39 (22.3%)	30 (13.8%)	79 (16.7%)
P (Perianal disease)	5 (6.3%)	10 (5.7%)	19 (8.7%)	34 (7.2%)
Behaviour at follow-up				
B1 (Non-stricturing/non-penetrating)	33 (41.8%)	98 (56.0%)	146 (67.0%)	277 (58.7%)
B2 (Stricturing)	30 (38.0%)	36 (20.6%)	31 (14.2%)	100 (20.6%)
B3 (Penetrating)	13 (16.5%)	41 (23.4%)	41 (18.8%)	95 (20.1%)

^a Disease location was not known for one patient at diagnosis and at follow-up

^b Disease behaviour was not known for three patients at diagnosis and at follow-up

Change in location of Crohn's disease

Starting the observation period from day of diagnosis, and assuming ileocolonic (L3) disease occurring before or at diagnosis occurred on diagnosis day (day 0), the proportion of patients with ileocolonic (L3) disease at 5 years after diagnosis differed between the cohorts ($p=0.029$), figure 1 panel a and supplement table 1. When restricting the analysis to patients with ileal (L1) or colonic (L2) disease at diagnosis, the differences between cohorts persisted ($p=0.002$), figure 1 panel b. Among patients with ileal (L1) or colonic (L2) disease at diagnosis, 18.0% (95%CI, 10.1-30.9) progressed to ileocolonic disease at 5 years follow-up in patients diagnosed 1963-1975, 3.9% (95%CI, 1.7-9.2) and 6.1% (95%CI, 3.3-11.1) in patients diagnosed 1976-1990 and 1991-2005, respectively, supplement table 2.

Figure 1. Progression of disease location in the cohorts. Panel a. All patients irrespective of disease location at diagnosis. Panel b. Patients with ileal, colonic and isolated upper gastrointestinal disease at diagnosis.

Change in Crohn's disease behaviour

Starting the observation period from day of diagnosis, and assuming complications, that is stricturing (B2) or penetrating (B3) disease, occurring before or at diagnosis occurred on diagnosis day (day 0), the proportion of patients with complicated disease behaviour at 5 years after diagnosis differed between the cohorts ($p=0.002$), figure 2 panel a. The proportion of patients with complicated disease behaviour at 5 years decreased from 54.4% (95%CI, 43.9-65.6) in patients diagnosed 1963-1975 to 44.2% (95%CI, 37.2-51.9) and 33.3% (95%CI, 27.4-40.0) in patients diagnosed 1976-1990 and 1991-2005, respectively, supplement table 3. When restricting the analyses to patients with non-stricturing, non-penetrating (B1) disease at diagnosis, no difference in the proportion of patients who progressed to complicated disease behaviour was observed ($p=0.435$), figure 2 panel b and supplement table 4.

Figure 2. Progression of disease behaviour in the cohorts. Panel a. All patients irrespective of disease behaviour at diagnosis. Panel b. Patients with non-stricturing, non-penetrating disease at diagnosis.

Medication

5-aminosalicylic acid

The proportion of patients that received treatment with 5-aminosalicylic acid in all three cohorts together (1963-2005) was 40.4% (95%CI, 36.1-45.0) at 1 year and 50.8% (95%CI, 46.4-55.5) at 5 years after diagnosis. No notable difference was observed between the three

cohorts in terms of 5-year cumulative probability of 5-ASA treatment ($p=0.182$; data not shown).

Corticosteroids and budesonide

At 5 years after diagnosis, 5/79 (6.3%), 14/175 (8.0%) and 13/218 (5.9%) patients diagnosed in 1963-1975, 1976-1990 and 1991-2005, respectively, had received long-term corticosteroid treatment ($p=0.710$).

Among patients diagnosed 1995-2005, the proportion of patient that received budesonide was 10.3% (95%CI, 6.5-16.1) at 1 year and 18.7% (95%CI, 13.4-25.7) at 5 years after diagnosis.

Immunomodulators

The proportion of patients treated with immunomodulators in 5 years from diagnosis was significantly different between the cohorts ($p<0.001$), figure 3. The proportion of patients exposed to immunomodulators in the first year from diagnosis year increased from 1.3% (95%CI, 0.2-8.7) and 1.2% (95%CI, 0.3-4.6) in patients diagnosed 1963-1975 and 1976-1990, respectively, to 22.2% (95%CI, 17.3-28.4) in patients diagnosed 1991-2005, supplement table 5. The corresponding proportions at five years were 7.6% (95%CI, 3.5-16.1), 7.2% (95%CI, 4.2-12.4) and 37.7% (95%CI, 31.6-44.7), respectively. The median time to initiation of immunomodulators in those treated with the drug within 5 years from diagnosis was 2.2 years (IQR 1.0-2.9), 2.0 years (IQR 1.2-3.3) and 0.6 years (IQR 0.1-1.7) in patients diagnosed 1963-1975, 1976-1990 and 1991-2005, respectively.

Figure 3. The proportion of patients treated with immunomodulators by cohort.

Anti-TNF therapy

Among patients diagnosed 2000-2005 ($n=104$), the proportion treated with anti-TNF therapy was 2.0% (95%CI, 0.5-7.6) at 1 year and 8.4% (95%CI, 4.3-16.1) at 5 years after diagnosis.

Surgery

In total, 196/472 (41.5%) patients had undergone surgery related to Crohn's disease at 5 years after diagnosis; details of the first surgery are presented in table 2. In 70 patients (14.8%), Crohn's disease was diagnosed at the first surgical procedure.

Table 2. Details of the first Crohn's disease related surgery within 5 years from diagnosis in the cohorts.

	Cohort 1963-1975	Cohort 1976-1990	Cohort 1991-2005	Total 1963-2005	Chi2 for trend
Ileocaecal resection	29 (36.7%)	47 (26.9%)	42 (19.3%)	118 (25.0%)	p<0.001
Colectomy	2 (2.5%)	3 (1.7%)	3 (1.4%)	8 (1.7%)	p=0.493
Other resection	21 (26.6%)	21 (12.0%)	23 (10.6%)	65 (13.8%)	p=0.002
Defunctioning stoma	0 (0%)	0 (0%)	5 (2.3%)	5 (1.1%)	p=0.019
No surgery	27 (34.2%)	104 (59.4%)	145 (66.5%)	276 (58.5%)	p<0.001

The proportions of patients that were subject to surgery were significantly different between the cohorts ($p<0.001$), figure 4. The proportion of patients undergoing Crohn's disease related surgery within 5 years from diagnosis decreased from 65.8% (95%CI, 55.4-76.0) in patients diagnosed 1963-1975 to 41.4% (95%CI, 34.4-49.2) and 34.6% (95%CI, 28.6-41.5) in patients diagnosed 1976-1990 and 1991-2005, respectively, supplement table 6. The decrease in surgery was due to a decrease in the proportion of ileocaecal resections and other resections (primarily small-bowel resections and hemicolectomies), while the proportion of patients undergoing colectomy remained stable, table 2. The decrease in surgery is largely explained by a decrease in early surgery, since the cumulative probability of surgery at 3 months after diagnosis dropped from 34.2% (95%CI, 24.9-45.8) in patients diagnosed in 1963-1975 to 24.5% (95%CI, 18.9-31.7) and 14.7% (95%CI, 10.6-20.1) in patients diagnosed in 1976-1990 and 1991-2005, respectively ($p=0.001$), supplement table 6.

Figure 4. The proportion of patients who underwent Crohn's disease related surgery in the cohorts.

In total, 14 (2.9%) patients were subject to permanent stoma formation during the 5-year follow-up, 5.1% in patients diagnosed 1963-1975, 1.7% in patients diagnosed 1976-1990 and 3.2% in patients diagnosed 1991-2005 ($p=0.332$).

Discussion

A reduction in surgical rates has been reported in Crohn's disease during recent decades, potentially due to increased use of immunomodulators and biologics (8, 15, 16). Especially early introduction of biologics seems to induce mucosal healing (17-20), thereby theoretically inhibiting progression towards complicated disease behaviour with strictures and fistulas and ultimately reducing the need of surgery. However, whether the observed decrease in surgery reflects entirely treatment effects remains largely unknown. In this large retrospective

population-based study of patients diagnosed with Crohn's disease in 1963-2005 we confirm that the proportion of patients undergoing surgery within five years from diagnosis has decreased over time. The reduction in surgery preceded the widespread use of immunomodulators as well as the introduction of biologics. In parallel with the drop in surgery rates, a reduction in the proportion of patients with complicated disease behaviour during follow-up was observed. The difference in surgery rates over time seemed to be driven primarily by a decrease in early surgery within three months from diagnosis, reflecting the increasing proportion of patients with non-stricturing, non-penetrating (B1) disease at diagnosis (13). These novel findings suggest that the introduction of new treatments alternatives alone do not explain the decreasing surgical rates in Crohn's disease. Differences in the phenotypic presentation over time may also have played an important role.

Historically, Crohn's disease has been associated with a pronounced risk of surgery, with almost all patients undergoing surgery in their lifetime (21-25). In our population-based cohort, the 5-year cumulative risk of Crohn's disease related surgery decreased from 65.8% to 34.6% in patients diagnosed 1963-1975 and 1991-2005, respectively. A similar trend has been observed in several other population cohorts like the Cardiff cohort, UK as well as in Denmark (2, 7), although some have reported unchanged rates (4, 26, 27). The decrease in surgery rates was mainly due to decreasing rates of hemicolectomies, small-bowel- and ileocaecal resections. In contrast, the proportion of patients undergoing colectomy remained low. According to linkage analyses of national Danish registries the 5-year cumulative risk of intestinal resection has decreased from 44.7% to 19.6% in patients diagnosed 1979-1986 and 2003-2011, respectively (2). Similar to other studies (3, 7, 8), we observed an increased use and a decreased time to initiation of immunomodulators during the study period. However, the use of immunomodulators did not increase until the last cohort, that is patients diagnosed 1991-2005, where the 5-year cumulative probability of treatment with immunomodulator was

37.7% compared with around 7% in patients diagnosed 1963-1990. In contrast, the 5-year cumulative risk of surgery dropped already in the cohort of patients diagnosed 1976-1990. The decrease in surgery was not explained by an increased long-term corticosteroid use, since the 5-year cumulative probability of long-term corticosteroid treatment remained low (6-8%) throughout the study period. Higher rates of long-term corticosteroids have been reported from Cardiff, UK (29%) and Australia (59.2%), although the definition of long-term corticosteroids included budesonide, or was slightly different to our study (7, 15). It can only be speculated if improved registration of prescriptions might have introduced a time dependent bias, where the use of long-term corticosteroids is underestimated in the early cohorts, although all prescriptions should be documented in the medical notes according to Swedish law. In contrast, the reduction in surgery was largely explained by a decrease in early surgery, the 3 months cumulative risk of surgery decreased from 34.2% in patients diagnosed in cohort 1963-1975 to 24.5% and 14.7% in patients diagnosed in cohort 1976-1990 and 1991-2005, respectively. Similar figures for early surgery have been reported from New England USA, where 13.1% of patients diagnosed with Crohn's disease 1991-1997 had undergone surgical resections due to the disease within six months from diagnosis (28). Our data are also supported by the observed reduction in Crohn's disease related surgery rate within one year from diagnosis in the Copenhagen cohort, Denmark (29). In parallel with the drop in surgery a decrease in the 5-year proportion of patients with complicated disease behaviour, that is stricturing (B2) or penetrating (B3) disease was observed. At 5 years after diagnosis the proportions of patients with complicated disease behaviour were 54.4%, 44.2% and 33.3% in patients diagnosed 1963-1975, 1976-1990 and 1991-2005, respectively. Our data seem consistent with the data from Olmsted county, Minnesota where 33.7% of patients diagnosed with Crohn's disease in 1970-2004 had complicated disease behaviour at 5 years after diagnosis (30). Similarly, 49% of patients diagnosed 1990-1993 in the Inflammatory

Bowel South-Eastern Norway (IBSEN) cohort had complicated disease behaviour 5 years after diagnosis, although this figure included all patients with perianal fistulas (31). Interestingly, the relative proportion of patients with non-stricturing, non-penetrating (B1) disease at diagnosis who progressed to complicated behaviour was stable during our study period. Thus, the difference in disease behaviour over time was explained entirely by our previously reported increased proportion of patients in non-stricturing, non-penetrating (B1) status at diagnosis (13). Complicated disease behaviour is intimately associated with increased risk of surgery (32, 33). Therefore, it seems likely that the decrease in surgery rates, and specifically early surgery, is explained by the observed increasing proportions of patients with non-stricturing, non-penetrating (B1) disease at diagnosis (13). These findings probably reflect that patients are diagnosed earlier in their disease course today than in the past, and that this improves treatment outcomes in terms of surgery at five years after diagnosis. This theory is supported by the previous reported association between diagnostic delay and increased risk for surgery (12). Improved diagnostic procedures leading to the identification of a subset of patients with non-stricturing, non-penetrating disease and a milder disease course might also have played a role, since we previously observed an increasing incidence over time in the cohorts (13). Theoretically such a subgroup could have a very low need for surgery and might not have been diagnosed at such an early point in the disease course in the past. Increased access to specialist care within one year from diagnosis has also been associated with decreasing surgery rates over time (5), and might also have contributed to the decrease in surgery rates, since the number of specialists increased during the study period (data not shown). Older age at diagnosis has also been associated with a milder disease and less need of surgery (34). Therefore, the increase in non-stricturing, non-penetrating (B1) disease at diagnosis and the observed decrease in surgery within 5 years from diagnosis might be related to aging population structure. Together, these findings suggest that the introduction

of new treatment alternatives alone do not explain the decreasing surgical rates in Crohn's disease (35, 36), differences in disease phenotype at diagnosis, where patients seem to be diagnosed at an earlier stage, may also play an important role.

Permanent stoma formation is a consequence of severe longstanding treatment resistance, especially when accompanied by severe perianal disease, and a marker of decreased quality of life in Crohn's disease (37). No difference was observed in the 5-year proportion of patients who received a permanent stoma during the study period. This finding is supported by a previous French report, where the proportion of patients receiving a permanent stoma within 5 years from diagnosis was stable in patients diagnosed with Crohn's disease at Rothschild hospital between 1978 and 2003 (9). However, it can only be speculated if the duration of follow-up was too short to observe such a difference, since permanent stoma often reflects an end-stage of the disease (38). The proportion of patients that experienced progression from ileal or colonic disease to ileocolonic decreased during the study period. Theoretically, this temporal trend could be explained by improved clinical work-up at diagnosis and especially the introduction of new methods like magnetic resonance imaging, capsule endoscopy, ultrasound and high-resolution endoscopes. Alternatively, implementation of these techniques during follow-up, rather than at diagnosis, would have had the opposite effect, leading to a spurious indication of progression (39, 40). To reduce the risk of bias, due to the introduction of these novel techniques in different years, upper gastrointestinal disease (L4) was regarded as a modifier of disease location only and was not included in the definition of progression in disease location. The observed proportions of patients that progressed in disease location within five years from diagnosis are within the lower range of the Danish report (3), although the differences in definition of progression between studies complicate any comparisons. The proportions of patients that received anti-TNF therapy among patient diagnosed 2000-2005 were 2.0% and 8.4% at 1 and 5 years, respectively, from diagnosis and are lower than in some

earlier reports from referral centres. However, the time period represents the early years within the era of biologics, when the treatment strategies were yet to be established and biologics often introduced late during the disease course as a third-line treatment, and other population-based studies from these years have revealed similar figures (2, 5, 7, 8). Therefore, the study was not designed to address the question of disease modification due to anti-TNF therapy.

The strengths of our study include the strict population-based design, allowing almost complete follow-up, and the thorough scrutiny of each patient's medical notes, providing information on disease phenotype, medical and surgical history at an individual level. The retrospective design is a potential limitation of the study. All diagnoses were re-assessed to reduce the risk of bias due to historical differences in diagnostic procedures and management. However, differential bias by period might still have occurred, since perception of symptoms qualifying for referral to the Department of Gastroenterology might have differed over time (41, 42). Furthermore, completeness in registration of patients with Crohn's disease may differ the cohorts, since computerised search of records was available from 1988 and onwards only. Prescription dates do not necessarily reflect drug intake, therefore, start and termination dates might reflect approximate dates. Our study reports trends over time rather than associations between specific medications and outcomes like Crohn's disease related surgery or progression in disease behaviour. This was not performed as such analyses are prone to influence of confounding by indication, where patients with most severe disease course are those treated most aggressively.

In this large population-based study we observed a decrease in surgery and complicated disease behaviour as well as an increase in the use of immunomodulators at five years after diagnosis over time. The decrease in surgery and complicated disease behaviour preceded the increased use of immunomodulators and seemed to be explained by a decrease in early

surgery within three months from diagnosis, reflecting the increasing proportion of patients with non-stricturing, non-penetrating (B1) disease at diagnosis.

Our novel findings suggest that the introduction of new treatment alternatives alone do not explain the decreasing surgical rates in Crohn's disease, differences in disease phenotype at diagnosis, where patients seem to be diagnosed at an earlier stage, also play an important role.

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Supplementary data

Supplementary table 1. Proportion of patients and corresponding 95% CI with ileocolonic (L3) disease location in all patients irrespectively of location at diagnosis, and overall log-rank test of equality of survivor functions between study cohorts on diagnosis day, one and five years from diagnosis.

	On diagnosis day	1 year after diagnosis	5 years after diagnosis
Cohort 1963-1975	29.1% (20.4-40.5)	34.2% (24.9-45.8)	41.9% (31.9-53.6)
Cohort 1976-1990	23.4% (17.8-30.4)	24.0% (18.4-31.0)	26.5% (20.5-33.7)
Cohort 1991-2005	22.0% (17.1-28.1)	24.8% (19.6-31.1)	26.8% (21.4-32.2)
Total 1963-2005	23.8% (20.2-27.9)	26.2% (22.4-30.3)	29.3% (25.4-33.6)
Log-rank test	p = 0.444	p = 0.199	p = 0.029

Supplementary table 2. Proportion of patients and corresponding 95% CI with progression from ileal (L1) or colonic (L2) disease to ileocolonic (L3) location and overall log-rank test of equality of survivor functions between study cohorts, one and five years from diagnosis.

	1 year after diagnosis	5 years after diagnosis
Cohort 1963-1975	8.9% (3.8-20.1)	18.0% (10.1-30.9)
Cohort 1976-1990	0.8% (0.1-5.3)	3.9% (1.7-9.2)
Cohort 1991-2005	3.6% (1.6-7.9)	6.1% (3.3-11.1)
Total 1963-2005	3.4% (2.0-5.9)	7.3% (5.0-10.6)
Log-rank test	p = 0.019	p = 0.002

Supplement table 3. Proportion of patients and corresponding 95% CI with complicating (stricturing or penetrating) disease, irrespective of disease behaviour at diagnosis, and overall log-rank test of equality of survivor functions between study cohorts on diagnosis day, one and five years from diagnosis.

	On diagnosis day	1 year from diagnosis	5 years from diagnosis
Cohort 1963-1975	51.9% (41.4-63.2)	51.9% (41.4-63.2)	54.4% (43.9-65.6)
Cohort 1976-1990	41.1% (34.3-48.8)	42.3% (35.4-50.0)	44.2% (37.2-51.9)
Cohort 1991-2005	26.6% (21.3-33.0)	28.5% (23.0-35.0)	33.3% (27.4-40.0)
Total 1963-2005	36.2% (32.0-40.7)	37.5% (33.3-42.0)	40.9% (36.6-45.5)
Log-rank test	p < 0.001	p < 0.001	p = 0.002

Supplement table 4. Proportion of patients and corresponding 95% CI that developed complication (stricturing or penetrating disease whichever came first) in patients with non-stricturing non-penetrating disease at diagnosis, and overall log-rank test of equality of survivor functions between study cohorts one and five years from diagnosis.

	1 year	5 years
Cohort 1963-1975	0	5.3% (1.3-19.4)
Cohort 1976-1990	1.9% (0.4-7.5)	5.1% (2.2-11.9)
Cohort 1991-2005	2.5% (1.0-6.5)	9.0% (5.5-14.8)
Total 1963-2005	2.0% (0.9-4.4)	7.3% (4.8-10.9)
Log-rank test	p = 0.611	p = 0.435

Supplement table 5. Proportion of patients treated with immunomodulators with corresponding 95% CI and overall log-rank test of equality of survivor functions between study cohorts at 1 year and 5 years from diagnosis.

	1 year from diagnosis	5 years from diagnosis
Cohort 1963-1975	1.3% (0.2-8.7)	7.6% (3.5-16.1)
Cohort 1976-1990	1.2% (0.3-4.6)	7.2% (4.2-12.4)
Cohort 1991-2005	22.2% (17.3-28.4)	37.7% (31.6-44.7)
Total 1963-2005	10.9% (8.4-14.1)	21.3% (17.9-25.4)
Log-rank test	p < 0.001	p < 0.001

Supplement table 6. Proportion of patients and corresponding 95% CI of Crohn's disease related surgery and overall log-rank test of equality of survivor functions between study cohorts at 3 months, 1 year and 5 years from diagnosis.

	3 months from diagnosis	1 year from diagnosis	5 years from diagnosis
Cohort 1963-1975	34.2% (24.9-45.8)	51.9% (41.4-63.2)	65.8% (55.4-76.0)
Cohort 1976-1990	24.5% (18.9-31.7)	32.2% (25.8-39.7)	41.4% (34.4-49.2)
Cohort 1991-2005	14.7% (10.6-20.1)	22.6% (17.6-28.8)	34.6% (28.6-41.5)
Total 1963-2005	21.6% (18.2-25.6)	31.1% (27.1-35.5)	42.5% (38.1-47.1)
Log-rank test	p = 0.001	p < 0.001	p < 0.001

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