

Trends in Overall and Cause-Specific Mortality Among Patients With Inflammatory Bowel Disease From 1982 to 2010

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BACKGROUND & AIMS: Treatments for inflammatory bowel diseases (IBDs) such as ulcerative colitis (UC) and Crohn's disease (CD) have changed over time, with unclear effects on prognosis. We assessed overall and cause-specific mortality in a Danish cohort of patients with IBD during a 30-year time period. **METHODS:** We compared data from 36,080 patients with UC and 15,361 with CD, who were diagnosed in Denmark from 1982 to 2010, and compared them with data from 2,858,096 matched individuals from the general population (controls). Overall and cause-specific mortality were estimated by Cox regression analysis, adjusted for age, sex, disease duration, and known comorbidities before IBD diagnosis. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). **RESULTS:** Mortality greatly increased in the first year after individuals were diagnosed with IBD; intermediate-term and long-term mortalities increased by approximately 10% among individuals with UC and 50% among those with CD, compared with the general population. Compared with the time period of 1982-1989, overall mortalities decreased among patients diagnosed with UC from 1990 to 1999 (HR, 0.96; 95% CI, 0.90-1.02) and from 2000 to 2010 (HR, 0.88; 95% CI, 0.82-0.95). These reductions were mainly due to decreased mortality from colorectal cancer, gastrointestinal disorders, and suicide. For individuals with CD, mortality did not change among these time periods because of long-term increases in mortality from infections, cancer, respiratory diseases, and gastrointestinal diseases. **CONCLUSIONS:** In a Danish cohort, mortality from UC decreased from 1982 to 2010, largely because of reduced mortalities from gastrointestinal disorders and colorectal cancer. People with CD had 50% greater mortality than the general population, and this value did not change during this time period.

Keywords: Epidemiology; Death Rate; Complications; Colon Tumor.

Patients with inflammatory bowel disease (IBD), in particular Crohn's disease (CD), may have higher mortality than individuals without IBD.^{1,2} Meta-analyses of population-based cohort studies have revealed standardized mortality ratios (SMRs) of 1.1 (95% confidence interval [CI], 0.9-1.2) in ulcerative colitis (UC)² and 1.4 (95% CI, 1.3-1.5) in CD.¹ Patients with UC are at increased risk of dying of gastrointestinal diseases, nonalcoholic liver diseases, pulmonary embolisms, and respiratory diseases, counterweighted by decreased mortality from pulmonary cancer,² whereas patients with CD are at increased risk of dying of cancer, in particular pulmonary cancer, chronic obstructive pulmonary disease, gastrointestinal diseases, and genitourinary diseases.¹ However, these results apply

to cohorts of IBD patients diagnosed as far back as the 1940s and 1950s. Both overall and cause-specific mortality may have changed since then. Treatment of IBD is no longer characterized by exclusive use of salazopyrine, mesalamine, and local and systemic corticosteroids but also includes immunomodulatory agents, such as thiopurines, and tumor necrosis factor- α antagonists.³⁻⁵

Our aim was to study overall and cause-specific mortality in successive cohorts of patients diagnosed with IBD in Denmark from 1982 to 2010, a period characterized by noticeable changes in treatment of IBD.

Methods

Study Population

A national cohort of all individuals alive and residing in Denmark between 1982 and 2010 (on average 5.3 million) was established by use of the Danish Civil Registration System, a national demographic register with continuously updated information on sex, place of birth, address, marital status, and dates of immigration, emigration, and death for all Danish citizens.⁶ Coding of information in Danish registers and linkage between registers rely on a unique 10-digit personal identification number in use since April 1, 1968.

In the Danish National Patient Register, which contains complete information on nonpsychiatric inpatient hospitalizations in Denmark since 1977 and outpatient hospital contacts since 1995,⁷ we identified patients with a first hospital contact (as inpatients or, since 1995, patients treated in ambulatory outpatient settings) for IBD between 1982 (to allow for 5 years of information on comorbidities before diagnosis of IBD) and 2010. IBD patients were defined by a diagnosis of UC (International Classification of Diseases, eighth revision [ICD-8] codes 56319 or 56904 or tenth revision code group K51) or CD (ICD-8 codes 56300-56309 or ICD-10 code group K50). To avoid diagnostic ambiguity, we excluded patients recorded with a diagnosis of both UC and CD.

For each IBD patient, we randomly sampled 50 sex- and age-matched (born within ± 6 months from the IBD patient) control persons from the general population who were alive at the first recorded hospital contact for IBD in the matched case,

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; SMR, standardized mortality ratio; UC, ulcerative colitis.

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had no recorded history of IBD, and lived in the same municipality as the IBD patient at the time of IBD diagnosis.

Mortality and Causes of Death

Information on dates of death between January 1, 1982, and December 31, 2010, were obtained from the Civil Registration System. Information about specific causes of death within the same period were obtained from the Danish Register of Causes of Death.⁸

Statistical Analyses

Relative mortality after a diagnosis of IBD was estimated in a matched cohort design. For IBD patients and matched controls, we defined the index date as the date of first IBD hospitalization in the IBD patient. The risk of death in IBD patients as compared with matched controls was estimated by hazard ratios (HRs) obtained in Cox proportional hazard models where each stratum was defined by 1 IBD patient and then corresponding up to 50 control persons (1.2% had less than 50 controls). Time since index date was used as the underlying time scale. All persons were followed from index date until date of emigration, death, or end of the study (December 31, 2010). We estimated HRs (with 95% CIs) for overall mortality, gender-specific mortality, age-specific mortality, calendar period-specific mortality, and cause-specific mortality, with adjustment for gender (male/female), age, calendar time, disease duration for gender (male/female), age, calendar time, disease duration (all as continuous variables), and comorbidities before IBD diagnosis. Comorbidities were determined by using the method of Charlson et al.⁹ We distinguished between comorbidities occurring in the last year and those occurring 1–5 years before the first IBD hospitalization. Furthermore, we allowed each of the diseases to have a time-dependent effect on the log (HR) parameterized by an intercept and a slope parameter (one for each of the two periods, <1 year and 1–5 years before the index date). Hence, the total comorbidity adjustment consisted of 4 parameters.

HRs of dying according to duration of IBD were presented graphically by using restricted cubic splines.¹⁰ All analyses were performed by using SAS v9.3 (SAS Institute, Cary, NC).

Table 1. Characteristics of Patients With UC and CD, Denmark 1982–2010

	UC, n	CD, n
Sex		
Female	19,160	8806
Male	16,920	6555
Total	36,080	15,361
Age at IBD diagnosis (y)		
0–19	2609	2425
20–39	12,526	6104
40–59	10,242	3540
60–79	8707	2607
80+	1996	685
Calendar period at IBD diagnosis		
1982–1989	4868	2691
1990–1999	11,023	4858
2000–2010	20,189	7812

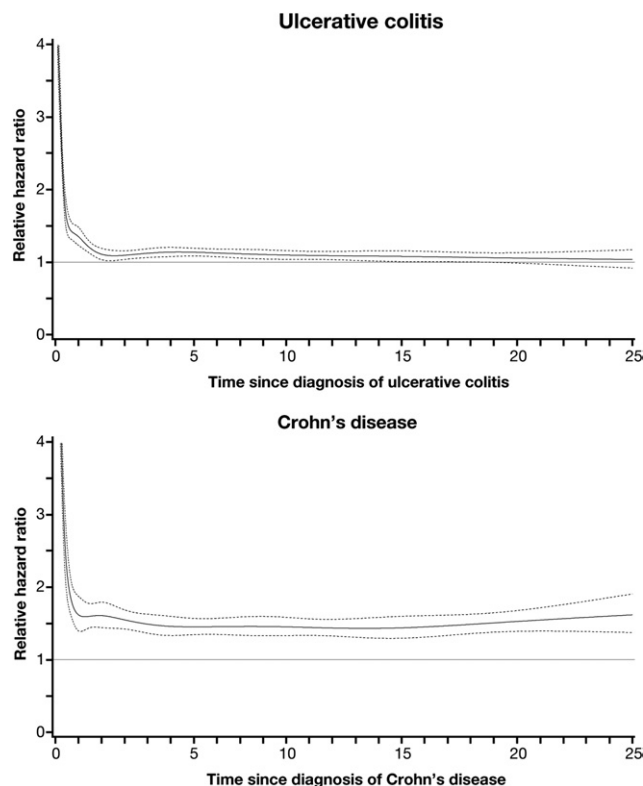


Figure 1. Relative HR for death by time since diagnosis of UC (upper panel) or CD (lower panel). Estimates are adjusted for age, sex, and calendar time. Broken lines indicate 95% CIs.

Ethics

The study was register-based and followed the regulations and instructions set up by the Danish Data Protection Agency (approval no. 2008-41-2374).

Results

From 1982 to 2010, 36,080 individuals were diagnosed with UC (median age, 45.2 years; 53% women), and 15,361

Table 2. Relative Mortality in Patients With IBD in Denmark (1982–2010) According to Sex, Age, and Calendar Period of IBD Diagnosis

	UC, HR (95% CI)	CD, HR (95% CI)
Sex		
Female	1 (reference)	1 (reference)
Male	0.91 (0.86–0.95)	0.86 (0.80–0.93)
Age at IBD diagnosis (y)		
0–19	2.15 (1.67–2.76)	1.62 (1.25–2.09)
20–39	1.07 (0.97–1.19)	1.31 (1.16–1.50)
40–59	1.05 (0.99–1.12)	1.35 (1.23–1.48)
60–79	1 (reference)	1 (reference)
80+	0.82 (0.77–0.88)	0.61 (0.54–0.68)
Calendar period of IBD diagnosis		
1982–1989	1 (reference)	1 (reference)
1990–1999	0.96 (0.90–1.02)	1.02 (0.93–1.12)
2000–2010	0.88 (0.82–0.95)	1.01 (0.91–1.13)

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