Gastro Hep Advances 2023;2:853–859

ORIGINAL RESEARCH—CLINICAL

Rectal Cancer Risk After Colectomy in Patients With Inflammatory Bowel Disease—A Population-Based Danish Cohort Study 1978–2018

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BACKGROUND AND AIMS: Selected patient groups with ulcerative colitis and Crohn's disease are at increased risk of colorectal cancer. Surveillance guidelines rarely cover patients after colectomy. We performed a nationwide population-based cohort study to estimate the risk of developing rectal cancer in patients with inflammatory bowel disease after subtotal colectomy. **METHODS:** Through the Danish Civil Registration System, a source population of all individuals living in Denmark between 1978 and 2018 was retrieved. The risk of rectal cancer in patients with diverted rectum was assessed using Cox regression analyses with comparison to both the individuals with inflammatory bowel diseases without subtotal colectomy and the background population. **RESULTS:** Rectal cancer occurred in 42 of 4931 patients (0.9%) after subtotal colectomy and diverted rectum, compared to 209 of 49,251 (0.4%) in the matched inflammatory bowel diseases cohort without colectomy and 941 of 246,550 (0.4%) in the background population. The hazard ratio (HR) for rectal cancer in patients with inflammatory bowel disease and diverted rectum vs patients without colectomy was 0.76 (95% CI, 0.28, 2.07) before 10 years and 7.56 (95% CI, 5.21, 10.86) 10 years after colectomy. The HR for patients with diverted rectum compared to the background population was 0.84 (95% CI, 0.31, 2.24) and 10.01 (95% CI, 7.20, 13.94) respectively. **CONCLUSION:** In our nationwide population-based Danish cohort study, we found the risk of rectal cancer in the diverted rectum to be markedly increased 10 years post-colectomy. This calls for better long-term surveillance of colectomized patients with inflammatory bowel diseases.

Keywords: Crohn's Disease; Diverted Rectum; IBD Management; Surveillance; Ulcerative Colitis

Introduction

Ulcerative colitis (UC)[1] and Crohn's disease (CD)[2] are chronic inflammatory diseases (IBD) with increasing incidence and prevalence in Denmark[3] and worldwide.[4]

UC carries a cumulative risk of subtotal colectomy of 7.5% after 5 years,[5] and consequently, a similar risk of ileostomy with diverted rectum. In CD, although decreasing over the last decades,[6] the risk of surgery remains even higher. A meta-analysis of unselected population-based studies found the risk of surgery to be 27.7% after 5 years and 38.7% after 10 years with CD.[6] In Europe, the 5-year colectomy rate in CD is 7.5%.[7] Following colectomy for UC or CD, patients may either get an ileostomy with diverted rectum as a permanent solution, or bowel continuity can be restored with ileo-rectal anastomosis (IRA) or with ileal pouch-anal anastomosis (IPAA).

The risk of colorectal cancer (CRC) in IBD is debated, but at least in specific subgroups of patients with early onset of the disease, concomitant primary sclerosing cholangitis (PSC), or long disease duration, the risk of CRC is increased.[8] To reduce the risk of CRC in IBD, endoscopic surveillance guidelines have been developed both nationally[9] and internationally.[10–12] However, guidelines do not include clear recommendations for patients with a residual rectum, IRA or IPAA. The Danish guidelines, the Danish Society of Gastroenterology and Hepatology,[9] mention a potential increased risk of rectal cancer (RC) postcolectomy according to studies from the 1980s[13,14] and a referral center study from 2012.[15] The European Crohn's and Colitis Organization guideline/consensus paper "European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies" mentions that "the risk of rectal cancer is relatively high in IBD patients after subtotal colectomy" without further recommendation.[10]

The lack of evidence-based guidelines is due to shortness of methodologically well-conducted studies on the long-term outcomes of the rectal remnant. A meta-analysis from 2016 based on a variety of mostly selected patient populations[16] reported a pooled prevalence of carcinoma of

Abbreviations used in this paper: **CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; NPR, national Patient Registry; RC, rectal cancer.**

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2772-5723
https://doi.org/10.1016/j.gastha.2023.05.001

0.5% in IPAA, 2.1% in rectal stump patients and 2.4% in IRA. In a nationwide population-based Swedish cohort study of cancer postcolectomy,[17] the 20-year cumulative risk of RC was <1% in IPAA, 2.2% with a diverted rectum and 5.6% after IRA, corresponding to a 4- and 9-fold increased risk in the latter 2 groups. These data support surveillance for RC after colectomy in patients with IBD but cannot stand alone. In order to develop evidence-based surveillance strategies, the Swedish findings need to be confirmed in other unselected patient cohorts.

We therefore performed a nationwide population-based cohort study (1978–2018) to estimate the long-term risk of RC after colectomy for IBD in Denmark.

Material and methods

Study population

The study population covered all individuals alive and residing in Denmark between 1978 and 2018 (n = 9,083,980), according to the Danish Civil Registration System. Using the unique 10-digit personal identification number given to all Danish citizens at birth, we linked the source population to the Danish National Patient Register (NPR) and to the Danish Cancer Registry to obtain information on disease diagnoses, surgical procedures, and cancer. In the NPR, we first identified all patients with at least 2 IBD diagnoses or 1 long hospital contact for IBD (n = 80,404) using the following codes from the International Classification of Diseases (ICD), 8th and 10th revisions (CD: ICD-8 codes 563.01, 563.02, 563.08, 563.09 and ICD-10 code K50, UC: ICD-8 codes 563.19, 569.04 and ICD-10 code K51). Date of diagnosis was the date of the second contact or, in case of 1 long contact, date of the first long contact + 7 days. For patients registered with diagnoses of both CD and UC, patients were classified as CD or UC according to the most recent diagnosis recorded. Among the identified patients with IBD we distinguished patients who had undergone subtotal colectomy with diverted rectum using surgical procedure codes for colectomy (NCSP codes KJFH10, KJFH11, KJFH96; DOTC codes 45020, 45021, 45060, 45061, 46530, 46490) or the combination of right hemicolectomy, resection of colon transversum, left hemicolectomy and sigmoidectomy (NCSP codes KJFB30, KJFB31, KJFB40, KJFB41, KJFB46, KJFB47, KJFB60, KJFB61; DOTC codes 44900, 44901, 46410, 44940, 46430, 44920, 44921, 44960, 44961, 46400, 44980, 44981, 46440). Patients with recorded IRA/IPAA, proctectomy or rectal cancer before subtotal colectomy or who lived outside Denmark at the date of the surgical procedure were excluded. Each patient in the subsequent cohort was matched with up to 10 patients with IBD and no history of subtotal colectomy on sex, birth date (within 5 years), IBD subtype (CD or UC), and IBD duration (within −6 months to +2 years), and also matched with up to 50 individuals from the general population on age and sex.

Cases of RC were identified in the Danish Cancer Registry, using ICD-10 code C20.

No individuals were lost to follow-up.

Statistical analysis

Due to few RC events in the groups with IRA and IPAA, analyses were restricted to risk of RC in the population with diverted rectum.

All patients who had undergone colectomy and their matched IBD and non-IBD reference individuals were followed from index date (date of IBD with colectomy/ match date) until diagnosis with RC, date of proctectomy + 30 days, emigration, death, end of follow-up (31st December 2018), or by 30 years of follow-up (truncation due to sparse data after 30 years), whichever event occurred first.

The cumulative incidence of RC in colectomized patients as well as in IBD and in non-IBD reference individuals was estimated by the Kaplan-Meier estimator. Using Cox regression analysis, we estimated hazard ratios (HRs) with 95% confidence intervals (95% CIs) of RC in individuals with IBD and colectomy vs IBD and non-IBD reference individuals with time since index date as the underlying time scale. All analyses were conducted using SAS 9.4.

Ethical considerations

The study was approved by the Danish Data Protection Agency. We analyzed data on a secure research server at the Danish Health Data Authority. In Denmark, ethical approval for register studies is not required.

Results

We identified 80,404 patients with IBD and among those 4931 colectomized patients living in Denmark at procedure date (Figure 1).

These patients (CD, 1248; UC, 3683) were followed for 31,243 person-years and compared to 49,203 patients with IBD (CD, 12,397; UC, 36,806), who had not undergone colectomy and followed for 620,808 person-years. They were also compared to 246,550 non-IBD individuals from the

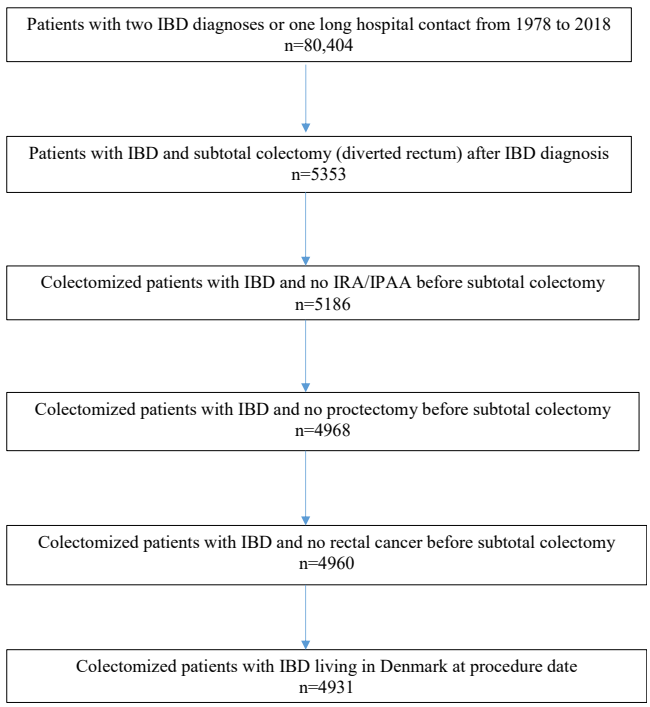

Figure 1. Flow chart of the study population.

Table 1. Characteristics of 4931 Colectomized Patients With Inflammatory Bowel Disease

Characteristic	All patients with IBD and subtotal colectomy	IBD type	
		CD	UC
All, n (%)	4931 (100.0)	1248 (100.0)	3683 (100.0)
Sex			
Female, n (%)	2491 (50.5)	757 (60.7)	1734 (47.1)
Male, n (%)	2440 (49.5)	491 (39.3)	1949 (52.9)
Age at IBD (y), mean (SD)	37.47 (18.12)	34.39 (17.62)	38.51 (18.17)
Age at subtotal colectomy (y), mean (SD)	41.56 (18.30)	38.97 (17.72)	42.43 (18.41)
Duration of IBD at subtotal colectomy (y), mean (SD), in y	4.09 (5.68)	4.58 (5.56)	3.93 (5.72)

SD, standard deviation.

general population followed for 3,352,864 person-years. Characteristics of the 3 groups are presented in Tables 1 and 2. The female:male distribution was 50:50 among colectomized patients with IBD and in the 2 reference groups. Approximately 1/3 of patients were <30 years at colectomy, 1/3 was 30–50 years, and 1/3 was above 50 years at colectomy. The mean age at IBD diagnosis among colectomized patients was 37.5 years (standard deviation (SD), 18.1) and slightly higher in UC (38.5 years; SD, 18.2) than in CD (34.4 years; SD, 17.6). Mean age at colectomy was 41.6 years (SD, 18.3) among IBD patients overall, 42.4 years (SD, 18.4) among UC patients, and 39.0 (SD, 17.7) among CD patients. More than 40% of the colectomized IBD patients were from recent calendar years (2006–2018) (Table 2).

Table 3 shows the occurrence of rectal cancer in the population of colectomized IBD patients. We identified 305 patients with IRA and 1381 patients with IPAA and among them, 5 and <5 patients, respectively, developed RC. Due to a lack of RC events in the group with IRA and IPAA, analyses were restricted to risk of RC in the population with diverted rectum.

Rectal cancer

Of the 4931 colectomized patients with IBD, 42 (0.9%) patients developed RC during follow-up, compared to 207 (0.4%) in the matched non-colectomized IBD population and 941 (0.4%) in the matched background population. In the colectomized IBD population, 11 (0.9%) of the 42 cases were in patients diagnosed with CD and 31 (0.8%) were in patients diagnosed with UC. Among these 42 individuals, there were 15 women and 27 men.

Figure 2 illustrates the cumulative incidence functions for RC in patients with IBD and diverted rectum after subtotal colectomy compared to patients with IBD and no history of subtotal colectomy and the background population. A markedly increased incidence of RC 10 years after colectomy can be appreciated when comparing patients with IBD and no history of subtotal colectomy and the background population ($P < .0001$). This finding is consistent for patients with CD and UC.

The HR (95% CI) of RC for patients with IBD and diverted rectum vs matched IBD population without diverted rectum when adjusting for both IBD type and sex was

Table 2. Characteristics of the Study Population

Characteristic	IBD and subtotal colectomy		IBD and no subtotal colectomy		Background population	
	N	%	N	%	N	%
All	4931	100.0	49,203	100.0	246,550	100.0
Sex						
Female	2491	50.5	24,844	50.5	124,550	50.5
Male	2440	49.5	24,359	49.5	122,000	49.5
IBD type						
CD	1248	25.3	12,397	25.2	-	-
UC	3683	74.7	36,806	74.8	-	-
Age at cohort entry						
<30 y	1642	33.3%	15,862	32.2%	82,110	33.3
30–50 y	1750	35.5	17,974	36.5	87,546	35.5
>50 y	1539	31.2	15,367	31.2	76,894	31.2
Year at cohort entry						
1978–1991	975	19.8	9709	19.7	48,750	19.8
1992–2005	1819	36.9	18,155	36.9	90,950	36.9
2006–2018	2137	43.3	21,339	43.4	106,850	43.3

Table 3. Cancer Events in the Group of Colectomized Patients With IBD

	Subtotal colectomy (diverted rectum)	IRA	IPAA
Rectal cancer			
Exposed	4931	305	1381
Occurrence	42	5	<5

0.77 (95% CI, 0.28, 2.09) before 10 years and 7.56 (95% CI, 5.23, 10.92) after 10 years of follow-up. The corresponding HR for patients with IBD and diverted rectum vs matched background population when adjusting for both IBD type and sex was 0.85 (95% CI, 0.32, 2.26) before 10 years and 10.01 (95% CI, 7.19, 13.93) after 10 years of follow-up (Table 4). When analyzing the risk of RC separately for patients with CD and UC, we found that compared to the matched IBD population, the HR of RC after 10 years postcolectomy was 5.10 (95% CI, 2.41, 10.81) in CD patients and 9.42 (95% CI, 6.18, 14.36) in UC patients. The risk of RC was similar in women and men (Table 4). In order to examine the stability of the matched IBD population with no history of subtotal colectomy we repeated the matching procedure 100 times with different random seeds. The mean HR before 10 years was 0.86 and standart deviation (SD) was 0.09, and the mean HR after 10 years postcolectomy was 7.90 and the SD was 0.78.

Discussion

In this nationwide population-based Danish cohort study of 4931 individuals undergoing subtotal colectomy with a diverted rectum as a result of IBD, we observed a markedly increased risk of RC 10 years postcolectomy. The risk was increased 8-fold when compared to a matched IBD-cohort without colectomy and increased 10-fold when compared to the background population. The risk of RC was not increased during the first 10 years after colectomy.

In younger patients, and especially in women considering pregnancy before pelvic surgery, a diverted rectum may serve as a temporary solution, but the long-term risk of RC should be considered if avoiding proctectomy.

Recommendations for long-term colorectal cancer surveillance in patients with IBD have been developed both nationally[9] and internationally.[10–12] However, guidelines do not include clear recommendations for patients after colectomy. There has been no systematic surveillance of these type of patients in Denmark with practice varying in between hospitals. To evaluate the need of such a surveillance was 1 of the reasons of the study.

Our results are somewhat in line with case reports, a multicenter study[18] and another population-based study[17] assessing the risk of RC in patients with IBD after colectomy. In the Swedish nationwide population-based study, the authors studied risk of RC after subtotal colectomy with either IPAA, diverted rectum, or IRA, and showed a 4- and 9-fold increased risk of cancer after 20 years of follow-up in the latter 2 groups compared to the background population.[17] A previous Danish study investigating risk of RC postcolectomy lacked estimates on absolute cancer risk and did not perform regression analyses to take time-variation in cancer risk into account.[19]

In a French retrospective multicenter study[18] of patients with UC undergoing IRA from 1960 to 2013 in 13 centers in France, with a total of 343 patients included, the incidence of RC was 3.2% 10 years and 7.3% 20 years postcolectomy. These results suggest surveillance program for the population of patients with IBD postcolectomy and this is in line with our results. The difference in the patient populations with IRA postcolectomy in the French study and patients with diverted rectum in Danish national cohort reflects differences in local and national practices. The Swedish cohort included 3 groups with 1112 patients with IRA, 1796 with IPAA and 4358 with diverted rectum postcolectomy. In our study because of small numbers of cases in IRA and IPAA groups (Table 3) we restricted the study population to the individuals with diverted rectum.

Overall, our results together with those of the Swedish cohort study and the French multicenter study suggest that, despite variation in surgical solutions studied, the long-term risk of RC postcolectomy is increased. This calls for attention and should inform current surveillance guidelines.

The primary strength of the present study was the availability of unselected population-based data on a nationwide cohort of patients with IBD (CD and UC) and a diverted rectum after a subtotal colectomy. We compared RC incidence in patients with the diverted rectum not only to that in the background population, but also to a matched IBD population without colectomy. The latter stands out from previous studies[16–19] where the risk for RC was not compared to the IBD population without colectomy. Another strength was the long-term follow-up with 31,243 person-years of follow-up for 4931 colectomized patients with IBD, high quality standard in terms of completeness and accuracy of the Danish Cancer Registry,[20] and the validity of NPR with positive predictive value for CD of 97% and UC of 90%.[21] The validity of IBD diagnosis in the Danish NPR was recently re-evaluated with PPV 0.95 (95% CI, 0.95–0.96) for patients registered with at least 2 diagnoses with similar results for UC and CD separately.[22]

Our study does also have some potential limitations to consider. Despite been nationwide population-based cohort study, the small number of cases in the IRA and IPAA groups precluded analyses for these specific subgroups (Table 3). The same reason did not allow us to assess risk according to PSC or other subgroups eg patients with severe perianal CD. Also we did not have data on smoking, prior colorectal neoplasia, indication for colectomy or other potential confounders.

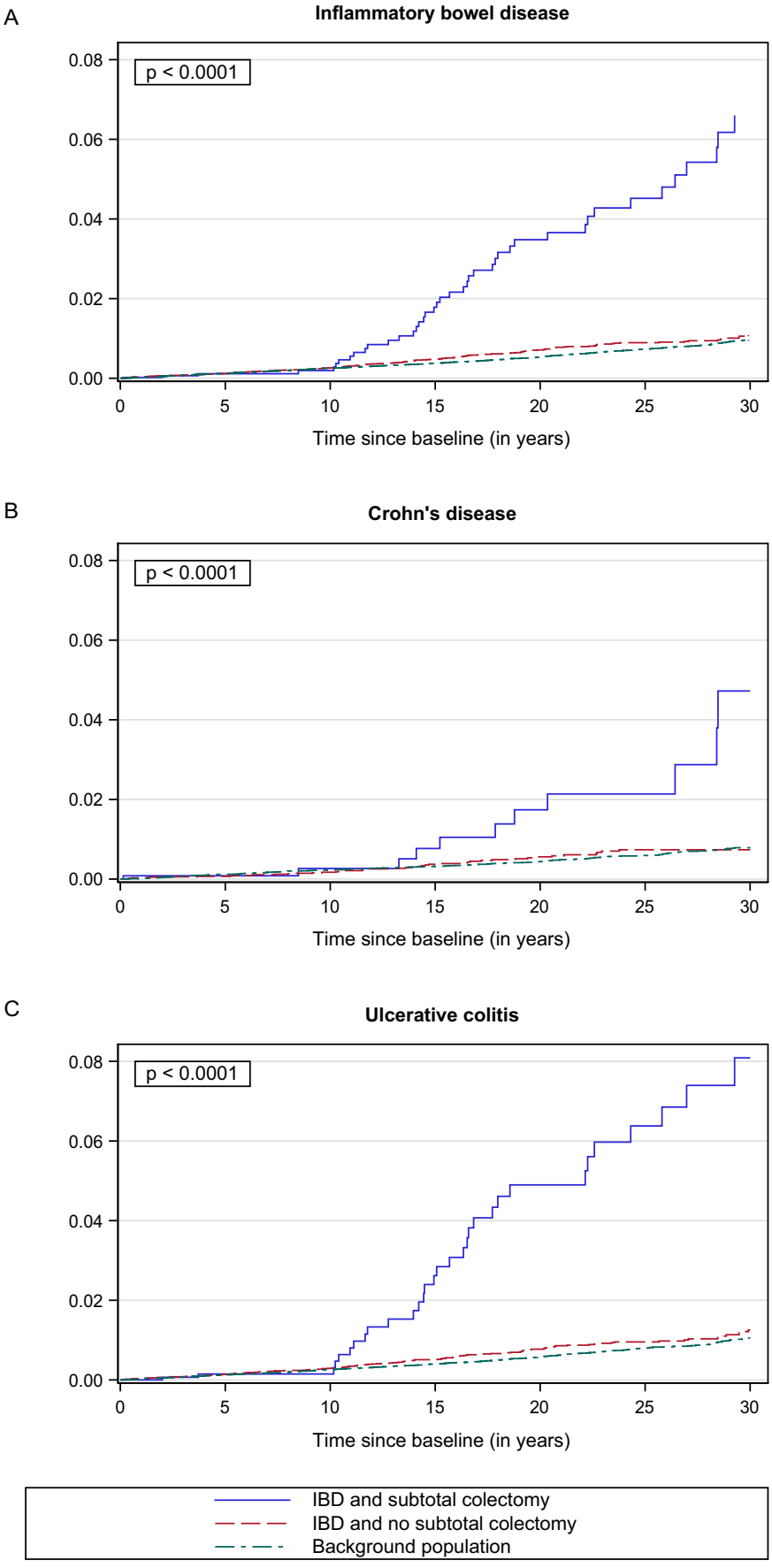

Figure 2. Cumulative incidence functions for rectal cancer in patients with IBD after subtotal colectomy (with diverted rectum) compared to patients with IBD and no history of subtotal colectomy (diverted rectum) and to the background population in Denmark, 1978–2018.

Table 4. Hazard Ratios for Patients With IBD and Diverted Rectum vs Matched IBD Population Without Colectomy and a Matched Background Population

Patient population	HR (95% CI) Patients with IBD and diverted rectum vs matched IBD population without diverted rectum	*P* value for interaction	HR (95% CI) Patients with IBD and diverted rectum vs matched background population	*P* value for interaction
Overall[a]	4.15 (2.98, 5.79)		4.92 (3.61, 6.70)	
< 10 years of follow-up	0.76 (0.28, 2.07)		0.84 (0.31, 2.24)	
>10 years of follow-up	7.52 (5.21, 10.86)		10.02 (7.20, 13.94)	
By IBD type				
Overall[a]	4.37 (3.13, 6.11)		5.06 (3.71, 6.89)	
<10 years[b] of follow-up	0.79 (0.29, 2.16)		0.85 (0.31, 2.23)	
>10 years[b] of follow-up	7.99 (5.52, 11.57)		10.40 (7.47, 14.48)	
CD				
<10 years of follow-up	1.57 (0.36, 6.80)	.21	1.21 (0.30, 4.89)	.23
>10 years of follow-up	5.10 (2.41, 10.81)		6.72 (3.42, 13.22)	
UC				
<10 years of folow-up	0.53 (0.13, 2.18)		0.65 (0.16, 2.62)	
>10 years of folow-up	9.42 (6.18, 14.36)		12.41 (8.49, 18.13)	
By sex				
Overall[a]	4.18 (3.00, 5.83)		4.97 (3.65, 6.77)	
<10 years[c] of follow-up	0.77 (0.28, 2.09)		0.85 (0.32, 2.26)	
>10 years[c] of folow-up	7.56 (5.23, 10.92)		10.01 (7.19, 13.93)	
Female				
<10 years of folow-up	0.45 (0.06, 3.28)	.67	0.51 (0.07,3.65)	.78
>10 years of follow-up	6.69 (3.68, 12.17)		10.33 (5.99, 17.82)	
Male				
<10 years of follow-up	1.00 (0.31, 3.21)		1.08 (0.35, 3.38)	
>10 years of follow-up	8.17 (5.13, 13.03)		9.84 (6.49, 14.91)	

[a]Proportional hazards assumption not satisfied.
[b]Adjusted for IBD, type (allowing for interaction with time).
[c]Adjusted for sex (allowing for interaction with time).

As we did not include data on treatment, potential chemopreventive effect in this population could not been shown.

Conclusion

Our nationwide population-based cohort study covering 4 decades shows that despite a relatively low absolute number of RC cases following colectomy for IBD, the risk of RC is markedly increased 10 years after the surgery. This calls for better long-term surveillance of colectomized IBD patients.

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Received November 30, 2022. Accepted May 8, 2023.

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Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The study was supported by a grant from Laege Carl Emil Friis og Hustru Olga Doris Friis and by the Danish National Research Foundation (grant no. DNRF148). The foundations had no role in the conduct of the study.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The study is based on data from the Danish National Health registers (https://sundhedsdatastyrelsen.dk). The register data are protected by the Danish Act on Processing of Personal Data and are accessed through application to and approval from the Danish Data Protection Agency and the Danish Health Data Authority.

Reporting Guidelines:
STROBE.