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Risk of hepato-pancreato-biliary cancer is increased by primary sclerosing cholangitis in patients with inflammatory bowel disease: A population-based cohort study

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Abstract

Background: There is continued uncertainty regarding the risks of hepato-pancreato-biliary cancers in patients with inflammatory bowel disease (IBD) with or without concomitant primary sclerosing cholangitis (PSC).

Objective: To give updated estimates on risk of hepato-pancreato-biliary cancers in patients with IBD, including pancreatic cancer, hepatocellular carcinoma, gall bladder cancer, and intra – and extrahepatic cholangiocarcinoma.

Methods: In a population-based cohort study, we included all patients diagnosed with IBD in Norway and Sweden from 1987 to 2016. The cohort comprised of 141,960 patients, identified through hospital databases and the National Patient Register. Participants were followed through linkage to national cancer, cause of

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death, and population registries. We calculated absolute risk and standardized incidence ratios (SIRs) of hepato-pancreato-biliary cancers by PSC and other clinical characteristics.

Results: Of the 141,960 IBD patients, 3.2% were diagnosed with PSC. During a median follow-up of 10.0 years, we identified 443 biliary tract cancers (SIR 5.2, 95% confidence interval [CI] 4.8–5.7), 161 hepatocellular carcinomas (SIR 2.4, 95% CI 2.0–2.7) and 282 pancreatic cancers (SIR 1.3, 95% CI 1.2–1.5). The relative risks were considerably higher in PSC-IBD patients, with SIR of 140 (95% CI 123–159) for biliary tract, 38.6 (95% CI 29.2–50.0) for hepatocellular, and 9.0 (95% CI 6.3–12.6) for pancreatic cancer. The SIRs were still slightly increased in non-PSC-IBD patients, compared to the general population. For biliary tract cancer, the cumulative probability at 25 years was 15.6% in PSC-IBD patients, and 0.4% in non-PSC-IBD patients.

Conclusions: The dramatically increased risks of hepato-pancreato-biliary cancers in PSC-IBD patients support periodic surveillance for these malignancies. While much lower, the excess relative risks in non-PSC-IBD patients were not trivial compared to non-IBD related risk factors.

KEYWORDS
biliary tract cancer, cholangiocarcinoma, hepato-pancreato-biliary cancer, hepatocellular carcinoma, IBD, inflammatory bowel disease, pancreatic cancer, primary sclerosing cholangitis, PSC, PSC-IBD

INTRODUCTION

Inflammatory bowel disease – including ulcerative colitis, Crohn's disease and unclassified IBD – is the most common non-malignant chronic disease affecting the gastrointestinal tract. The estimated prevalence of IBD exceeds 0.3% in North America and most countries in Europe.[1] There is a lack of robust epidemiological data on the risk of hepatocellular carcinoma and biliary tract cancer (with detailed classification) in IBD patients,[2,3] and inconsistent findings on the risk of pancreatic cancer.[4–6] Existing evidence from population-based studies[7] is characterised by older cohorts,[8] small cohorts,[9,10] lack of classification of extent of IBD[3] or information on PSC,[2,11] or no detailed classification of cancer outcomes.[12]

Hepato-pancreato-biliary cancers develop in the liver (mainly hepatocellular carcinoma), the intra- and extra-hepatic biliary ducts, or the pancreas. Despite of the low incidence rates (IRs) of hepato-pancreato-biliary cancers globally,[13] these cancers are associated with an extremely poor prognosis as they are often detected at advanced stages due to the paucity of symptoms at early stages. Early detection is therefore pivotal for potentially curative resection. Thus, identifying robust risk factors of hepato-pancreato-biliary cancer are important to guide surveillance strategies and increase survival of these malignancies.

Although the exact prevalence is unclear, approximately 2%–5% of patients with IBD develop PSC, a chronic disorder characterized by fibrotic biliary strictures, progressing to liver cirrhosis.[14] About 60%–80% of PSC patients have concomitant IBD.[15] PSC might be an independent risk factor for developing gastrointestinal malignancies and it has become increasingly clear that IBD co-existing with PSC may be distinct from IBD alone,[16] though the aetiology and pathogenesis of PSC remain unclear. Compared to IBD patients alone, patients with IBD and PSC experience a substantially higher excess risk of colorectal cancer,[17,18] but few studies of adequate size and design have provided precise long-term risk estimates of other gastrointestinal cancers in IBD.[19] Therefore, we aimed to investigate the absolute and relative risks of hepato-pancreato-biliary cancers in Norwegian and Swedish IBD patients with and without PSC in a large population-based study with long-term follow-up.

MATERIAL AND METHODS

Study population

Cohort members were identified from hospital databases across Norway and the National Patient Register in Sweden. We identified all patients with a first diagnosis of IBD from 1 January 1987 to 31 December 2015 in Norway, and to 31 December 2016 in Sweden. The individually unique national registration numbers assigned to all residents in Norway and Sweden enabled linkage to registries containing data on morbidity (Norway: hospital databases, Sweden: National Patient Register), cancer (Cancer Registry of Norway, The

Swedish Cancer Register), mortality (The Norwegian Cause of Death Registry, The Swedish Cause of Death Register), demographics and migration (Norway: The National Population Register, Sweden: The Total Population Register). Each patient was followed from date of IBD onset until cancer diagnosis, emigration, death, or end of follow-up (Norway: 31 December 2015; Sweden: 31 December 2016), whichever came first. Patients were not censored due to other cancer outcomes.

Exposure ascertainment

In both countries, in-patient diagnoses were collected during the whole study period. In Norway, out-patient diagnoses became gradually available in the hospital databases. In Sweden, out-patient data were only available starting in 2001; patients diagnosed up until 2003 therefore represent a mix of patients with incident and prevalent IBD (Figure S1). To increase specificity of disease classification, we required at least two hospital contacts, out-patient visits or hospital admissions with a diagnosis of IBD.[20]

We defined IBD subtypes using the first two diagnostic listings: Patients were classified as having ulcerative colitis (International Classification of Disease [ICD] version 9: 556, ICD-10: K51) or Crohn's disease (ICD-9: 555, ICD-10: K50) if their first two codes were for ulcerative colitis or Crohn's disease, respectively, and unclassified IBD if their first two codes were ICD-10 K523 or any combination of codes for ulcerative colitis, Crohn's disease, or indeterminate colitis. In all main analyses, the date of the second diagnostic listing was defined as date of IBD onset. We used the Montreal classification to define extent of disease during follow-up, using ICD-9 and ICD-10 codes (see Table S1 for details).[21] The most severe disease extension during follow-up was used to classify patients. Additionally, the IBD diagnosis definitions was validated in a subset of Norwegian patients, by comparing registry data to medical records (Table S2).

Outcomes

We used the nationwide cancer registers in Norway and Sweden to ascertain the main outcomes: biliary tract cancer (including intrahepatic cholangiocarcinoma [iCCA], extrahepatic cholangiocarcinoma [eCCA], gallbladder cancer [GBC], ampulla of Vater cancer, and unspecified/overlapped types), hepatocellular carcinoma, and pancreatic cancer (Table S3). The Norwegian cancer registry collects information reported by both clinicians and pathologists, and information on cancers from death certificates. The Swedish Cancer Register also collects information reported by both clinicians and pathologists. However, because cancers with a poor prognosis are less likely to be reported, a subset of cancers can only be identified from death certificates in Sweden.[22,23] To keep consistency between the two countries, we therefore excluded cancers which were only recorded from death certificates in Norway. In sensitivity analyses, we included cancers captured from both cancer and cause of death registries.

Key summary

Established knowledge:

- Patients with inflammatory bowel disease (IBD) and concomitant primary sclerosing cholangitis (PSC) have for long been recognised as having a particular increased risk of hepato-pancreato-biliary cancers.
- Previous estimates of the cancer risks in IBD patients with and without PSC have been limited due to the lack of large, population-based cohort studies with long-term follow-up.

New findings:

- We present a large bi-national population-based cohort study estimating risks of hepato-pancreato-biliary cancers in IBD patients with and without PSC.
- In PSC-IBD patients, we found, as expected, a significantly increased risk of hepato-pancreato-biliary cancers compared to the general population, with up to 140-fold increased risk for biliary tract cancer.
- Cumulative incidence was highest for biliary tract cancer, at more than 15% after 25 years in patients with PSC-IBD. These patients also had an increased risk of hepatocellular carcinoma and pancreatic cancer, with cumulative incidence of 3.7% and 2.3% after 25 years, respectively.
- In IBD patients without PSC, there was a more than two-fold increased risk of biliary tract cancer compared to the general population, but the cumulative incidence was lower than 1% after 25 years.

Other variables

We used hospital databases (Norway) and the National Patient Register (Sweden) to ascertain possible diagnosis of PSC using ICD codes (Norway: ICD-9 5761, ICD-10 K830; Sweden: ICD-8 57,505, ICD-9 576B, ICD-10 K830). In Norway, the PSC definition was validated using the patient registry of the Norwegian PSC Research Centre, which holds data on all PSC patients treated at the Norwegian tertiary referral centre for PSC at Oslo University Hospital, Rikshospitalet (https://www.ous-research.no/nopsc; Table S11). Information on liver transplantation in Norway was ascertained through the Nordic liver transplant registry, which holds all liver transplants performed in Norway (www.scandiatransplant.org).

Information on liver transplantation in Swedish IBD cohort was collected from the National Patient Register (surgery codes in Norway and Sweden: fifth and sixth revision [1963–1996] codes 5200/5202, seventh revision [1997-present] code JJC).

Statistical analysis

We calculated crude IRs for each cancer site and country, and IRs standardized to the age- and sex-structure of the Norwegian IBD cohort as of 1987. Cumulative probabilities were calculated by Kaplan-Meier method. The general population of Norway and Sweden served as reference, as reporting of all cases of cancer in the two countries is mandatory. Next, standardized incidence ratios (SIRs, the ratios of observed cancer cases divided by expected cancer cases in the population) with 95% confidence intervals (CIs) were calculated to estimate the relative risk of each cancer in IBD patients, compared to the general population in Norway and Sweden. The expected number was derived by multiplying the person-years at risk with country-, age- (5 year strata), sex-, and calendar year-specific IRs in the general population. We calculated SIRs totally and stratified by co-existing PSC (as a time-varying covariate), with different characteristics. Patients with PSC contributed person-time to the non-PSC group until the date of PSC diagnosis. Thus, patients could contribute person-time in both groups, depending on when they were diagnosed with PSC. Cochran-Armitage Trend test was used to evaluate cancer risks across age groups and follow-up years since IBD onset. Standardized incidence ratios using data from Norway and Sweden were analysed separately and combined. More details on sensitivity analyses are shown in Supporting Information. There was no missing data.

All analyses were performed using Stata software (Version 15.0; StataCorp, College Station, TX). Two-sided *p*-values <0.05 were considered statistically significant.

RESULTS

Overall risk of hepato-pancreato-biliary cancers in IBD patients

We included 141,960 IBD patients, 84,887 with ulcerative colitis, 45,077 with Crohn's disease, and 11,996 with unclassified IBD, with a mean age of 45.1, 41.1, and 43.7 years at IBD diagnosis, respectively (Table 1, Table S4). The total follow-up included 1,537,188 person-years, with a median follow-up of 10.0 years. Flowchart of patients included from Norway and Sweden is shown in Figure 1. Primary sclerosing cholangitis was diagnosed at baseline or during follow-up in 3.2% of all IBD patients. The mean time from IBD onset to first diagnostic listing of PSC was 6.8 years (standard deviation [SD] = 6.2).

We ascertained 443 biliary tract cancers, 161 hepatocellular carcinomas and 282 pancreatic cancers yielding crude IRs of 28.8, 10.5, and 18.3 per 100,000 person-years, respectively (Table 2). Patients with Crohn's disease had lower incidence of all three cancers than patients with ulcerative colitis and unclassified IBD. Moreover, IBD patients had a higher age- and sex-standardized IR of biliary tract cancer compared to the background population (Figures S2 and S3).

For biliary tract cancer, the relative risk was increased 5-fold (SIR 5.2, 95% CI 4.8–5.7). The risk increase was higher in males (SIR 7.7, 95% CI 6.9–8.6) than in females (SIR 3.1, 95% CI 2.6–3.6). The 2-fold increased risk of hepatocellular carcinoma (SIR 2.4, 95% CI 2.0–2.7) was similar in males and females but was higher in patients younger than 20 years at IBD diagnosis (trend test, *p*-value = 0.005). Risk of pancreatic cancer was only slightly increased (SIR 1.3, 95% CI 1.2–1.5). For both biliary tract and pancreatic cancer, SIRs were higher during the first year after IBD onset. After this first year, we observed no trend towards higher risk with longer follow-up for any cancer (Table 2).

Risk of hepato-pancreato-biliary cancers in IBD patients by PSC

Among the 4548 IBD patients with PSC, the mean age at PSC diagnosis was 40.2 years, 66.2% were male, and 72.8% were classified as having ulcerative colitis (Table 1). Crude IRs of PSC in the IBD cohort are shown in Figure S4. Table 3 shows that the crude IRs of three cancers in PSC-IBD patients are much higher than those in patients with IBD alone. The cumulative probability of each cancer was significantly higher in PSC-IBD patients than patients with IBD alone, with the 25 year cumulative probabilities of 15.6%, 3.7% and 2.3% for three cancers, respectively (Figure 2, Table S5).

Patients with both PSC and IBD diagnosed with biliary tract cancer were predominantly male with ulcerative colitis, with a high proportion of pancolitis during follow-up. These characteristics were not consistent in patients with hepatocellular carcinoma or pancreatic cancer (Table 4). Biliary tract cancer was diagnosed in 234 IBD patients with PSC, compared to two expected (SIR 140, 95% CI 123–159), a 56 times higher SIR than that among IBD patients alone; SIRs were 38.6 (95% CI 29.2–50.0) and 1.6 (95% CI 1.3–1.9) in patients with PSC-IBD and IBD alone for hepatocellular carcinoma, and 9.0 (95% CI 6.3–12.6) and 1.2 (95% CI 1.0–1.3) for pancreatic cancer, respectively. Standardized incidence ratios were higher in the first year of follow-up in both patients with and without PSC, but had no trend in the longer follow-up years (Table 4).

Crude IRs and SIRs for GBC and subtypes of other biliary tract cancers are listed in Table S6. The subtype iCCA had the highest SIRs, with 220 (95% CI 179–269) and 3.5 (95% CI 2.6–4.5) in IBD patients with PSC and without PSC, respectively.

TABLE 1 General characteristics of patients with inflammatory bowel disease (IBD) by primary sclerosing cholangitis (PSC), in Norway and Sweden, 1987–2016

	Total patients (n, %)		
Parameters	**PSC-IBD**	**Non-PSC-IBD**	**Total**
Total patients	4548	137,412	141,960
Total person-years	38,867	1,498,321	1,537,188
Median follow-up years (IQR)	12.7 (6.7–17.6)	9.9 (4.3–15.5)	10.0 (4.5–15.6)
Sex			
Female	1536 (33.8)	67,631 (49.2)	69,167 (48.7)
Male	3012 (66.2)	69,781 (50.8)	72,793 (51.3)
Age at IBD diagnosis			
Mean ± SD	37.6 ± 18.7	43.9 ± 19.3	43.7 ± 19.4
<20	959 (21.1)	14,515 (10.6)	15,474 (10.9)
≥20 and <40	1710 (37.6)	48,920 (35.6)	50,630 (35.7)
≥40 and <60	1242 (27.3)	42,317 (30.8)	30,789 (21.7)
≥60	637 (14.0)	31,660 (23.0)	32,297 (22.8)
Calendar year of IBD diagnosis[a]			
1987–2002	2589 (56.9)	57,917 (42.1)	60,506 (42.6)
2003–2015/6	1959 (43.1)	79,495 (57.9)	81,454 (57.4)
IBD subtype			
Ulcerative colitis	3313 (72.8)	81,574 (59.4)	84,887 (59.8)
Crohn's disease	830 (18.2)	44,247 (32.2)	45,077 (31.7)
IBD unclassified	405 (8.9)	11,591 (8.4)	11,996 (8.5)
Extent of ulcerative colitis[b]			
Total, n	3313	81,574	84,887
E1 (proctitis)	125 (3.8)	12,856 (15.8)	12,981 (15.3)
E2 (left-sided)	72 (2.2)	13,925 (17.1)	13,997 (16.5)
E3 (extensive)	2590 (78.2)	38,754 (47.5)	41,344 (48.7)
Ex (not defined)	526 (15.9)	16,039 (19.7)	16,565 (19.5)
Age at PSC diagnosis[c]	40.2 ± 18.5		
Calendar year of PSC diagnosis[a]			
Before 1980	50 (1.1)	-	-
1980–1989	323 (7.1)	-	-
1990–1999	882 (19.4)	-	-
2000–2009	1801 (39.6)	-	-
2010–2016	1492 (32.8)	-	-
Cancer types of outcomes			
Biliary tract cancer	234 (5.2)	209 (0.2)	443 (0.3)
Hepatocellular carcinoma	57 (1.3)	104 (0.1)	161 (0.1)
Pancreatic cancer	35 (0.8)	247 (0.2)	282 (0.2)

Abbreviations: IQR, interquartile range; Non-PSC-IBD, IBD patients without PSC; PSC-IBD, IBD patients with PSC; SD, standard deviation.

[a]Patients diagnosed before 2002 could represent a mix of prevalent and incident patients with IBD, as outpatient data were gradually included in hospital databases and the Swedish national patient register, see Figure S1 for details.

[b]Definitions and diagnostic codes were used according to the Montreal classifications using ICD-9 and ICD-10 in Norwegian data and ICD-10 in Swedish data, representing maximum disease involvement during follow-up, see Table S1 for details.

[c]Age at PSC diagnosis (mean ± SD) defined as the age or calendar year that patients had PSC, no matter with IBD or not.

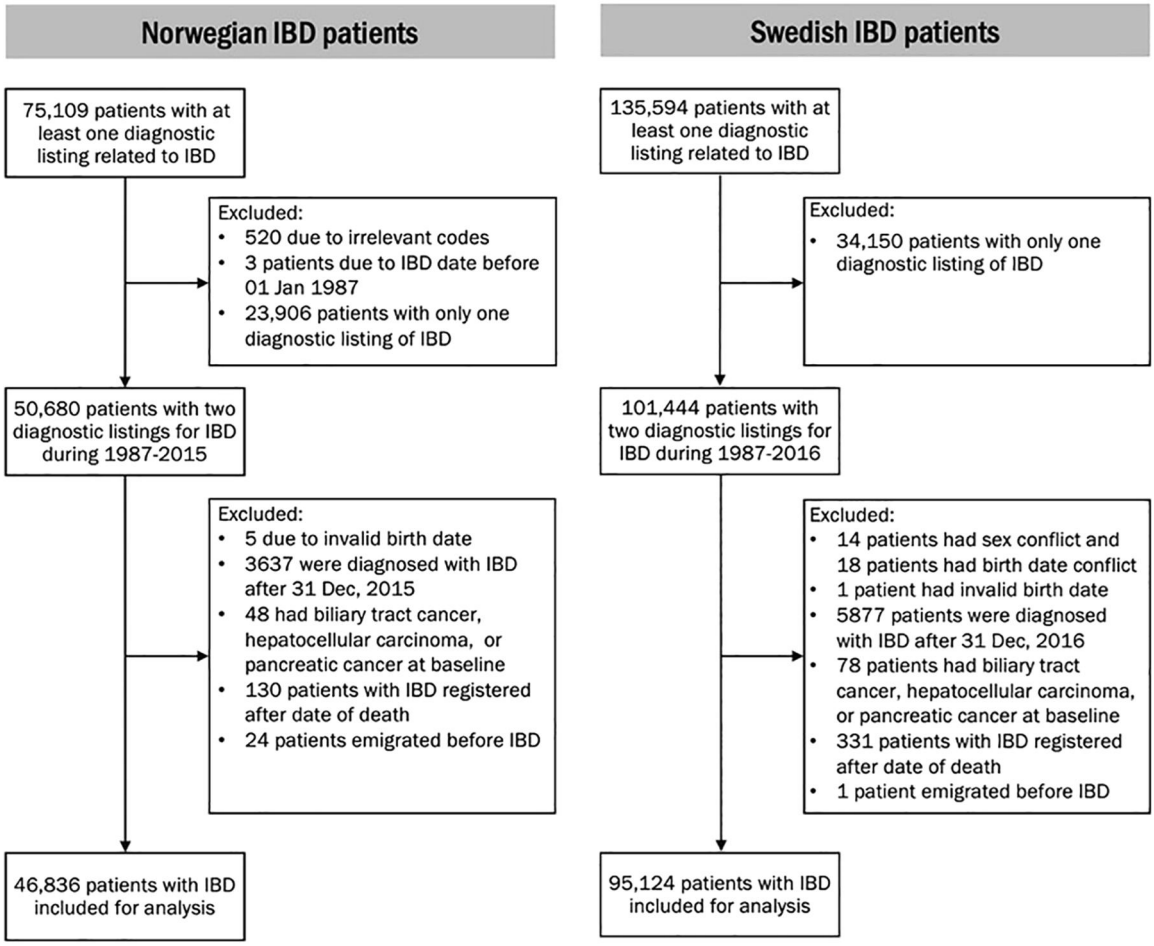

FIGURE 1 Flowchart of study population with inflammatory bowel disease (IBD) in Norway and Sweden, 1987–2016

Additionally, there was a higher proportion of pancreatic cancer located in the head of pancreas in PSC-IBD patients (17/35 for PSC-IBD and 84/247 for non-PSC-IBD, Table S7).

Sensitivity analyses

Analyses where Swedish patients were limited to those diagnosed with IBD between 2003 and 2016 showed similar results as the main analyses (data not shown). Crude IRs per 100,000 person-years increased with 37.0% biliary tract cancer, 12.4% for hepatocellular carcinoma and 59.0% for pancreatic cancer when we included cancers both from the cancer and cause of death registries; however, the SIRs changed only marginally as more cancers were also captured in the background population (Figure S3 and Table S8). The sensitivity analyses on onset of IBD showed similar results as the main analyses (Table S9). In sensitivity analyses where onset of PSC was set back 2, 5, and 10 years resulted in no statistically significant changes to the results (Table S10). Additionally, censoring for liver transplantation did not change the results (data not shown).

DISCUSSION

In our cohort of patients with IBD, we found a 5.2-, 2.4-, and 1.3-fold higher risk for biliary tract cancer, hepatocellular carcinoma, and pancreatic cancer than the general population, respectively. The excess risk of biliary tract cancer and hepatocellular carcinoma decreased with age at onset of IBD. Our most seminal finding was the 140-, 38.6-, and 9.0-fold increased risk of these three cancers among PSC-IBD patients, respectively; at the same time, slightly increased risks were also found in IBD patients without a recognized diagnosis of PSC.

The main strengths of this study are its large size, prospective population-based design, and virtually complete long-term follow-up and coverage, which allow accurate calculation of risks. Our definitions of IBD and PSC exposure proved trustworthy against validation of medical records and quality registers, respectively. Few previous studies have allowed separate analyses of cancer risk in PSC-IBD patients and IBD patients alone with adequate statistical power. Methodologic challenges might explain why prior evidence in this field is limited and inconsistent; the studied population, methodology, and potential environmental factors may explain variations between

TABLE 2 Crude incidence rates per 100,000 person-years, absolute numbers and standardized incidence ratios of hepato-pancreato-biliary cancers in patients with inflammatory bowel disease (IBD) with different characteristics in Norway and Sweden, 1987–2016

	Biliary tract cancer			Hepatocellular carcinoma			Pancreatic cancer		
Parameters	**IR (95% CI)**	**O/E**	**SIR (95% CI)**	**IR (95% CI)**	**O/E**	**SIR (95% CI)**	**IR (95% CI)**	**O/E**	**SIR (95% CI)**
Overall	28.8 (26.2–31.6)	443/84.7	5.2 (4.8–5.7)	10.5 (8.9–12.2)	161/68.4	2.4 (2.0–2.7)	18.3 (16.3–20.6)	282/212.1	1.3 (1.2–1.5)
Sex									
Female	18.5 (15.5–21.8)	139/45.3	3.1 (2.6–3.6)	6.5 (4.8–8.6)	49/17.4	2.8 (2.1–3.7)	16.7 (13.9–19.9)	126/98.9	1.3 (1.1–1.5)
Male	38.8 (34.5–43.4)	304/39.4	7.7 (6.9–8.6)	14.3 (11.8–17.2)	112/51.1	2.2 (1.8–2.6)	19.9 (16.9–23.3)	156/113.3	1.4 (1.2–1.6)
Age at IBD diagnosis									
<20	15.7 (10.4–22.9)	27/0.3	100 (66.0–147)	4.7 (2.0–9.2)	8/0.2	39.1 (16.9–77.6)	..	0/0.3	..
≥20 and <40	22.9 (19.3–27.1)	141/7.0	20.2 (17.0–23.9)	5.0 (3.4–7.2)	31/5.5	5.7 (3.8–8.0)	3.9 (2.5–5.8)	24/13.9	1.7 (1.1–2.6)
≥40 and <60	35.2 (30.3–40.7)	180/34.4	5.2 (4.5–6.0)	12.7 (9.8–16.2)	65/30.1	2.2 (1.7–2.8)	26.2 (22.0–31.0)	134/89.4	1.5 (1.3–1.8)
≥60	39.6 (32.1–48.5)	95/43.0	2.2 (1.8–2.7)	23.8 (18.0–30.8)	57/32.7	1.7 (1.3–2.2)	51.8 (43.0–61.7)	124/108.5	1.1 (1.0–1.4)
P_{trend}[a]			<0.001			0.005			0.105
Calendar year of IBD diagnosis[b]									
1987–2002	32.5 (29.1–36.2)	331/56.7	5.8 (5.2–6.5)	11.3 (9.3–13.5)	115/43.9	2.6 (2.1–3.1)	18.9 (16.4–21.8)	193/144.0	1.3 (1.2–1.5)
2003–2015/6	21.6 (17.8–26.0)	112/28.0	4.0 (3.3–4.8)	8.9 (6.5–11.8)	46/24.5	1.9 (1.4–2.5)	17.2 (13.8–21.1)	89/68.1	1.3 (1.0–1.6)
Years since IBD diagnosis									
≤1	46.0 (35.4–58.9)	63/6.3	10.0 (7.7–12.8)	10.2 (5.6–17.2)	14/4.7	3.0 (1.6–5.1)	30.0 (21.5–40.6)	41/15.2	2.7 (1.9–3.7)
>1 and ≤2	17.1 (10.7–25.9)	22/6.0	3.7 (2.3–5.5)	6.2 (2.7–12.3)	8/4.5	1.8 (0.8–3.7)	18.7 (12.0–27.8)	24/14.5	1.6 (1.1–2.5)
>2 and ≤5	21.4 (16.8–26.9)	73/16.5	4.4 (3.4–5.6)	11.4 (8.1–15.6)	39/12.6	3.1 (2.2–4.3)	13.5 (9.9–18.0)	46/40.6	1.1 (0.8–1.5)
>5 and ≤10	23.6 (19.2–28.6)	102/23.0	4.4 (3.6–5.4)	7.2 (4.9–10.2)	31/18.4	1.7 (1.2–2.4)	13.2 (10.0–17.1)	57/57.4	1.0 (0.8–1.3)
>10	36.8 (31.6–42.5)	183/32.9	5.6 (4.8–6.4)	13.9 (10.8–17.5)	69/28.3	2.4 (1.9–3.0)	22.9 (18.9–27.5)	114/84.4	1.4 (1.1–1.6)
P_{trend}[c]			0.314			0.946			0.935
IBD subtype									
Ulcerative colitis	36.3 (32.5–40.4)	335/53.6	6.2 (5.6–7.0)	11.5 (9.4–13.9)	106/44.3	2.4 (2.0–2.9)	19.2 (16.5–22.2)	177/139.2	1.3 (1.1–1.5)
Crohn's disease	14.1 (11.0–17.7)	72/25.6	2.8 (2.2–3.5)	9.0 (6.6–12.0)	46/19.8	2.3 (1.7–3.1)	16.0 (12.8–19.9)	82/59.0	1.4 (1.1–1.7)
IBD unclassified	34.8 (24.4–48.2)	36/5.4	6.6 (4.6–9.2)	8.7 (4.0–16.5)	9/4.4	2.1 (0.9–3.9)	22.2 (14.1–33.3)	23/13.9	1.7 (1.0–2.5)
Extent of ulcerative colitis[d]									
E1 (proctitis)	27.6 (19.5–38.1)	37/7.2	5.1 (3.6–7.0)	4.5 (1.6–9.8)	6/5.3	1.1 (0.4–2.4)	23.2 (15.7–32.9)	31/25.0	1.2 (0.8–1.7)
E2 (left-sided)	14.2 (8.4–22.5)	18/8.2	2.2 (1.3–3.5)	3.9 (1.3–9.2)	5/7.4	0.7 (0.2–1.6)	17.8 (11.3–26.8)	23/19.1	1.2 (0.8–1.8)

TABLE 2 (Continued)

Parameters	Biliary tract cancer			Hepatocellular carcinoma			Pancreatic cancer		
	IR (95% CI)	O/E	SIR (95% CI)	IR (95% CI)	O/E	SIR (95% CI)	IR (95% CI)	O/E	SIR (95% CI)
E3 (extensive)	38.9 (33.6–44.7)	193/24.8	7.8 (6.7–9.0)	12.1 (9.2–15.5)	60/21.1	2.8 (2.2–3.7)	14.8 (11.6–18.6)	74/65.2	1.1 (0.9–1.4)
Ex (not defined)	52.6 (42.1–64.9)	87/13.4	6.5 (5.2–8.0)	21.2 (14.7–29.4)	35/10.5	3.3 (2.3–4.6)	24.1 (18.2–31.2)	57/37.6	1.5 (1.1–1.9)
PSC[e]									
No	13.9 (12.1–16.0)	209/83.0	2.5 (2.2–2.9)	6.9 (5.7–8.4)	104/66.9	1.6 (1.3–1.9)	16.5 (14.5–18.7)	247/208.3	1.2 (1.0–1.3)
Yes	602 (527–684)	234/1.7	140 (123–159)	147 (111–190)	57/1.5	38.6 (29.2–50.0)	90.1 (62.7–125)	35/3.9	9.0 (6.3–12.6)

Abbreviations: CI, confidence interval; E, expected number of cases; IR, incidence rate, per 100,000 person-years; O, observed number of cases; SIR, standardized incidence ratio.

[a]*p* values were estimated by Cochran-Armitage test for trend.

[b]Patients diagnosed before 2002 could represent a mix of prevalent and incident patients with IBD, as outpatient data were gradually included in hospital databases and the Swedish national patient register, see Figure S1 for details.

[c]*p* values were estimated by Cochran-Armitage test for trend, excluding the first year of follow-up.

[d]Definitions and diagnostic codes were used according to the Montreal classifications using ICD-9 and ICD-10 in Norwegian data and ICD-10 in Swedish data, representing maximum disease involvement during follow-up, see Table S1 for details.

[e]IBD patients with PSC contributed person-time to the non-PSC group until the date of PSC diagnosis.

different studies. Most previous studies did not have adequate statistical precision or the necessary data to quantify risk separately for the three cancer sites and by co-existing PSC status.[9–11] Studies based on small numbers have reported a 1.3- to 4-fold increased risk of biliary tract cancer or merged with liver cancer in IBD patients,[8,12,24] and inconsistent findings for pancreatic cancer.[5,6,8,12,25] More compelling evidence supports that IBD with concomitant PSC substantially increases the risk of biliary tract cancer although these studies were usually based on small numbers.[3,26,27]

Two of the aforementioned studies[3,6] had quite large sample size of IBD patients, however, the Danish-Swedish study on pancreatic cancer have shorter follow-up and did not report risks in IBD patients without a diagnosis of PSC.[6] They found an overall IR in IBD patients of 22.1 per 100,000 person-years (95% CI 20.1–24.2), which is comparable to our results (18.3 per 100,000 person-years [95% CI 16.3–20.6]). The UK study[3] lacked information on extent of IBD, merged intra- and eCCA, and had a follow-up period of only 10 years. The short follow-up period could lead to inflated estimates since many cancers in PSC-IBD are detected within the first year after onset.[28] They reported an overall IR (IR) of pancreatic cancer of 5.5 (95% CI 4.4–6.8), hepatocellular carcinoma IR of 3.2 (95% CI 2.3–4.2), and cholangiocarcinoma of IR 11.8 (95% CI 10.1–13.7) per 1000 person-years in PSC-IBD. The rates are considerably higher than in our study, with pancreatic cancer IR of 0.9 (0.63–1.3), hepatocellular carcinoma IR of 1.5 (95% CI 1.1–1.9), and IR for intra- and eCCA of 1.9 (95% CI 1.5–2.3) and 1.30 (95% CI 0.96–1.7) per 1000 person-years, respectively. The study confirmed our finding of increasing risk with onset of PSC-IBD at a young age.

Moreover, another recent study based on Nordic population, focused on death of hepatobiliary cancers instead of incidence and reported a two- to 7-fold risk of HCC-, iCCA- and eCCA-deaths in IBD patients than the matched general population.[29]

Our study confirms the extremely increased risk for hepato-pancreato-biliary cancers in PSC-IBD patients, especially for biliary tract cancer, compared to the general population. However, precisely how PSC increases the risk of hepato-pancreato-biliary cancers in IBD patients remains unknown. The development of malignancies may involve an inflammation-dysplasia-carcinoma sequence. Due to the known increased risk, patients with PSC and IBD often undergo annual examination for colon cancer and hepatobiliary neoplasia as recommended by international societies.[30,31] The majority of IBD patients (about 95%–97%) do not have concomitant PSC. In this study, non-PSC-IBD patients had 2.5-fold higher risk for biliary tract cancer, 60% increased risk for hepatocellular carcinoma, and 20% increased risk for pancreatic cancer than the general population, much lower than those in PSC-IBD patients. However, compared with most known risk factors for these three cancers, the effects cannot be ignored. On the one hand, the chronic and persistent mucosal inflammation and perhaps microbiota alterations in the gastrointestinal tract in patients with IBD may increase the risk for malignant transformation. On the other hand, the associations are possibly affected by underdiagnosis

TABLE 3 Crude incidence rates per 100,000 person-years and observed numbers of hepato-pancreato-biliary cancers in patients with inflammatory bowel disease (IBD) by primary sclerosing cholangitis (PSC), in Norway and Sweden, 1987–2016

	PSC-IBD		Non-PSC-IBD	
Parameters	**No. of events**	**IR (95% CI)**	**No. of events**	**IR (95% CI)**
Biliary tract cancer				
Overall	234	602 (527–684)	209	13.9 (12.1–16.0)
Ulcerative colitis	195	657 (568–756)	140	15.7 (13.2–18.5)
Crohn's disease	23	372 (236–558)	49	9.7 (7.2–12.8)
IBD unclassified	16	534 (305–867)	20	19.9 (12.2–30.7)
Hepatocellular carcinoma				
Overall	57	147 (111–190)	104	6.9 (5.7–8.4)
Ulcerative colitis	46	155 (113–207)	60	6.7 (5.1–8.6)
Crohn's disease	10	162 (77.5–297)	36	7.1 (5.0–9.9)
IBD unclassified	1	33.4 (0.8–186)	8	8.0 (3.4–15.7)
Pancreatic cancer				
Overall	35	90.1 (62.7–125)	247	16.5 (14.5–18.7)
Ulcerative colitis	24	80.9 (51.8–120)	153	17.1 (14.5–20.1)
Crohn's disease	9	146 (66.5–276)	73	14.5 (11.3–18.2)
IBD unclassified	2	66.7 (8.1–241)	21	20.9 (12.9–31.9)

Note: Patients with PSC contributed person-time to the non-PSC group until the date of PSC diagnosis.

Abbreviations: CI, confidence interval; IR, incidence rate, per 100,000 person-years; Non-PSC-IBD, IBD patients without PSC; PSC-IBD, IBD patients with PSC.

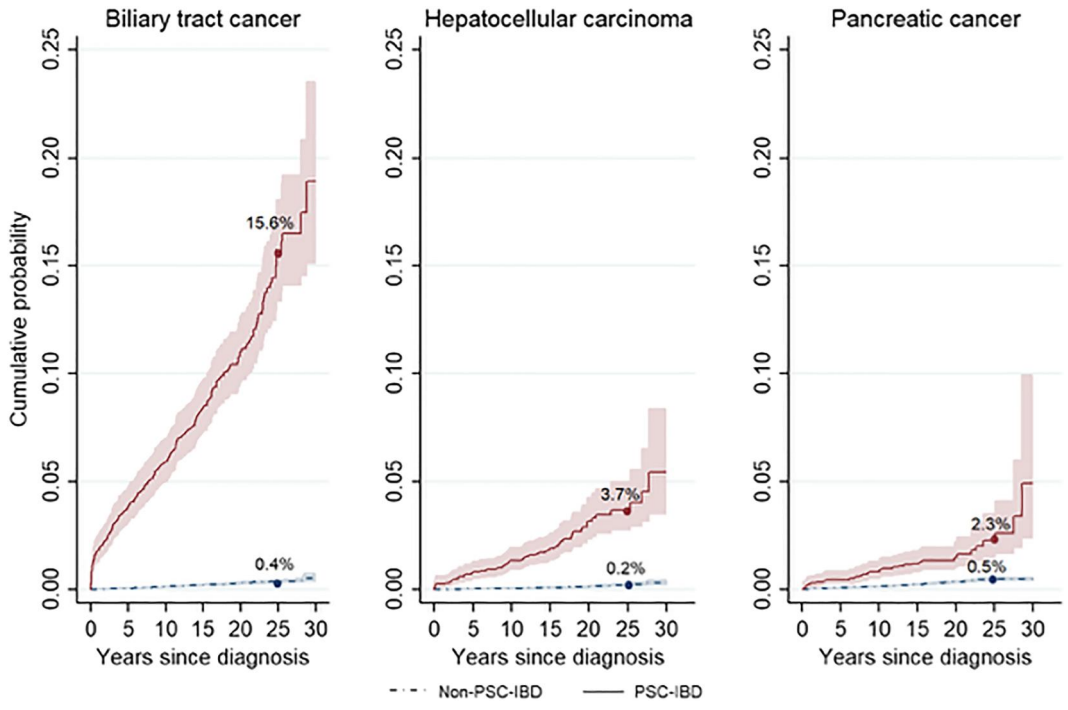

FIGURE 2 Cumulative probability with 95% confidence intervals of hepato-pancreato-biliary cancers in patients with inflammatory bowel disease (IBD) with and without primary sclerosing cholangitis (PSC), by years after diagnosis in Norway and Sweden, 1987–2016. PSC-IBD, IBD patients with PSC; Non-PSC-IBD, IBD patients without PSC. Since PSC is treated as a time-varying covariate, years since diagnosis represents time with PSC for the PSC-IBD group, and time since IBD diagnosis for the non-PSC group. Log-rank test, p-value <0.001 for all outcomes

TABLE 4 Standardized incidence ratios of hepato-pancreato-biliary cancers in patients with inflammatory bowel disease (IBD) by primary sclerosing cholangitis (PSC), in Norway and Sweden, 1987–2016

	Biliary tract cancer, SIR (95% CI)		Hepatocellular carcinoma, SIR (95% CI)		Pancreatic cancer, SIR (95% CI)	
Parameters	**PSC-IBD**	**Non- PSC-IBD**	**PSC-IBD**	**Non- PSC-IBD**	**PSC-IBD**	**Non- PSC-IBD**
Overall	140 (123–159)	2.5 (2.2–2.9)	38.6 (29.2–50.0)	1.6 (1.3–1.9)	9.0 (6.3–12.6)	1.2 (1.0–1.3)
Sex						
Female	71.0 (53.3–92.8)	1.9 (1.5–2.4)	54.4 (31.1–88.4)	1.9 (1.3–2.7)	7.3 (3.6–13.3)	1.2 (1.0–1.4)
Male	198 (170–229)	3.2 (2.7–3.8)	34.6 (24.9–47.0)	1.4 (1.1–1.8)	10.2 (6.5–15.3)	1.2 (1.0–1.4)
Age at IBD diagnosis						
<20	924 (564–1441)	28.2 (11.3–60.4)	357 (97.4–915)	20.7 (5.6–52.9)	-	-
≥20 and <40	436 (354–531)	6.2 (4.5–8.4)	87.1 (51.6–138)	2.5 (1.3–4.2)	20.5 (9.4–40.0)	1.1 (0.6–1.8)
≥40 and <60	115 (92.3–142)	2.7 (2.2–3.3)	34.9 (22.8–51.1)	1.3 (0.9–1.8)	8.6 (5.0–13.9)	1.3 (1.1–1.6)
≥60	40.2 (26.3–59.3)	1.6 (1.2–2.0)	17.5 (8.0–33.2)	1.5 (1.1–2.0)	6.2 (2.8–12.1)	1.1 (0.9–1.3)
P_{trend}[a]	0.266	<0.001	0.476	0.253	0.495	0.425
Calendar year of IBD diagnosis[b]						
1987–2002	148 (127–171)	2.7 (2.3–3.2)	45.5 (33.8–60.0)	1.5 (1.2–1.9)	9.2 (6.1–13.5)	1.2 (1.0–1.4)
2003–2015/6	118 (87.6–156)	2.2 (1.7–2.8)	18.5 (7.4–38.1)	1.6 (1.1–2.2)	8.4 (3.6–17.1)	1.2 (1.0–1.5)
Years since diagnosis						
≤1	466 (326–648)	4.3 (2.8–6.3)	88.1 (28.6–206)	2.0 (0.9–3.7)	30.8 (9.9–76.4)	2.4 (1.7–3.3)
>1 and ≤2	129 (61.8–243)	2.0 (1.0–3.6)	52.1 (10.7–152)	1.1 (0.4–2.6)	12.2 (1.4–52.9)	1.5 (1.0–2.3)
>2 and ≤5	152 (107–210)	2.2 (1.5–3.1)	53.3 (25.5–98)	2.3 (1.6–3.4)	5.6 (1.1–18.3)	1.1 (0.8–1.4)
>5 and ≤10	114 (83.9–152)	2.4 (1.8–3.1)	31.5 (15.7–56.4))	1.1 (0.7–1.7)	8.4 (3.6–17.1)	0.9 (0.6–1.1)
>10	121 (98.7–147)	2.5 (2.0–3.1)	33.9 (22.5–49.0)	1.5 (1.1–2.0)	8.3 (4.8–13.4)	1.2 (1.0–1.4)
P_{trend}[c]	0.919	0.678	0.946	0.612	0.972	0.822
IBD subtype						
Ulcerative colitis	154 (134–178)	2.7 (2.3–3.2)	40.9 (30.0–54.6)	1.4 (1.1–1.8)	8.1 (5.2–12.1)	1.1 (0.9–1.3)
Crohn's disease	78.1 (49.5–118)	1.9 (1.4–2.5)	40.7 (19.5–74.9)	1.8 (1.3–2.6)	14.0 (6.4–27.3)	1.3 (1.0–1.6)
IBD unclassified	140 (80.0–230)	3.8 (2.3–5.9)	9.2 (0.2–51.4)	1.9 (0.8–3.7)	7.7 (0.9–33.4)	1.5 (1.0–2.4)
Extent of ulcerative colitis[d]						
E1 (proctitis)	322 (184–529)	2.9 (1.8–4.5)	52.6 (6.4–190)	0.8 (0.2–1.9)	5.8 (0.1–47.3)	1.2 (0.8–1.7)
E2 (left-sided)	58.1 (6.5–252)	2.0 (1.1–3.3)	-	0.7 (0.2–1.6)	13.7 (0.2–112)	1.2 (0.7–1.8)
E3 (extensive)	128 (107–153)	3.0 (2.3–3.8)	37.9 (26.1–53.2)	1.3 (0.9–1.9)	6.7 (3.7–11.2)	0.9 (0.7–1.2)
Ex (not defined)	242 (182–315)	2.4 (1.6–3.4)	60.1 (30.0–108)	2.3 (1.5–3.5)	14.9 (6.0–31.9)	1.4 (1.0–1.9)

Note: Patients with PSC contributed person-time to the non-PSC group until the date of PSC diagnosis.

Abbreviations: CI, confidence interval; Non-PSC-IBD, IBD patients without PSC; PSC-IBD, IBD patients with PSC; SIR, standardized incidence ratio;

[a]*p* values were estimated by Cochran-Armitage test for trend.

[b]Patients diagnosed before 2002 could represent a mix of prevalent and incident patients with IBD, as outpatient data were gradually included in hospital databases and the Swedish national patient register, see Figure S1 for details.

[c]*p* values were estimated by Cochran-Armitage test for trend, excluding the first year of follow-up.

[d]Definitions and diagnostic codes were used according to the Montreal classifications using ICD-9 and ICD-10 in Norwegian data and ICD-10 in Swedish data, representing maximum disease involvement during follow-up, see Table S1 for details.

of PSC, residual confounding, or surveillance bias. The increased risk in the years immediately following IBD diagnosis point towards a level of detection bias, and symptoms of IBD and hepatobiliary cancer may overlap.

Underdiagnosis of PSC in IBD patients would lead to increased risk estimates in the group we defined as non-PSC IBD patients, and a certain level of clinically unrecognized PSC cannot be excluded. Indeed, in one study of patients with IBD

lasting at least 20 years where only 2.2% were known to have PSC, magnetic resonance cholangiography screening revealed a prevalence of PSC-like lesions of 8.1%.[32] We validated our definition of PSC in IBD patients against a regional PSC patient register in Norway, with a reassuring sensitivity of 97%, which suggests that we miss very few clinically recognized PSC cases among IBD patients (Table 11). To our knowledge, capture of PSC in the Swedish National Patient register should be equally complete. Sensitivity analyses where the date of PSC diagnosis was set back in time did not affect our estimates. We did not consider the fact that diagnostic modalities for PSC have changed throughout the study period, but estimates based on patients diagnosed from 2003 were similar to those diagnosed in the prior period.

Several limitations of our study deserve emphasis. First of all, there may be misclassification of cancer outcomes. The close anatomical location, often advanced stage with extensive and metastatic tumour growth at diagnosis, and difficulties to obtain biopsies for precise histopathologic diagnosis, may muddle the distinction between cancer in the pancreatic head and distal biliary tract cancers. For biliary tract cancers, 11% were classified as overlapping or unspecified, while for pancreatic cancers, this was about 47%. Such difficulty motivates cautious interpretation of the increased risk for hepatocellular and particularly pancreatic cancer, especially in non-PSC-IBD patients, because misclassification of some biliary tract cancers might have contributed to the increased estimates. Conversely, it also means that the rate of biliary tract cancer among IBD patients might be underestimated. Although there is no clear mechanism behind the increased risk of hepatocellular and pancreatic cancers in IBD patients, we chose to analyse the three cancer outcomes together, to elucidate any possible misclassifications. Another limitation is that early symptoms of these three cancers might prompt detection of a yet undiagnosed PSC and/or IBD (surveillance bias). We used the second diagnostic listing of IBD in main analyses, which has already attenuated the bias and consequently limited the impact on the risk estimates, although the excess risk remained high during the first year of follow-up. Our main analysis was based on capture from cancer registries, but considerable underreporting of hepato-pancreato-biliary cancers has been demonstrated in the Swedish cancer registry.[22,23,33] In sensitivity analyses we therefore also included cancers detected in cause of death registry, but there is a chance that we missed cancers that were only recorded at hospitals. While any comparisons to the general population are still valid, this would lead to an underestimation of IRs. Another limitation of the present study, as to be expected of register-based studies, is the lack of information on potential confounding variables. Incidence rates could be expected to be higher in certain subgroups of patients according to factors such as smoking status, alcohol use, autoimmune hepatitis, and hepatitis virus C or B status. However, with the exception of autoimmune hepatitis, we expect the distribution of these to be balanced in patients with IBD compared to the general population, and the relative estimates should therefore not be severely biased. Furthermore, we did not assess the effects of surveillance, which could have varied throughout the study period and between different centres, or any immunomodulatory or surgical therapies on cancer risk. Finally, our cohort focused on Nordic population, and there may be ethnic differences in the occurrence of IBD with or without PSC.[3] Caution is recommended when generalizing the cancer risks to other populations.

In conclusion, our large population-based study indicates that patients with IBD experience increased risks of both biliary tract cancer, hepatocellular carcinoma, and pancreatic cancer. Onset of PSC substantially increases risks of all hepato-pancreato-biliary cancers in IBD patients, which justifies periodic surveillance to detect hepato-pancreato-biliary malignancies.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

The study was approved by the Ethics Review Board in Stockholm (approval no. 2018/1626-31/1) and the Regional Ethics Committee of South-East Norway (approval no. 2016/359). Since this was a strictly register-based study, individual informed consent was not required.

AUTHOR CONTRIBUTIONS

Jingru Yu, Erle Refsum, Lise M Helsingen, Trine Folseraas, Magnus Løberg, Johannes Blom, Michael Bretthauer, Hans-Olov Adami, Mette Kalager, and Weimin Ye contributed to the design of the study. Jingru Yu, Erle Refsum, Lise M Helsingen, Trine Folseraas, Henriette C Jodal, Espen Melum, Magnus Løberg, Michael Bretthauer, Mette Kalager, and Weimin Ye contributed to data acquisition. Jingru Yu, Erle Refsum, Alexander Ploner, Paulina Wieszczy, Magnus Løberg, and Mette Kalager contributed with analyses. Jingru Yu, Erle Refsum, Lise M Helsingen, Trine Folseraas, Ishita Barua, Magnus Løberg, Michael Bretthauer, Hans-Olov Adami, Mette Kalager, and Weimin Ye contributed with interpretation of the data. Jingru Yu, Lise M Helsingen, and Erle Refsum verified the underlying data. Jingru Yu, Erle Refsum, Michael Bretthauer, and Hans-Olov Adami draughted the manuscript. Erle Refsum acts as

the guarantor for the paper. All authors edited and reviewed manuscript draughts, approved the final version, and agree to be accountable for all aspects of the work.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to their containing information that could compromise the privacy of research participants, but summary data can be made available from the corresponding author on reasonable request.

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REFERENCES

1. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769–78.
2. 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(9):513–20.
3. Trivedi PJ, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with inflammatory bowel disease, based on sex, race, and age. Gastroenterol. 2020;159(3):915–28.
4. Hemminki K, Li X, Sundquist J, Sundquist K. Cancer risks in ulcerative colitis patients. Int J Cancer. 2008;123(6):1417–21.
5. 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(2):265–73: e1.
6. Everhov AH, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Inflammatory bowel disease and pancreatic cancer: a Scandinavian register-based cohort study 1969-2017. Aliment Pharmacol Ther. 2020;52(1):143–54.
7. Lo B, Zhao M, Vind I, Burisch J. The risk of extraintestinal cancer in inflammatory bowel disease: a systematic review and meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol. 2021;19(6):1117–38: e19.
8. Ekbom A, Helmick C, Zack M, Adami HO. Extracolonic malignancies in inflammatory bowel disease. Cancer. 1991;67(7):2015–20.
9. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Aliment Pharmacol Ther. 2004;19(3):287–93.
10. Jess T, Horvath-Puho E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. Am J Gastroenterol. 2013;108(12):1869–76.
11. Jussila A, Virta LJ, Pukkala E, Farkkila MA. Malignancies in patients with inflammatory bowel disease: a nationwide register study in Finland. Scand J Gastroenterol. 2013;48(12):1405–13.
12. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91(4):854–62.
13. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca - Cancer J Clin. 2018;68(6):394–424.
14. Barberio B, Massimi D, Cazzagon N, Zingone F, Ford AC, Savarino EV. Prevalence of primary sclerosing cholangitis in patients with inflammatory bowel disease: a systematic review and meta-analysis. Gastroenterol. 2021;161(6):1865–77.
15. Karlsen TH, Schrumpf E, Boberg KM. Primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol. 2010;24(5):655–66.
16. Ricciuto A, Kamath BM, Griffiths AM. The IBD and PSC phenotypes of PSC-IBD. Curr Gastroenterol Rep. 2018;20(4):16.
17. 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(5):475–84.
18. 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(10218):123–31.
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(6):889–93.
20. Jakobsson GL, Sternegard E, Olen 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(2):216–21.
21. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749–53.
22. Kilander C, Mattsson F, Ljung R, Lagergren J, Sadr-Azodi O. Systematic underreporting of the population-based incidence of pancreatic and biliary tract cancers. Acta Oncol. 2014;53(6):822–9.
23. Torner A, Stokkeland K, Svensson A, Dickman PW, Hultcrantz R, Montgomery S, et al. The underreporting of hepatocellular carcinoma to the cancer register and a log-linear model to estimate a more correct incidence. Hepatol. 2017;65(3):885–92.
24. Hovde O, Hoivik ML, Henriksen M, Solberg IC, Smastuen MC, Moum BA. Malignancies in patients with inflammatory bowel disease: results from 20 Years of follow-up in the IBSEN study. J Crohns Colitis. 2017;11(5):571–7.
25. 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 Crohn's & Colitis. 2017;11(8):954–62.
26. Sorensen JO, Nielsen OH, Andersson M, Ainsworth MA, Ytting H, Belard E, et al. Inflammatory bowel disease with primary sclerosing cholangitis: a Danish population-based cohort study 1977-2011. Liver Int. 2018;38(3):532–41.
27. Ananthakrishnan AN, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, et al. Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease. J Crohns Colitis. 2014;8(9):956–63.
28. Weismuller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, et al. Patient Age, sex, and inflammatory bowel disease phenotype Associate with course of primary sclerosing cholangitis. Gastroenterol. 2017;152(8):1975–84: e8.
29. Erichsen R, Olén O, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Hepatobiliary cancer risk in patients with inflammatory bowel

disease: a Scandinavian population-based cohort study. Cancer Epidemiol Biomark Prev. 2021;30(5).
30. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatol. 2010;51(2):660–78.
31. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut. 2002;51(Suppl 6): Vi1–9.
32. Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of sclerosing cholangitis detected by magnetic resonance cholangiography in patients with long-term inflammatory bowel disease. Gastroenterol. 2016;151(4):660–9: e4.
33. Lambe M, Eloranta S, Wigertz A, Blomqvist P. Pancreatic cancer; reporting and long-term survival in Sweden. Acta Oncol. 2011;50(8):1220–7.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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