Hepatobiliary Cancer Risk in Patients with Inflammatory Bowel Disease: A Scandinavian Population-Based Cohort Study A C

Rune Erichsen[1,2], Ola Olén[3,4,5], Michael C. Sachs[3], Lars Pedersen[1], Jonas Halfvarson[6], Johan Askling[3], Anders Ekbom[3], Jonas F. Ludvigsson[7,8,9,10], and Henrik Toft Sørensen[1]

ABSTRACT

Background: Inflammatory bowel disease (IBD) has been associated with hepatobiliary cancer, but existing evidence is poor. We evaluated risk of death from hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (ECC) among patients with IBD.

Methods: This Swedish/Danish population-based cohort study (1969–2017) followed patients with IBD and 1:10 matched population comparators from their diagnosis/match date until death, emigration, or end of follow-up.

Results: Among the 97,496 patients with ulcerative colitis/963,026 comparators, we found 66/390 HCC-deaths, 120/173 ICC-deaths, and 91/220 ECC-deaths (median follow-up 10 years); the 10-year-mortality was 0.5‰ (per mille) for HCC, 0.6‰ for ICC, and 0.4‰ for ECC, which decreased to 0.3‰, 0.4‰, and 0.2‰, respectively, in 2003–2017. Overall hazard ratios (HR) were 1.83 [95% confidence interval (CI), 1.41–2.38] for HCC-, 7.33 (95% CI, 5.81–9.25) for ICC-, and 4.46 (95% CI, 3.49–5.70) for ECC-deaths. A total of 22/66 HCC-deaths, 87/120 ICC-deaths, and 55/91 ECC-deaths occurred among patients with ulcerative colitis with primary sclerosing cholangitis (PSC), corresponding to 10-year-mortality of 6.7‰, 26.2‰, and 17.2‰, respectively. Among 47,399 patients with Crohn's disease (median follow-up 11 years), 10-year-mortality from HCC ($n = 28$), ICC ($n = 28$), and ECC ($n = 24$) were 0.3‰, 0.1‰, and 0.3‰, respectively, and corresponding HRs were 1.96 (95% CI, 1.31–2.93), 3.33 (95% CI, 2.19–5.09), and 3.10 (95% CI, 1.97–4.87). One of 28 HCC-deaths, 14/28 ICC-deaths (10-year-mortality 19‰), and 12/24 ECC-deaths (10-year-mortality 14‰) occurred after PSC.

Conclusions: Risk of HCC-, ICC-, and ECC-deaths was low in patients with IBD and decreased over time. However, a large proportion of deaths occurred after PSC.

Impact: Guidelines on specific surveillance strategies for patients with IBD with PSC, but not those without PSC, are needed.

Introduction

Inflammatory bowel disease (IBD), that is, ulcerative colitis and Crohn's disease are widely acknowledged as risk factors for intestinal cancers. This is likely related at least in part to chronic inflammation (1–5). In up to 30% of patients with IBD, extraintestinal manifestations complicate the disease course and some manifestations may represent an underlying reason for the association between IBD and increased risk of extraintestinal cancer (1, 6). Especially primary sclerosing cholangitis (PSC) has been identified as a risk factor for hepatobiliary cancer (7, 8).

Although the relative risk of hepatobiliary cancer seems to be increased among patients with IBD (1, 3, 7, 9–16), existing evidence suggests that the overall absolute 10-year risk is lower than 1% (10). Despite this low absolute risk, updated detailed evidence about the association between IBD and hepatobiliary cancer is pivotal for several reasons. First, hepatobiliary cancer is associated with an extremely grave prognosis with median survival of less than one year (10, 17). Early detection of hepatobiliary cancer is crucial for potentially curative treatment (18). Second, much existing evidence is limited as it does not allow categorization of IBD or hepatobiliary cancer into subtypes, does not capture age of IBD onset, disease extent, duration, or severity of inflammation in IBD, and lacks valid information on PSC (1, 7, 9–16). Such data are important, as they may reveal subgroups of patients at particularly high cancer risk and may improve understanding of the disease. Third, there is a striking lack of updated evidence focusing on absolute risks. Hence, clinicians make decisions based on data that in some instances are more than 20 years old and often are expressed as relative risks. Updated evidence reflecting patients exposed to modern IBD treatment becomes important as improved treatment and healthcare could impact hepatobiliary cancer risk. Finally, existing evidence presents methodological challenges identical to those recently outlined for studies of colorectal cancer risk in patients with IBD (2, 5, 19). In particular, closer surveillance of patients with IBD, especially those with PSC, may lead to earlier hepatobiliary cancer diagnosis potentially introducing lead time bias in

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark. [2]Department of Surgery, Randers Regional Hospital, Randers, Denmark. [3]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. [4]Sachs' Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden. [5]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden. [6]Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden. [7]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden. [8]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden. [9]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, United Kingdom. [10]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

R. Erichsen and O. Olén contributed equally as co-authors of this article.

Corresponding Author: Rune Erichsen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, Aarhus N, 8200 Denmark. Phone: 45-8716-8201; Fax: 45-8716-7215; E-mail: re@clin.au.dk

studies of cancer incidence. In addition, as clinicians are well aware of hepatobiliary cancer as a complication of IBD, differential misclassification may be an issue. Evaluating risk of hepatobiliary cancer–related death rather than hepatobiliary cancer diagnosis may be one way to reduce these limitations. To our knowledge, no studies to date have addressed these methodological challenges.

In this context, we evaluated absolute and relative risk of hepatobiliary cancer–related death and hepatobiliary cancer diagnosis in Swedish and Danish patients with IBD using detailed, prospectively recorded, population-based data with long-term follow-up.

Materials and Methods

This binational cohort study was based on existing health registries. Both Sweden and Denmark have tax-supported healthcare providing equal access for all residents (20–22). Their combined population was 15.7 million in 2018 (10.1 million in Sweden and 5.6 million in Denmark). Data were linked among registries by using the unique personal identity numbers assigned to all residents in both countries. Lost-to-follow-up did not occur, as the unique personal identity numbers are used in all registries and population registries to keep track of emigration and vital status for all residents.

Patients with IBD

We identified patients with IBD from the Swedish and Danish national patient registries, as previously described (2, 5, 23–27). Data spanned January 1, 1969–December 31, 2017 (outpatient data since 2001) in Sweden and January 1, 1979–December 31, 2011 (outpatient data since 1995) in Denmark. In brief, IBD was defined as ≥2 records (inpatient or hospital-based outpatient) with a relevant International Classification of Disease (ICD) code or one ICD code plus a biopsy with morphology suggestive of IBD (Supplementary Table S1). We defined date of first IBD diagnosis as the date of the first record (diagnosis or biopsy) of IBD. However, to avoid immortal time bias, follow-up started on the date of the second record. The median time period between first and second record is between 0.04 and 0.9 years for 2003–2017 data (detailed data previously published; refs. 2, 5). Patients diagnosed with hepatobiliary cancer before the start of follow-up were excluded ($n = 66$). Patients with IBD were categorized according to subtype [ulcerative colitis, Crohn's disease, and unclassified IBD (IBD-U)], age at diagnosis (<18, 18 ≤ 40, 40 ≤ 60, and ≥60 years), maximum disease extent or location during follow-up according to the Montreal classification (Supplementary Table S2), and presence/absence of PSC or extraintestinal manifestations during follow-up (Supplementary Table S3). Of note, ICD-7/8 codes were non-specific for PSC. Relevant analyses thus started in 1987 in Sweden and in 1994 in Denmark, when ICD-9/10 codes became available. Finally, patients with IBD were categorized according to surgical treatment during follow-up (Supplementary Table S4).

General population cohort

For each IBD patient, we matched up to 10 comparators from the general population on age, calendar year, sex, and residence using data from the population registries (20, 21, 28). Each matched comparator had to be alive and free of IBD at start of follow-up (date of second diagnostic listing or biopsy for their matched case) and stopped contributing risk-time as a comparator in the event of a future IBD diagnosis date. As for patients with IBD, we excluded population comparators with hepatobiliary cancer before the date of start of follow-up.

Hepatobiliary cancer

The primary outcome measure was death from hepatobiliary cancer, as defined in the causes of death registries (Supplementary Table S5; refs. 29, 30). The secondary outcome was incident hepatobiliary cancer as captured in the cancer registries (31, 32). For both the primary and the secondary outcomes, hepatobiliary cancer was categorized according to subtypes, that is, hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (ECC; ref. 33).

Comorbidity

For patients with IBD and comparators from the general population, we identified comorbidities present before or at start of follow-up, including chronic hepatitis, liver cirrhosis, chronic alcoholism, diabetes, and chronic obstructive pulmonary disease (proxy for heavy smoking). Relevant ICD codes are listed in Supplementary Table S6.

Statistical analysis

We followed patients with IBD from the second IBD diagnosis or pathology report suggestive of IBD, and from the corresponding date in matched comparators until death from HCC, ICC, or ECC, death from other causes, emigration, or end of follow-up (December 31, 2017 in Sweden and December 31, 2011 in Denmark), whichever came first. For the secondary outcome, that is, incident HCC, ICC, or ECC, we followed patients until date of diagnosis, death, emigration, or end of follow-up. As a measure of absolute risk, we calculated 10-year cumulative incidence proportions of death from HCC, ICC, and ECC (restricted to cancers diagnosed after start of follow-up), treating death from other causes as a competing risk (34). Adjusted differences in cause-specific cumulative incidences were estimated using linear regression with pseudo-observations of the 10-year cumulative incidence as the outcome variable (35). We calculated crude incidence rates as the number of HCC, ICC, and ECC deaths divided by total follow-up time. In stratum-specific analyses (IBD extent, PSC, other extraintestinal manifestations, and surgery), follow-up started on the date of the corresponding first registry record of extent/PSC/extraintestinal manifestations/surgery for the patients with IBD and the same date for comparators. We also calculated hazard ratios (HR) with 95% confidence intervals (CI) using stratified Cox proportional hazard regression associating IBD with death from HCC, ICC, or ECC. We adjusted the HR of HCC death for chronic hepatitis, alcohol-related diseases (other than liver cirrhosis), diabetes, and chronic obstructive pulmonary disease (the latter as a suboptimal surrogate for smoking). We did not adjust for liver cirrhosis because this could be an intermediate between IBD and HCC death (mediated through PSC).

For our secondary outcomes, that is, incident HCC, ICC, and ECC, we used a methodology similar to that described previously for deaths from HCC, ICC, and ECC.

We also assessed time trends of hepatobiliary cancer risk by (1) calculating HRs for hepatobiliary cancer–related mortality and for hepatobiliary cancer diagnosis stratified by calendar period of first IBD diagnosis; (2) using different years for the end of follow-up; and (3) contrasting HRs for all years of follow-up (1969–2017) with HRs for all persons at risk during 2013–2017.

Results

We identified a total of 161,905 patients with IBD and 1,598,769 matched population comparators during the study period (**Table 1**). Among the patients with IBD, 60% had ulcerative colitis (median follow-up 10 years), 29% had Crohn's disease (median follow-up 11

Table 1. Characteristics of patients with IBD and general population comparators in Sweden (1969–2017) and Denmark (1979–2011).

	IBD	Population comparators
Total	161,905 (100)	1,598,769 (100)
Ulcerative colitis	97,496 (60.2)	963,026 (60.2)
Crohn's disease	47,399 (29.3)	468,032 (29.3)
IBD unclassified	17,010 (10.5)	167,711 (10.5)
Country		
Sweden	112,839 (69.7)	1,110,730 (69.5)
Denmark	49,066 (30.3)	488,039 (30.5)
Sex		
Female	82,023 (50.7)	811,135 (50.7)
Male	79,882 (49.3)	787,634 (49.3)
Age at first diagnosis (y)		
Median (IQR)	38 (26–56)	38 (25–56)
<18	15,031 (9.3)	149,761 (9.4)
≥18–<40	70,464 (43.5)	699,044 (43.7)
≥40–<60	42,708 (26.4)	421,612 (26.4)
≥60	33,702 (20.8)	328,352 (20.5)
Year of first IBD diagnosis		
2003–2017	73,617 (45.5)	731,778 (45.8)
1991–2002	52,959 (32.7)	523,952 (32.8)
1977–1990	29,082 (18.0)	283,751 (17.7)
1969–1976	6,247 (3.9)	59,288 (3.7)
Age at end of follow-up (y)		
Median (IQR)	56 (41–71)	57 (41–72)
<18	2,347 (1.4)	23,410 (1.5)
≥18 to <40	36,961 (22.8)	368,593 (23.1)
≥40 to <60	50,991 (31.5)	496,793 (31.1)
≥60	71,606 (44.2)	709,973 (44.4)
Length of follow-up (y)		
≥0 to <1	10,740 (6.6)	83,450 (5.2)
≥1 to <5	32,593 (20.1)	316,602 (19.8)
≥5 to <10	35,487 (21.9)	353,728 (22.1)
≥10 to <20	53,727 (33.2)	539,092 (33.7)
≥20	29,358 (18.1)	305,897 (19.1)
Extraintestinal manifestations		
Number classified	159,932	NA
Primary sclerosing cholangitis	4,320 (2.7)	NA
Other extraintestinal manifestations	21,167 (13.2)	NA
Heredity		
Hepatobiliary cancer in 1st degree relative	889 (0.5)	8,066 (0.5)
Comorbidities at start of follow-up		
Chronic hepatitis	1,351 (0.8)	9,337 (0.6)
Liver cirrhosis	1,973 (1.2)	7,502 (0.5)
Alcohol-related diseases other than cirrhosis	11,795 (7.3)	89,209 (5.6)
Type 1 and 2 diabetes	24,525 (15.1)	196,937 (12.3)
Chronic obstructive pulmonary disease	13,985 (8.6)	89,932 (5.6)
Surgery during follow-up		
Total colectomy	18,288 (11.3)	NA
Other intestinal resections	31,285 (19.3)	NA
Perianal surgery	7,566 (4.7)	NA

Abbreviations: IQR, interquartile range; NA, not applicable.

years), and 11% had IBD-U (median follow-up 8 years). The female/male ratio was roughly 1:1, and median age at first diagnosis/match date was 38 years. Among patients with IBD, 3% had PSC, 13% had other extraintestinal manifestations, 11% underwent a total colectomy, and 19% had other intestinal resections during follow-up. At start of follow-up, comorbidities were more prevalent among patients with IBD than among population comparators (**Table 1**). As expected given country size, we identified approximately two thirds of the binational study population in Swedish registries (see Supplementary Tables S7 and S8 for country-specific details).

Hepatocellular carcinoma

Among 97,496 patients with ulcerative colitis, we observed 66 deaths from HCC. This corresponded to a 10-year risk of death from HCC of 0.5‰ (0.5/1,000 patients; **Table 2**), compared with 0.3‰ among matched population comparators (risk difference 0.2‰; 95% CI, 0.1‰–0.4‰; **Fig. 1**). Although the 10-year risks of HCC death varied across subgroups of patients with ulcerative colitis (higher in males vs. females, in those with onset at age <60 years vs. those with onset at age ≥60 years, and in patients with extensive colitis vs. proctitis/left-sided colitis), the absolute risk was low for all subgroups

Table 2. Ten-year cumulative incidence proportion [per mille (‰)] of hepatobiliary cancer–related deaths in patients with ulcerative colitis.

	Hepatocellular carcinoma		Intrahepatic cholangiocarcinoma		Extrahepatic cholangiocarcinoma	
	Ulcerative colitis	Comparators	Ulcerative colitis	Comparators	Ulcerative colitis	Comparators
Total	0.5 (0.3–0.6)	0.3 (0.2–0.3)	0.6 (0.4–0.7)	0.1 (0.1–0.1)	0.4 (0.3–0.6)	0.1 (0.1–0.2)
Sweden	0.5 (0.3–0.7)	0.3 (0.2–0.3)	0.6 (0.4–0.8)	0.1 (0.1–0.2)	0.6 (0.4–0.8)	0.2 (0.1–0.2)
Denmark	0.5 (0.2–0.7)	0.2 (0.2–0.3)	0.4 (0.2–0.6)	0.1 (0.1–0.2)	0.1 (0.0–0.2)	0.1 (0.0–0.1)
Sex						
Female	0.2 (0.0–0.3)	0.1 (0.1–0.1)	0.3 (0.2–0.5)	0.1 (0.1–0.2)	0.3 (0.1–0.4)	0.1 (0.1–0.2)
Male	0.8 (0.5–1.0)	0.4 (0.3–0.5)	0.8 (0.5–1.0)	0.1 (0.1–0.1)	0.6 (0.4–0.9)	0.1 (0.1–0.2)
Age at first IBD diagnosis (y)						
<18	Too few events	Too few events	0.4 (0.0–0.9)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
18 to <40	0.1 (0.0–0.3)	0.0 (0.0–0.0)	0.4 (0.2–0.6)	0.0 (0.0–0.0)	0.4 (0.2–0.6)	0.0 (0.0–0.0)
40 to <60	0.8 (0.4–1.2)	0.3 (0.2–0.4)	0.6 (0.3–0.9)	0.1 (0.1–0.2)	0.5 (0.2–0.8)	0.1 (0.1–0.1)
≥60	0.8 (0.4–1.3)	0.8 (0.6–0.9)	0.9 (0.5–1.4)	0.4 (0.3–0.5)	0.6 (0.3–1.0)	0.5 (0.4–0.6)
Year of first diagnosis						
2003–2017	0.3 (0.1–0.4)	0.3 (0.2–0.4)	0.4 (0.2–0.7)	0.1 (0.1–0.2)	0.2 (0.1–0.4)	0.1 (0.1–0.2)
1990–2002	0.3 (0.1–0.5)	0.2 (0.2–0.3)	0.6 (0.3–0.8)	0.1 (0.1–0.2)	0.6 (0.3–0.8)	0.1 (0.1–0.2)
1977–1989	0.7 (0.3–1.2)	0.3 (0.2–0.4)	0.5 (0.2–0.9)	0.0 (0.0–0.1)	0.4 (0.1–0.7)	0.2 (0.1–0.2)
1969–1976	2.4 (0.6–4.2)	0.5 (0.2–0.8)	1.0 (0.0–2.2)	0.0 (0.0–0.1)	0.7 (0.0–1.6)	0.1 (0.0–0.2)
Montreal classification						
E1 (ulcerative proctitis)	0.0 (0.0–0.0)	0.3 (0.2–0.5)	0.1 (0.0–0.3)	0.2 (0.1–0.4)	0.3 (0.0–0.7)	0.1 (0.1–0.2)
E2 (left-sided colitis)	0.0 (0.0–0.0)	0.3 (0.1–0.4)	0.3 (0.0–0.7)	0.1 (0.0–0.2)	0.4 (0.0–0.8)	0.2 (0.1–0.3)
E3 (extensive colitis)	0.6 (0.3–0.8)	0.2 (0.2–0.3)	1.7 (1.3–2.2)	0.1 (0.1–0.2)	1.0 (0.6–1.4)	0.1 (0.1–0.1)
EX (extent not defined)	0.6 (0.2–1.0)	0.4 (0.3–0.4)	0.9 (0.5–1.4)	0.1 (0.1–0.2)	0.9 (0.4–1.3)	0.1 (0.1–0.2)
Extraintestinal manifestations						
Primary sclerosing cholangitis	6.7 (3.5–9.9)	0.3 (0.1–0.5)	26.2 (19.9–32.5)	0.1 (0.0–0.3)	17.2 (12.2–22.2)	0.1 (0.0–0.2)
Other extraintestinal manifestations	0.6 (0.0–1.1)	0.4 (0.2–0.5)	1.0 (0.3–1.8)	0.1 (0.0–0.2)	0.7 (0.1–1.3)	0.1 (0.0–0.2)
Surgery during follow-up						
Total colectomy	1.1 (0.5–1.7)	0.2 (0.1–0.3)	0.9 (0.3–1.5)	0.0 (0.0–0.1)	0.5 (0.1–0.9)	0.1 (0.0–0.2)
Other intestinal resections	1.0 (0.3–1.6)	0.1 (0.1–0.2)	0.6 (0.1–1.1)	0.0 (0.0–0.1)	0.9 (0.3–1.5)	0.1 (0.0–0.2)
Perianal surgery	0.0 (0.0–0.0)	0.2 (0.0–0.5)	Too few events	Too few events	Too few events	Too few events

Note: Numbers in parentheses are 95% confidence intervals.

(**Table 2**). Even among patients with ulcerative colitis with PSC, the 10-year risk of death from HCC was below 10‰. Of note, however, 22/66 deaths from HCC occurred in patients with ulcerative colitis with PSC. The overall adjusted HR for death from HCC was 1.53 (95% CI, 1.18–1.99) among patients with ulcerative colitis and 21.6 (95% CI, 10.8–43.2) among patients with ulcerative colitis with PSC.

Among 47,399 patients with Crohn's disease, we observed 28 deaths from HCC, resulting in a 10-year risk of 0.3‰, versus 0.2‰ among population comparators (**Table 3** and **Fig. 2**). The risk was generally lower than 1‰ for all subgroups (only one patient with PSC died from HCC-preventing statistical analysis). The overall adjusted HR for HCC death was 1.74 (95% CI, 1.16–2.60) among patients with Crohn's disease.

Only 14 HCC deaths occurred among patients with IBD-U. The limited power in this subanalysis prevented a detailed statistical analysis.

For our secondary outcome, HCC incidence, we generally observed patterns similar to those for death from HCC, although absolute risks were higher.

Intrahepatic cholangiocarcinoma

Among patients with ulcerative colitis, we observed 120 deaths from ICC, resulting in a 10-year risk of 0.6‰, versus 0.1‰ for the matched population comparators (risk difference 0.4‰; 95% CI, 0.3‰–0.6‰; **Table 2** and **Fig. 1**). As for HCC, we observed that the risk of death varied within subgroups of patients with ulcerative

colitis, but it remained low. As many as 87 out of 120 deaths from ICC occurred in patients with ulcerative colitis with PSC resulting in a 10-year risk of 26.2‰. The overall HRs for death from ICC were 7.33 (95% CI, 5.81–9.25) among all patients with ulcerative colitis and 334 (95% CI, 106–1,057) among those patients with ulcerative colitis with PSC.
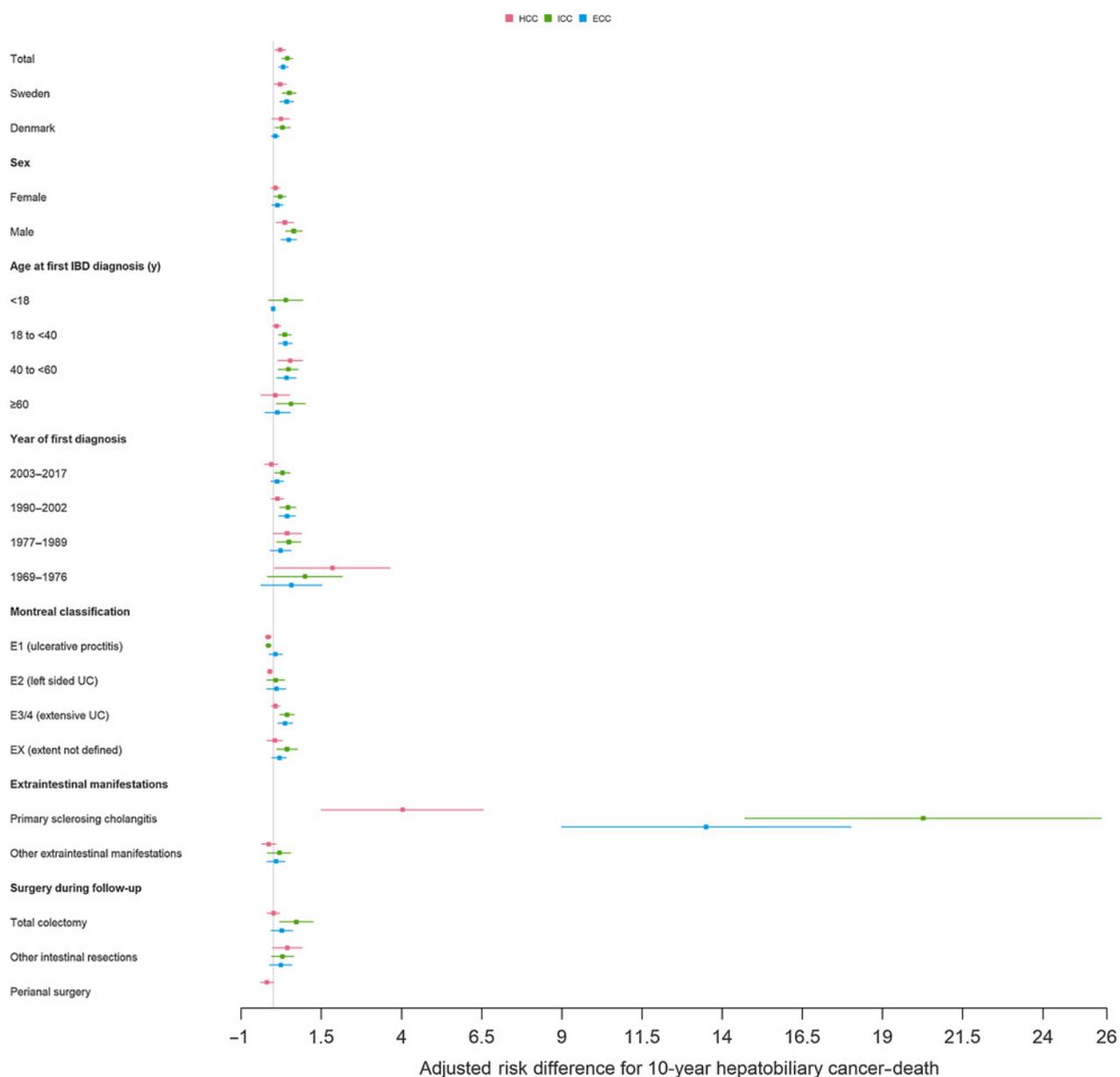
Among patients with Crohn's disease, we observed 28 deaths from ICC, corresponding to a 10-year risk of 0.1‰ (**Table 3** and **Fig. 2**). Among the 28 deaths, 14 deaths occurred in patients with Crohn's disease with PSC with a 10-year risk of 19.0‰ (**Table 3**). The overall HR for ICC death was 3.33 (95% CI, 2.19–5.09) for patients with Crohn's disease overall and as high as 58.6 (95% CI, 16.6–206) for patients with Crohn's disease with PSC. For patients with IBD-U, only 17 deaths from ICC were registered during follow-up, preventing a detailed subgroup analysis of the 10-year risk.

For the secondary outcome, that is, ICC incidence, we observed patterns similar to those for ICC death.

Extrahepatic cholangiocarcinoma

We observed 91 deaths from ECC in patients with ulcerative colitis, yielding a 10-year risk of 0.4‰. The 10-year risk was 0.1‰ for population comparators (risk difference 0.3‰; 95% CI, 0.2‰– 0.5‰; **Table 2**, **Fig. 1**). We also observed differences between subgroups of patients with ulcerative colitis, but the 10-year risk was below 1‰ except for patients with ulcerative colitis with PSC (17.2‰). Of note, 55 out of 91 deaths occurred in patients with ulcerative colitis with PSC. The overall HRs for ECC death were 4.46 (95% CI,

Erichsen et al.

Figure 1.
Risk differences [per mille (‰)] in the 10-year cumulative incidence of hepatobiliary cancer–related deaths in patients with ulcerative colitis compared with population comparators, Sweden (1969–2017) and Denmark (1979–2011). Abbreviation: UC, ulcerative colitis.

3.49–5.70) among patients with ulcerative colitis and 156 (95% CI, 56.4–430) among patients with ulcerative colitis with PSC.

Among patients with Crohn's disease, we observed 24 deaths from ECC, corresponding to a 10-year risk of 0.3‰ (**Table 3** and **Fig. 2**). A total of 12 out of 24 ECC deaths occurred in patients with Crohn's disease with PSC resulting in a 14.2‰ 10-year risk of ECC death. The overall HR for ECC death was 3.10 (95% CI, 1.97–4.87) in patients with Crohn's disease and 147 (95% CI, 19.1–1,140) for patients with Crohn's disease with PSC.

Among patients with IBD-U, only 14 deaths due to ECC were recorded.

Analyses for the secondary outcome of ECC incidence yielded results similar to those for death from ECC.

Time trends

Overall, the absolute risk of death from HCC, ICC, and ECC decreased over time particularly for ulcerative colitis, supported by the findings of lower absolute 10-year risks in most recent calendar periods (**Tables 2** and **3**), decrease in HRs over the different calendar periods of first IBD diagnosis (Supplementary Tables S9 and S10), the analyses using different years as end of follow-up (Supplementary Figs. S1 and S2), and by contrasting HRs for all years of follow-up with HRs

Table 3. Ten-year cumulative incidence proportion [per mille (‰)] of hepatobiliary cancer–related deaths in patients with Crohn's disease.

	Hepatocellular carcinoma		Intrahepatic cholangiocarcinoma		Extrahepatic cholangiocarcinoma	
	Crohn's disease	Comparators	Crohn's disease	Comparators	Crohn's disease	Comparators
Total	0.3 (0.1–0.5)	0.2 (0.2–0.3)	0.1 (0.0–0.2)	0.1 (0.1–0.1)	0.3 (0.1–0.5)	0.1 (0.1–0.1)
Sweden	0.4 (0.2–0.6)	0.2 (0.2–0.3)	0.2 (0.0–0.3)	0.1 (0.1–0.2)	0.3 (0.1–0.5)	0.1 (0.1–0.2)
Denmark	0.1 (0.0–0.2)	0.2 (0.1–0.2)	−0.0 (0.0–0.0)	0.1 (0.0–0.1)	Too few events	Too few events
Sex						
Female	0.0 (0.0–0.1)	0.2 (0.1–0.2)	0.1 (0.0–0.2)	0.1 (0.1–0.2)	0.2 (0.0–0.3)	0.1 (0.0–0.1)
Male	0.6 (0.2–1.0)	0.2 (0.2–0.3)	0.2 (0.0–0.4)	0.1 (0.0–0.1)	0.5 (0.2–0.8)	0.1 (0.1–0.2)
Age at first IBD diagnosis (y)						
<18	Too few events	Too few events	Too few events	Too few events	Too few events	Too few events
18 to <40	0.1 (0.0–0.3)	0.0 (0.0–0.1)	−0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.1 (0.0–0.3)	0.0 (0.0–0.0)
40 to <60	0.5 (0.1–0.9)	0.3 (0.2–0.4)	0.4 (0.0–0.9)	0.1 (0.0–0.2)	0.4 (0.0–0.8)	0.2 (0.1–0.2)
≥60	0.6 (0.0–1.2)	0.7 (0.5–0.9)	0.1 (0.0–0.4)	0.4 (0.2–0.5)	0.9 (0.2–1.7)	0.4 (0.2–0.5)
Year of first diagnosis						
2003–2017	0.1 (0.0–0.2)	0.3 (0.2–0.4)	0.2 (0.0–0.4)	0.1 (0.1–0.2)	0.2 (0.0–0.4)	0.1 (0.0–0.1)
1990–2002	0.4 (0.1–0.7)	0.1 (0.1–0.2)	0.2 (0.0–0.4)	0.1 (0.0–0.1)	0.5 (0.2–0.9)	0.1 (0.1–0.2)
1977–1989	0.4 (0.0–0.8)	0.2 (0.1–0.2)	−0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.1 (0.0–0.4)	0.1 (0.0–0.2)
1969–1976	0.8 (0.0–1.9)	0.5 (0.2–0.8)	−0.0 (0.0–0.0)	0.2 (0.0–0.4)	−0.0 (0.0–0.0)	0.2 (0.0–0.3)
Montreal classification						
L1 (ileal)	0.2 (0.0–0.5)	0.2 (0.1–0.3)	0.6 (0.2–1.1)	0.1 (0.0–0.2)	−0.0 (0.0–0.0)	0.1 (0.0–0.1)
L2 (colonic)	0.3 (0.0–0.6)	0.2 (0.1–0.3)	0.4 (0.0–0.7)	0.1 (0.1–0.2)	0.7 (0.2–1.2)	0.1 (0.0–0.1)
L3/LX (ileocolonic/not defined)	1.1 (0.5–1.7)	0.2 (0.1–0.3)	0.5 (0.1–1.0)	0.1 (0.1–0.2)	0.3 (0.0–0.7)	0.1 (0.1–0.2)
Extraintestinal manifestations						
Primary sclerosing cholangitis	Too few events	Too few events	19.0 (7.8–30.1)	0.2 (0.0–0.7)	14.2 (3.8–24.7)	0.2 (0.0–0.6)
Other extraintestinal manifestations	0.6 (0.0–1.2)	0.1 (0.0–0.2)	0.8 (0.0–1.5)	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.2 (0.0–0.3)
Surgery during follow-up						
Total colectomy	0.8 (0.0–1.8)	0.1 (0.0–0.2)	0.8 (0.0–1.9)	0.0 (0.0–0.0)	0.4 (0.0–1.2)	0.1 (0.0–0.2)
Other intestinal resections	0.1 (0.0–0.3)	0.2 (0.1–0.2)	−0.0 (0.0–0.0)	0.1 (0.0–0.1)	0.1 (0.0–0.3)	0.1 (0.0–0.1)
Perianal surgery	0.5 (0.0–1.2)	0.1 (0.0–0.2)	0.5 (0.0–1.1)	0.1 (0.0–0.2)	Too few events	Too few events

Note: Numbers in parentheses are 95% confidence intervals.

for all persons at risk during the last 5 years (2013–2017, Sweden only; **Table 4**).

Discussion

In this Scandinavian population-based cohort study—one of the largest and most comprehensive study of hepatobiliary cancer risk in patients with IBD to date—the absolute risks of HCC, ICC, and ECC were low. Even in the presence of PSC, which is known to be associated with a very high relative risk particularly of ICC, 10-year risks of death from HCC, ICC, or ECC did not exceed 30‰. Of note, however, between one third and two thirds of all hepatobiliary cancer–related deaths occurred in patients with IBD with PSC. In part because of the very low absolute risk of HCC, ICC, and ECC death in matched population comparators, HRs were markedly increased. We observed that the risk of HCC, ICC, and ECC decreased over the study period; this was most evident in patients with ulcerative colitis.

Our findings extend the literature in several ways. They provide updated evidence reflecting modern IBD healthcare and show that the risk of hepatobiliary cancer has decreased over time and is generally lower than in earlier reports, typically showing relative risk estimates in the range of 3–4 (1, 7, 9–16). We can only speculate about potential reasons for the decreasing risk over time, but improved IBD diagnosis and treatment is likely to be a key reason. Because of its cohort design with long-term follow-up, our study also permitted calculation of absolute 10-year risks rather than just relative risks. These data are of major importance for clinical decision-making and patient guidance because they support current clinical management without systematic

follow-up for hepatobiliary cancer in all patients with IBD. To our knowledge, our 2009 study of cholangiocarcinoma (CC) risk in patients with IBD (based on Danish data from 1978–2003) is the only previous study to provide estimates of 10-year risks (10). In that study, we reported that the 10-year risk of a CC diagnosis was 0.08% for patients with ulcerative colitis and 0.03% for patients with Crohn's disease. However, the study was too small to differentiate between ICC and ECC, did not include data on HCC, and did not evaluate risk of hepatobiliary cancer–related death. The present study is also the first to include estimates of hepatobiliary cancer–related death in addition to hepatobiliary cancer diagnoses. By including hepatobiliary cancer–related death as the primary outcome, we were able to reduce the risk of lead time bias.

Although existing evidence has established IBD as a risk factor for CC (7), it has been less clear that IBD also is a risk factor for HCC. Only studies that included HCC as part of the overall definition of primary hepatobiliary cancer have reported this risk (1, 16). Our current findings suggest that IBD might be a risk factor for HCC, although the magnitude of the association decreased over time. In addition, the association was most pronounced among patients with IBD with PSC, which is known to carry a risk of evolving into cirrhosis and thereby eventually HCC (36).

PSC has been suggested as a likely intermediary between IBD and CC risk (7, 8). Although we did not directly evaluate intermediate steps, our findings did show that a large proportion of hepatobiliary cancer–related deaths occurred in patients with IBD with PSC and that PSC in patients with IBD was associated with a particularly high CC risk. A recent study reported that prolonged duration of IBD was

Erichsen et al.
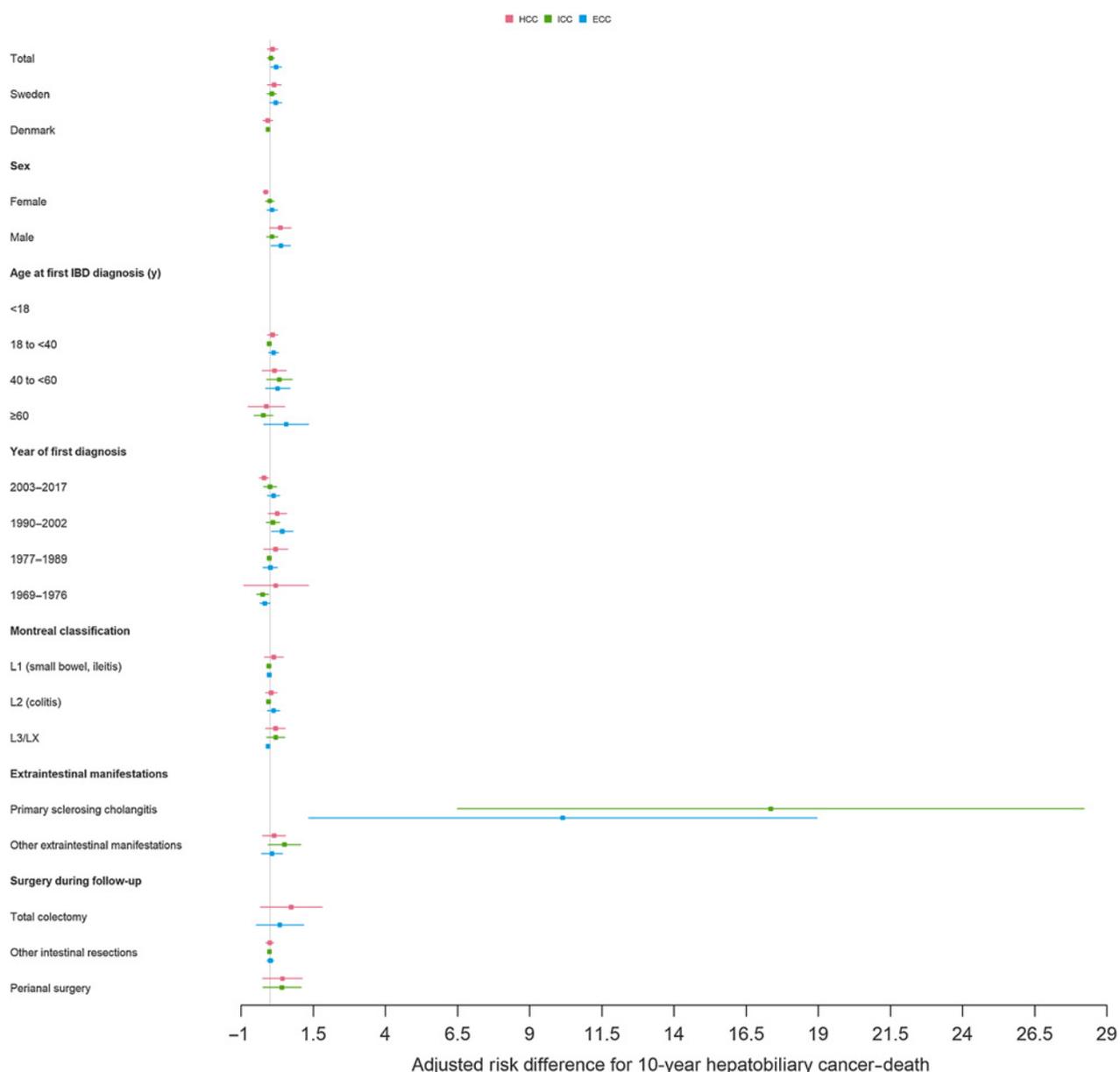
Figure 2.
Risk differences in 10-year cumulative incidence of hepatobiliary cancer–related death in patients with Crohn's disease compared with population comparators, Sweden (1969–2017) and Denmark (1979–2011).

associated with CC in patients with PSC (37% increased risk per 10 years of IBD presence; ref. 14), but other studies have not clearly demonstrated that IBD alters CC risk (37–39). The lifetime risk of CC in patients with PSC has been reported to range from 5% to 10%, which largely accords with our findings (33). International societies acknowledge that many clinicians offer surveillance with imaging and carbohydrate antigen 19–9 to patients with PSC because of the poor prognosis of CC. However, specific recommendations for surveillance are lacking due to paucity of evidence (40, 41). Because of the fairly large proportion of hepatobiliary cancers arising in patients with IBD with PSC, our study provides some support to the need for more evidence on specific surveillance strategies.

Methodological considerations

Our study's population-based cohort design within a setting (Sweden and Denmark) that provides free and equal access to healthcare essentially eliminated referral bias. Complete follow-up of all patients with IBD and population comparators prevented selection bias due to drop-outs. However, despite these strengths, our study also has limitations including the concern of misclassification. We used a validated method to identify patients with IBD (positive predictive value >90%; refs. 23, 25, 27), minimizing the risk of substantial exposure misclassification. Also, misclassification of the primary outcome, hepatobiliary cancer–related death, is a concern because causes of death data are known to be incomplete, and because liver

Table 4. Hepatobiliary cancer–related deaths during the last 5 years of the study (2013–2017, Sweden only) as opposed to the whole study period (1969–2017, Sweden only).

	2013–2017			1969–2017		
	IBD **n, IR (95% CI)**	**Population comparators** **n, IR (95% CI)**	**HR (95% CI)**	*IBD* *n, IR (95% CI)*	*Population comparators* *n, IR (95% CI)*	*HR (95% CI)*
Ulcerative colitis						
HCC	12, 0.05 (0.03–0.08)	107, 0.04 (0.03–0.05)	1.16 (0.64–2.10)	*53, 0.06 (0.05–0.08)*	*305, 0.04 (0.03–0.04)*	*1.89 (1.41–2.53)*
ICC	31, 0.12 (0.08–0.17)	72, 0.03 (0.02–0.03)	4.43 (2.91–6.75)	*100, 0.12 (0.10–0.14)*	*137, 0.02 (0.01–0.02)*	*7.75 (5.98–10.0)*
ECC	22, 0.08 (0.05–0.13)	67, 0.03 (0.02–0.03)	3.39 (2.09–5.48)	*86, 0.10 (0.08–0.12)*	*194, 0.02 (0.02–0.03)*	*4.78 (3.70–6.16)*
Crohn's disease						
HCC	8, 0.06 (0.03–0.11)	54, 0.04 (0.03–0.05)	1.57 (0.75–3.29)	*25, 0.05 (0.03–0.07)*	*137, 0.03 (0.02–0.03)*	*2.01 (1.31–3.08)*
ICC	9, 0.06 (0.03–0.12)	36, 0.02 (0.02–0.03)	2.71 (1.30–5.62)	*21, 0.04 (0.03–0.06)*	*82, 0.02 (0.01–0.02)*	*2.87 (1.78–4.64)*
ECC	6, 0.04 (0.02–0.09)	25, 0.02 (0.01–0.03)	2.56 (1.05–6.23)	*20, 0.04 (0.03–0.06)*	*83, 0.02 (0.01–0.02)*	*2.74 (1.68–4.46)*

Abbreviations: IR, incidence rate; *n*, number.

metastasis in some cases may have been misclassified as primary hepatobiliary cancers (29, 30). Nevertheless, because hepatobiliary cancer has a very poor prognosis, clinicians are likely to record hepatobiliary cancers as an underlying cause of death reducing the risk of highly incomplete data. In addition, if such misclassification differed among patients with IBD and their population comparators, it would underestimate HRs. Moreover, we cannot rule out that our findings of increased risk, particularly of HCC, may have been confounded by obesity, metabolic syndrome, smoking, and alcohol consumption. Unfortunately, we lacked information on these factors. As in all other observational studies, unknown confounding also may have affected our findings. However, a sensitivity analysis of the impact of unmeasured confounding showed that a confounder such as obesity would have to be both strongly associated with HCC (>2.0) and highly imbalanced between patients with IBD and the background populations (>60% prevalence difference) to lower the HR to 1.0, which is very unlikely. Finally, despite our study being the largest to date on hepatobiliary cancer risk in patients with IBD, we were challenged by sparse data issues that prevented us from examining hepatobiliary cancer risk in some subgroups of patients with IBD. We also did not include data on liver transplantation, and thus could not evaluate if some of the decrease in death from hepatobiliary cancer over time was caused by an increase in rate of liver transplantation in patients with PSC over time.

Conclusion

In summary, HRs for hepatobiliary cancer–related deaths were high in IBD and even higher in patients with IBD with PSC. However, absolute risks were very low for IBD overall and the 10-year risk of hepatobiliary cancer–related deaths was below 3%–5% also in patients with IBD with PSC. The absolute and relative risks of hepatobiliary cancer–related deaths in IBD have decreased over time. There is insufficient evidence to support recommendations of specific surveillance strategies for hepatobiliary cancers in patients with IBD with PSC.

Authors' Disclosures

Disclaimer

None of the funding organizations had any role in the design and conduct of the study; in the collection, management, and analysis of the data; or in the preparation, review, and approval of the article.

Authors' Contributions

R. Erichsen: Conceptualization, resources, data curation, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **O. Olén:** Conceptualization, data curation, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing–review and editing. **M.C. Sachs:** Conceptualization, data curation, formal analysis, investigation, visualization, writing–review and editing. **L. Pedersen:** Conceptualization, data curation, writing–review and editing. **J. Halfvarson:** Conceptualization, writing–review and editing. **J. Askling:** Conceptualization, writing–review and editing. **A. Ekbom:** Conceptualization, writing–review and editing. **J.F. Ludvigsson:** Conceptualization, data curation, funding acquisition, writing–review and editing. **H.T. Sørensen:** Conceptualization, data curation, funding acquisition, writing–review and editing.

Acknowledgments

Erichsen et al.

References

1. Kappelman MD, Farkas DK, Long MD, Erichsen R, Sandler RS, Sorensen HT, et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol 2014;12:265–73.
2. Olen O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet 2020;395:123–31.
3. Olen O, Askling J, Sachs MC, Frumento P, Neovius M, Smedby KE, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. BMJ 2017;358:j3951.
4. Bojesen RD, Riis LB, Hogdall E, Nielsen OH, Jess T. Inflammatory bowel disease and small bowel cancer risk, clinical characteristics, and histopathology: a population-based study. Clin Gastroenterol Hepatol 2017;15:1900–7.
5. Olen O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. Lancet Gastroenterol Hepatol 2020;5:475–84.
6. Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut 2006;55:i36–58.
7. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology 2011; 54:173–84.
8. Trivedi PJ, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, et al. Effects of primary sclerosing cholangitis on risks of cacner and death in people with inflammatory bowel disease, based on sex, race, and age. Gastroenterology. 2020; 159:915–28.
9. Huai JP, Ding J, Ye XH, Chen YP. Inflammatory bowel disease and risk of cholangiocarcinoma: evidence from a meta-analysis of population-based studies. Asian Pac J Cancer Prev 2014;15:3477–82.
10. Erichsen R, Jepsen P, Vilstrup H, Ekbom A, Sorensen HT. Incidence and prognosis of cholangiocarcinoma in Danish patients with and without inflammatory bowel disease: a national cohort study, 1978–2003. Eur J Epidemiol 2009; 24:513–20.
11. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case–control study. Clin Gastroenterol Hepatol 2007; 5:1221–8.
12. Welzel TM, Mellemkjaer L, Gloria G, Sakoda LC, Hsing AW, Ghormli El, et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case–control study. Int J Cancer 2007;120:638–41.
13. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors for intrahepatic cholangiocarcinoma in the United States: a case–control study. Gastroenterology 2005;128:620–6.
14. Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN. Duration of inflammatory bowel disease is associated with increased risk of cholangiocarcinoma in patients with primary sclerosing cholangitis and IBD. Am J Gastroenterol 2016;111:705–11.
15. Manninen P, Karvonen AL, Laukkarinen J, Aitola P, Huhtala H, Collin P. Colorectal cancer and cholangiocarcinoma in patients with primary sclerosing cholangitis and inflammatory bowel disease. Scand J Gastroenterol 2015;50: 423–8.
16. Jung YS, Han M, Park S, Kim WH, Cheon JH. Cancer risk in the early stages of inflammatory bowel disease in korean patients: a nationwide population-based study. J Crohns Colitis 2017;11:954–62.
17. Jepsen P, Andersen MW, Villadsen GE, Ott P, Vilstrup H. Time-trends in incidence and prognosis of hepatocellular carcinoma in Denmark: a nationwide register-based cohort study. Liver Int 2017;37:871–8.
18. Wang JH, Changchien CS, Hu TH, Lee CM, Kee KM, Lin CY, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma—Survival analysis of 3892 patients. Eur J Cancer 2008; 44:1000–6.
19. Adami HO, Bretthauer M, Emilsson L, Hernan MA, Kalager M, Ludvigsson JF, et al. The continuing uncertainty about cancer risk in inflammatory bowel disease. Gut 2016;65:889–93.
20. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.
21. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125–36.
22. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563–91.
23. Jakobsson GL, Sternegård E, Olén O, Myrelid P, Ljung R, Strid H, et al. Validating inflammatory bowel disease (IBD) in the Swedish national patient register and the Swedish quality register for IBD (SWIBREG). Scand J Gastroenterol 2017;52: 216–21.
24. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The danish national patient registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90.
25. Fonager K, Sorensen HT, Rasmussen SN, Moller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. Scand J Gastroenterol 1996;31:154–9.
26. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
27. Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980–2013: a nationwide cohort study. Aliment Pharmacol Ther 2017;45:961–72.
28. Heide-Jorgensen U, Adelborg K, Kahlert J, Sorensen HT, Pedersen L. Sampling strategies for selecting general population comparison cohorts. Clin Epidemiol 2018;10:1325–37.
29. Helweg-Larsen K. The danish register of causes of death. Scand J Public Health 2011;39:26–9.
30. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32:765–73.
31. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011;39:42–5.
32. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27–33.
33. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168–79.
34. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. The Annals of Statistics 1978;6:534–45.
35. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics 2005;61:223–9.
36. Harnois DM, Gores GJ, Ludwig J, Steers JL, LaRusso NF, Wiesner RH. Are patients with cirrhotic stage primary sclerosing cholangitis at risk for the development of hepatocellular cancer? J Hepatol 1997;27:512–6.
37. Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, et al. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case–control study. Hepatology 2000;31:7–11.
38. Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Danielsson A, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38:610–5.
39. Kornfeld D, Ekbom A, Ihre T. Survival and risk of cholangiocarcinoma in patients with primary sclerosing cholangitis. A population-based study. Scand J Gastroenterol 1997;32:1042–5.
40. Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut 2019; 68:1356–78.
41. European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237–67.

Cancer Epidemiology, Biomarkers & Prevention

Hepatobiliary Cancer Risk in Patients with Inflammatory Bowel Disease: A Scandinavian Population-Based Cohort Study

Rune Erichsen, Ola Olén, Michael C. Sachs, et al.

Updated version	Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-20-1241
Supplementary Material	Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2021/02/23/1055-9965.EPI-20-1241.DC1

Cited articles	This article cites 41 articles, 5 of which you can access for free at: http://cebp.aacrjournals.org/content/30/5/886.full#ref-list-1

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/30/5/886. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.