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Overall and Cause-Specific Mortality of Inflammatory Bowel Disease in Olmsted County, Minnesota, From 1970 through 2016

Satimai Aniwan, M.D.^{a,c}, W. Scott Harmsen, M.S.^b, William J. Tremaine, M.D.^a, Sunanda V. Kane, M.D.^a, and Edward V. Loftus Jr., M.D.^a

^aDivision of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA ^bDivision of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA ^cDivision of Gastroenterology, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Abstract

Objective: To determine the mortality of Crohn's disease (CD) and ulcerative colitis (UC) and temporal trends in mortality.

Patients and Methods: All 895 residents of Olmsted County, Minnesota, U.S.A., first diagnosed with inflammatory bowel disease (IBD) (411 CD, 484 UC) between January 1, 1970 and December 31, 2010 were followed through June 30, 2016. Standardized mortality ratios (SMR) were computed—expected rates were derived from the US 2010 background population. To determine overall and cause-specific mortality, each IBD patient was matched with five county residents, and Cox regression analysis was used to assess time to death.

Results: A total of 895 IBD patients and 4475 non-IBD patients were included. Seventy-four CD patients died compared with 59.2 expected (SMR, 1.25; 95%confidence interval [CI], 0.98-1.57), and 77 UC patients died compared with 108.1 expected (SMR, 0.71; 0.56-0.89). In CD, the risk of dying was significantly associated with calendar period of diagnosis 1970-79 (SMR, 1.90; 1.24-2.78). Among those diagnosed after calendar period of 1980, the risk of dying in CD patients

Corresponding Author: Edward V. Loftus, Jr., M.D., Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester MN 55905, USA, Loftus.Edward@mayo.edu.

Author contributions:

- Satimai Aniwan: writing the proposal, submitting the proposal to Institutional Review Board, collection of the data, and drafting of the manuscript.
- W. Scott Harmsen: matching controls and statistical analysis.
- William J. Tremaine: critical revision of the manuscript.
- Sunanda V. Kane: critical revision of the manuscript.
- Edward V. Loftus, Jr.: the conception and design of the study, interpretation of data, critical revision of the manuscript.

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was similar to the US background population. In UC, the risk of dying was less than expected in all groups of calendar period of diagnosis. In the Cox regression analysis, overall mortality was not significantly higher among CD (HR, 1.26; 95% CI, 0.97-1.63) or UC patients (HR, 0.89; 0.70-1.14) compared to the comparison cohort. The risk of dying from digestive diseases (HR, 3.70; 95%CI, 1.24-11.0) and respiratory diseases (HR, 2.72; 1.36-5.44) was increased in CD but not UC.

Conclusion: In this cohort, overall mortality among CD patients diagnosed after calendar period of 1980 did not differ from that of the US background population. Overall mortality in UC patients diagnosed in the calendar period of 1970-2010 was lower than the expected mortality.

Keywords

Inflammatory bowel disease; Mortality; Epidemiology

INTRODUCTION

Over the last two decades, the management of inflammatory bowel disease (IBD) has changed substantially due to increased use of immunomodulators, earlier introduction of biologic agents, improvements in surgical techniques, and increased awareness of colorectal cancer (CRC) surveillance.^{1,2} On the other hand, some of the medications used to treat IBD may cause serious adverse effects such as an increased risk of serious infection or malignancy.³⁻⁵ Thus, the impact of more effective management of IBD on the “hard endpoint” of mortality remains unknown.

The overall impact of IBD on long-term mortality in IBD varies worldwide. Recently, studies from the Netherlands⁶, Norway⁷, Australia⁸, and Korea⁹ demonstrated that mortality in Crohn’s disease (CD) and ulcerative colitis (UC) were comparable to their respective general populations. In contrast, population-based studies in Canada¹⁰, Denmark¹¹ and Finland¹² reported that all-cause mortality in IBD was increased among patients with CD and among those with UC.^{10,12} In addition, data regarding mortality trends over time vary from country to country. A nationwide Danish study of mortality trends from 1982 to 2010 showed that the mortality in patients with UC decreased, but the mortality trend in CD remained stable over the study period.¹³ In contrast, a study from Canada reported a decreasing mortality trend in both CD and UC between 1999 and 2008.¹⁰ One potential explanation for this variation in results could be different study designs. Thus, a population-based cohort in a well-defined geographic area targeting incident cases and following the natural history would be useful in studying long-term mortality and temporal trends.

The mortality of a population-based cohort of IBD patients from Olmsted County, Minnesota that had been diagnosed between 1940 and 2001 has been previously reported.¹⁴ Although not statistically significant, mortality in CD patients was higher than the expected US white population (standardized mortality ratio [SMR], 1.2; 95% confidence intervals [CI], 0.9-1.6). The overall survival of patients with UC was similar to or better than the expected US white population (SMR, 0.8; 95% CI, 0.6-1.0).¹⁴ After a period of improvement in the management of IBD, a more recent study of changes in mortality over time in a United States population-based IBD cohort has not been performed. The aim of

this study was to re-evaluate overall mortality and temporal trends in this population-based cohort of IBD patients.

METHODS

Rochester Epidemiology Project

The resources of the Rochester Epidemiology Project (REP) were used to identify permanent residents of Olmsted County, Minnesota, who were diagnosed with IBD. This unique medical records linkage system was developed in the 1960s and has been continuously funded by the National Institutes of Health since its inception.¹⁵ It exploits the fact that virtually all of the health care for the residents of Olmsted County is provided by two organizations: Mayo Medical Center, consisting of Mayo Clinic and its two affiliated hospitals (Rochester Methodist and St. Marys), and Olmsted Medical Center, consisting of a smaller multispecialty clinic and its affiliated hospital (Olmsted Community Hospital). In any four-year period, over 95% of county residents are examined at either one of the two health care systems.^{16,17} Diagnoses generated from all outpatients visits, emergency room visits, hospitalizations, nursing home visits, surgical procedures, autopsy examinations, and death certificates are recorded in a central diagnostic index. Thus, it is possible to identify all diagnosed cases of a given disease for which patients sought medical attention.¹⁷

Case Ascertainment

The institutional review boards of both Mayo Clinic and Olmsted Medical Center approved the protocol. The study cohort comprised 895 Olmsted County residents first diagnosed with IBD between January 1, 1970 and December 31, 2010 according to well-defined criteria as previously described.^{18–21} All patients were followed from diagnosis until death, emigration or the end of the study (June 30, 2016), whichever came first. For all deceased patients, death certificates were retrieved in order to identify cause of death based on the International Classification of Diseases (ICD-10), and medical records were reviewed to confirm the cause of death. To determine death related to IBD, two gastroenterologists (E.V.L. and S.A.) discussed all cases. The following data were recorded: date of birth, sex, date of IBD diagnosis, IBD phenotype at diagnosis, date of last follow-up, date of death and cause of death.

Statistical Analysis

Overall survival in the cohort was estimated using the Kaplan-Meier method. Overall mortality risk was calculated in two ways. SMRs (observed deaths/expected) were computed—expected deaths were derived from age- and sex-specific mortality rates in the US 2010 background population according to the United States Census Bureau. The SMR analysis was stratified by sex, age group at IBD diagnosis (0-18 years, 19-29 years, 30-49 years, 50 years) and calendar-period of IBD diagnosis (1970-79, 1980-89, 1990-99 and 2000-10). Secondly, to evaluate overall and cause-specific mortality in the cohort, each IBD patient was age-, sex- and index date of IBD diagnosis-matched with five Olmsted County residents who did not have IBD. We chose 5 matched comparisons for each case to improve statistical power; however, after 4 or 5 comparisons, not much incremental statistical power is gained by additional comparisons. Cox proportional hazard regression analysis was used to assess

the association of IBD with the risk of overall and cause-specific death and expressed in hazard ratios (HR) with 95% CI. An alpha- level of 0.05 was considered statistically significant.

RESULTS

A total of 895 incident IBD patients were followed for a total of 16,728 person-years, with a median follow-up time of 19 years (interquartile range [IQR], 10-27 years). Four hundred eleven patients with CD contributed a total of 7,540 person-years of observational time, with a median follow-up of 18 years (IQR, 10-26 years). Four hundred eighty-four patients with UC were observed for 9,188 person-years, with a median follow-up of 19 years (IQR, 10-27 years). Demographic data are shown in Table 1.

Overall Mortality

Crohn's disease—A total of 74 deaths occurred in 411 CD patients compared with 59.2 expected (SMR, 1.25; 95% CI, 0.98-1.57). The crude mortality rate of CD patients diagnosed in the calendar periods of 1970-2010 was 9.8 cases per 1000 person-years. The estimated overall survival of CD patients was 93% after 10 years, 83% after 20 years, 77% after 30 years and 61% after 40 years (Figure 1A). Although not statistically significant, thirty-eight men died compared with 29.6 expected (SMR, 1.28; 95% CI, 0.91-1.76) and 36 women died compared with 29.6 expected (SMR, 1.22; 0.85-1.68). Mortality risk stratified by age at CD diagnosis was not significantly different (Table 2).

When SMRs were stratified by calendar year at diagnosis, an increased mortality risk in CD patients diagnosed in the calendar period of 1970-79 was observed (SMR, 1.90; 95% CI, 1.24-2.78). Thereafter, the mortality risk in CD patients did not differ from that of the US background population (Table 2). Using the SMR in 1970-79 calendar period as a reference, CD patients diagnosed in 1990-99 had a significantly decreased risk of dying ($P=.04$) (Figure 1B).

Ulcerative colitis—Among 484 UC patients, 77 deaths were observed, significantly less than the 108.1 expected deaths of the US background population (SMR, 0.71; 95% CI, 0.56-0.89). The crude mortality rate of UC patients diagnosed in the calendar periods of 1970-2010 was 8.4 cases per 1000 person-years. The estimated overall survival of UC patients was 94% after 10 years, 86% after 20 years, 77% after 30 years and 60% after 40 years (Figure 1C). Stratifying SMR by sex showed significantly fewer observed deaths than expected among men (SMR, 0.70; 95% CI, 0.52-0.93). The mortality risk among women was the same as the US background population (SMR, 0.73; 95% CI, 0.48-1.05). The mortality risk stratified by age at UC diagnosis was similar to the US background population (Table 2).

As stratified by calendar period at diagnosis, the risk of dying in UC patients among each calendar period was comparable to that of the US background population (Table 2). There were no statistically significant differences between any two of four period-specific SMRs ($P=.05$ for all six comparisons) (Figure 1D).

Cause-Specific Mortality

A total of 2055 county residents with non-IBD diagnosis were matched 5:1 with the 411 CD patients, with a median follow-up of 15 years (IQR, 7-24 years) after the index date. A total of 258 deaths occurred in the CD comparison cohort. Two thousand four hundred twenty county residents with non-IBD diagnosis were matched 5:1 with the 484 UC patients, with a median follow-up of 16 years (IQR, 7-25 years) after the index date. A total of 371 deaths occurred in the UC comparison cohort. There were no significant differences in all-cause mortality among CD patients and their comparisons (HR, 1.26; 95% CI, 0.97-1.63) and among UC patients and their comparisons (HR, 0.89; 0.70-1.14). Table 3 lists cause-specific mortality in the CD and UC cohorts. CD patients had a significantly increased mortality due to digestive diseases (HR, 3.70; 95% CI, 1.24-11.0) and respiratory diseases (HR, 2.72; 1.36-5.44) compared with their comparisons. In the UC cohort, no significant differences in death from any cause were observed (Table 3).

Inflammatory Bowel Disease-Related Mortality

Of the 74 deaths in CD cohort, 14 deaths (19%) were identified as CD-related. Seven patients died from infections related to complicating CD (intestinal fistulizing, perforation, or abscess), accounting for 9% of all deaths in CD patients. Of the 77 deaths in UC cohort, 13 deaths (17%) were identified as UC-related. Two patients died from CRC. Six patients died from primary sclerosing cholangitis related to UC (decompensated cirrhosis and cholangiocarcinoma), accounting for 8% of all deaths in UC patients.

DISCUSSION

This population-based inception cohort of patients first diagnosed with IBD between January 1, 1970 and December 31, 2010 and followed up through June 30, 2016 showed that the overall mortality among CD patients did not differ significantly from that of the US 2010 background population. The overall mortality among UC patients was lower than the expected mortality of the US 2010 background population. Mortality risks due to digestive diseases and respiratory diseases were significantly increased in CD but not in UC. Less than one fifth of all deaths could be attributed to CD and UC.

This present study showed that the overall mortality in CD patients diagnosed in the calendar periods of 1970-2010 were higher than these of the US general population and these of the Olmsted County residents; however, they did not reach statistical significance. An increased risk of dying from digestive diseases (HR, 3.70; 95% CI, 1.24-11.0) remained a significant cause-specific mortality in CD as our previous report of an earlier cohort.¹⁴ However, a change in an excess mortality due to respiratory diseases (HR, 2.72; 95% CI, 1.36-5.44) in CD patients was observed, which was not previously observed. CD-related mortality appeared to decrease from the previous report¹⁴ from 32% (18 deaths) to 19% (14 deaths). As the majority of CD-related deaths occurred in patients diagnosed in the calendar period of 1970-79 (8 deaths, 57%), the excess risk of dying in this period was also significantly observed. These findings may be explained by an improvement in CD management. Increased use and earlier introduction of immunomodulators during the disease course began to take place in the early 1990s, and biologic agents have been utilized

since 1998. Furthermore, a practice of regular CRC surveillance for IBD (especially UC) has been widespread since 1980. Another reason for temporal differences in mortality may be explained by the higher active smoking rate in the patients diagnosed in the 1970s compared to other calendar years. We found that one-third of CD patients diagnosed in the 1970s were active smokers, while the proportion of active smokers in the later calendar periods of diagnosis declined to less than one-fifth. Current smoking at the time of CD diagnosis is a predictor for unfavorable CD outcomes (e.g., major abdominal surgery).²² In addition, cigarette smoking can directly contribute to respiratory diseases. It is worth noting that stopping cigarette smoking may play a role for the improved CD-related mortality and overall survival as much as the improved IBD care.

In UC cohort, we found a significantly decreased overall mortality in UC patients as compared to the US background population (SMR, 0.69; 95% CI, 0.54-0.86), while overall UC mortality was comparable to that of Olmsted County residents without IBD (HR, 0.89; 95% CI, 0.70-1.14). A previous study from the REP has shown the generalizability of age- and sex- specific mortality rates in their findings to Olmsted County and the entire United States.¹⁷ However, residents aged 20-60 years of Olmsted County had lower mortality than the U.S. population.¹⁷ Since those ages are common in UC patients, it may in part explain the lower risk of dying in UC when compared to the US general population, but not Olmsted County population. The prevalence of UC-related death in the present study was 17% (13 deaths), which did not differ from the previous report's 19% (12 deaths). We found that only 2.7% (2 deaths) of deaths among UC patients were caused by CRC, and this low proportion of CRC death is in keeping with our prior report of 8% (5 deaths), as well as a population-based study from Denmark.¹¹ In contrast, the proportion of deaths from UC-related PSC increased from 8% (1 death) in our previous report to 46% (6 deaths) in this present study. This may explain why the overall UC-related death rate did not decrease.

Even though there are several studies reporting on IBD mortality from different geographic regions, one must be cautious in comparing results due to different study populations and study designs. For instance, population-based nationwide registry studies that rely on diagnostic and billing codes have limitations. Deaths caused by IBD could not be verified and included in gastrointestinal disease causes.^{10,12} On the other hand, hospital-based studies are subject to referral bias, because patients with more severe disease are more likely to seek medical attention at referral centers, and this could eventually lead to a higher mortality rate. In the European Collaborative study group on Inflammatory Bowel Disease (EC-IBD), the mortality risk among CD patients was 1.8-fold higher than that of the general population.²³ In addition, studies consisting of a mix of prevalent and incident cases would have selection bias for patients with milder disease, and this too could lead to a lower mortality rate. In a prevalence Australian IBD cohort, overall mortality in IBD was lower than expected (SMR, 0.85; 95% CI, 0.74-0.97).⁸

The main strength of this study is that all ascertainment of IBD cases were based on strict diagnostic criteria and were derived from a well-defined geographic region. Because of the medical record linkage system (REP), we were able to review all available patients' data from index date of IBD diagnosis until the end of the study period. All death certificates were retrieved and the cause of death related to IBD was verified by medical record review

rather than on administrative data. For the comparison of mortality between the IBD and non-IBD county cohorts, we had 80% power to detect HR of 1.52 for CD and 1.43 for UC ($\alpha = 0.05$). However, there are some limitations in this study. First, the relatively high white population in the region may limit the generalizability of these data to populations with more diverse ethnicity. Secondly, socioeconomic factors are associated with healthy lifestyle and accessibility to health care utilization. Olmsted County had more high school graduated residents and a higher median household income compared with that of the entire U.S. population.¹⁷ This may explain why middle aged county residents had a slightly lower mortality compared to the entire United States. Thirdly, the relatively small number of cause-specific deaths in our study may have contributed to the lack of statistical significance. Fourthly, we did not collect data on comorbidities which may have contributed to the risk of dying. Finally, the information on death certificates was verified by medical record review for cases but not for the comparison cohort; while this would not have affected the estimate of overall mortality risk, it may have affected calculations of cause-specific mortality.

In conclusion, this population-based cohort study revealed that the overall mortality among CD patients diagnosed after calendar period of 1980 did not differ from that of the US background population. The overall mortality in UC patients diagnosed in the calendar period of 1970-2010 was lower than the expected mortality. For cause-specific mortality, an increased risk of dying from digestive diseases and respiratory diseases were observed in CD, but there were no differences in cause-specific mortality in UC.

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Abbreviations:

CD	Crohn's disease
CI	confident interval
CRC	colorectal cancer
HR	hazard ratio
IBD	inflammatory bowel disease
IQR	interquartile range
PSC	primary sclerosing cholangitis
UC	ulcerative colitis
REP	Rochester Epidemiologic Project
SMR	standardized mortality ratio

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Figure 1:

(A) Observed and expected cumulative survival from time of diagnosis in the Crohn's disease cohort between 1970 and 2016; (B) Overall mortality in Crohn's disease patients according to calendar year of diagnosis; (C) Observed and expected cumulative survival from time of diagnosis in the ulcerative colitis cohort between 1970 and 2016; (D) Overall mortality in ulcerative colitis patients according to calendar year of diagnosis

Table 1:

Demographic characteristic of IBD cohort and comparison cohort

	Crohn's disease		Ulcerative colitis	
	CD cohort (n=411)	Comparison cohort (n=2055)	UC cohort (n=484)	Comparison cohort (n=2420)
Median age at index date^a, years (IQR)	30 (21-47)	29 (22-47)	35 (25-48)	35 (25-48)
Median duration of follow-up, years (IQR)	18 (10-26)	15 (7-24)	19 (10-27)	16 (7-25)
Sex (n, %)				
Women	206 (50%)	1030 (50%)	210 (43%)	1050 (43%)
Men	205 (50%)	1025 (50%)	274 (57%)	1370 (57%)
Smoking status at index date^a (n, %)				
Never smoker	257 (63%)	not available	315 (65%)	not available
Former smoker	79 (19%)	not available	81 (17%)	not available
Current smoker	75 (18%)	not available	88 (18%)	not available

CD = Crohn's disease; UC; ulcerative colitis; IBD = inflammatory bowel disease; IQR = interquartile range

^aIndex date was defined as date of IBD diagnosis for IBD patients or the assigned index date corresponding to the date of IBD diagnosis for matched comparisons.

Table 2:

Standardized mortality ratios for overall causes according to calendar period of diagnosis, age at diagnosis and gender among patients with Crohn's disease and ulcerative colitis

	Crohn's disease			Ulcerative colitis		
	Observed deaths	Expected deaths	SMR (95%CI) ^a	Observed deaths	Expected deaths	SMR (95%CI) ^a
Overall	74	59.2	1.25 (0.98-1.57)	77	108.1	0.71 (0.56-0.89)
Calendar period of diagnosis						
1970-1979	26	13.7	1.90 (1.24-2.78)^b	23	30.8	0.75 (0.47-1.12)
1980-1989	13	11.5	1.13 (0.60-1.93)	22	32.5	0.68 (0.42-1.02)
1990-1999	19	18.8	1.01 (0.61-1.58)	15	23.4	0.64 (0.36-1.06)
2000-2010	16	15.3	1.05 (0.60-1.70)	17	21.4	0.79 (0.46-1.27)
Age at diagnosis						
0-18	1	1.4	0.71 (0.02-3.98)	0	0.9	0.00 (0.00-4.10)
19-29	10	7.3	1.37 (0.66-2.52)	3	7.2	0.42 (0.09-1.22)
30-49	18	11.8	1.53 (0.90-2.41)	21	31.7	0.66 (0.41-1.01)
50	45	38.6	1.17 (0.85-1.56)	53	68.3	0.78 (0.58-1.02)
Gender						
Female	36	29.6	1.22 (0.85-1.68)	28	38.5	0.73 (0.48-1.05)
Male	38	29.6	1.28 (0.91-1.76)	49	69.6	0.70 (0.52-0.93)^c

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; SMRs = standard mortality ratios

^a Mortality was standardized to the US 2010 background population.

^b P=.001

^c P=.01

Table 3:

Overall and cause-specific mortality in the IBD cohort compared to the comparison cohort from Olmsted County residents without IBD

Cause of Death (ICD-10 code)	Cohort	Crohn's disease			Ulcerative colitis		
		Deaths	HR (95% CI)	P value	Deaths	HR (95% CI)	P value
All Cause							
	Non-IBD	258	1.0 (reference)	.08	371	1.0 (reference)	.37
	IBD	74	1.26 (0.97-1.63)		77	0.89 (0.70-1.14)	
Infection (A00-B99)							
	Non-IBD	5	1.0 (reference)	.57	4	1.0 (reference)	.94
	IBD	0	0.40 (0.02-9.62)		1	1.10 (0.12-9.81)	
Neoplasm (C00-D49)							
	Non-IBD	73	1.0 (reference)	.72	110	1.0 (reference)	.24
	IBD	18	1.10 (0.66-1.85)		19	0.75 (0.46-1.21)	
GI cancer (C15-C26)							
	Non-IBD	23	1.0 (reference)	.15	33	1.0 (reference)	.93
	IBD	9	1.77 (0.82-3.83)		8	1.03 (0.48-2.24)	
Respiratory cancer (C30-C39)							
	Non-IBD	18	1.0 (reference)	.32	21	1.0 (reference)	.12
	IBD	2	0.48 (0.11-2.06)		1	0.20 (0.03-1.50)	
Breast, soft tissue, bone cancer (C40-C50)							
	Non-IBD	6	1.0 (reference)	.27	11	1.0 (reference)	.77
	IBD	3	2.18 (0.55-8.73)		2	0.80 (0.18-3.60)	
Genitourinary cancer (C51-C68)							
	Non-IBD	8	1.0 (reference)	.47	20	1.0 (reference)	.80
	IBD	3	1.64 (0.43-6.18)		4	0.87 (0.30-2.55)	
Hematologic cancer (C81-D48)							
	Non-IBD	9	1.0 (reference)	.34	12	1.0 (reference)	.90
	IBD	0	0.23 (0.01-4.61)		3	1.08 (0.31-3.84)	
Neurological diseases (G00-G99)							
	Non-IBD	17	1.0 (reference)	.16	21	1.0 (reference)	.40
	IBD	0	0.12 (0.01-2.25)		3	0.60 (0.18-2.01)	
Circulatory diseases (I00-I99)							
	Non-IBD	80	1.0 (reference)	.06	117	1.0 (reference)	.87
	IBD	28	1.51(0.98-2.33)		28	1.04 (0.69-1.56)	
Respiratory diseases (J00-J99)							
	Non-IBD	21	1.0 (reference)		35	1.0 (reference)	

Cause of Death (ICD-10 code)	Cohort	Crohn's disease			Ulcerative colitis		
		Deaths	HR (95% CI)	P value	Deaths	HR (95% CI)	P value
	IBD	13	2.72 (1.36-5.44)	.005	11	1.34 (0.68-2.65)	.39
Digestive diseases (K00-K95)							
	Non-IBD	7	1.0 (reference)		11	1.0 (reference)	
	IBD	6	3.70 (1.24-11.0)	.02	5	1.98 (0.69-5.70)	.21
Genitourinary diseases (N00-N99)							
	Non-IBD	3	1.0 (reference)		5	1.0 (reference)	
	IBD	1	1.49 (0.15-14.28)	.73	2	1.67 (0.32-8.61)	.54

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; HR = hazard ratio; CI = confidence interval; ICD = international classification of disease