Thieme

Risk of a post-colonoscopy colorectal cancer in patients with diverticular disease: a population-based cohort study

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ABSTRACT

Background Post-colonoscopy colorectal cancers (PCCRCs) may account for up to 30% of all colorectal cancers (CRCs) diagnosed in patients with diverticular disease; however, absolute and relative risks of PCCRC among these patients undergoing colonoscopy remain unknown.

Methods We performed a cohort study (1995–2015) including patients with and without diverticular disease who underwent colonoscopy. We calculated 7–36-month cumulative incidence proportions (CIPs) of PCCRC. We used Cox proportional hazards regression models to compute hazard ratios (HRs) of PCCRC, comparing patients with and without diverticular disease, as a measure of relative risk. We calculated 3-year PCCRC rates, as per World Endoscopy Organization recommendations, to estimate the proportion of CRC patients with and without diverticular disease who were considered to have PCCRC. We stratified all analyses by PCCRC location.

Results We observed 373 PCCRCs among 56 642 patients with diverticular disease and 1536 PCCRCs among 306 800 patients without diverticular disease. The PCCRC CIP after first-time colonoscopy was 0.45% (95%CI 0.40%–0.51%) for patients with and 0.36% (95%CI 0.34%–0.38%) for patients without diverticular disease. Comparing patients with and without diverticular disease undergoing first-time colonoscopy, the adjusted HR was 0.84 (95%CI 0.73–0.97) for PCCRC and 1.23 (95%CI 1.01–1.50) for proximal PCCRCs. The 3-year PCCRC rate was 19.0% (22.3% for proximal PCCRCs) for patients with and 6.5% for patients without diverticular disease.

Conclusions Although the absolute risk was low, the relative risk of proximal PCCRCs may be elevated in patients with diverticular disease undergoing colonoscopy compared with patients without the disease.

Introduction

The sensitivity of colonoscopy for detecting colorectal cancer (CRC) and its precursors is known to be high. Nonetheless, up to 8% of all CRCs are diagnosed within 10 years after a negative colonoscopy [1, 2, 3, 4, 5, 6]. These cancers are commonly referred to as post-colonoscopy CRCs (PCCRCs). As the majority of PCCRCs are assumed to arise from CRCs or precursors that were missed or incompletely resected during the preceding colonoscopy, several studies have sought to identify risk factors for missed colorectal lesions and thus PCCRC [3, 5, 7, 8, 9, 10]. In this context, numerous studies indicated that diverticular disease, a highly prevalent condition in the Western world [11], may be associated with an increased proportion of CRCs that can be classified as PCCRC [3, 5, 7, 10, 12].

This increased proportion of diverticular disease-related PCCRCs could be explained by diverticular disease-related colonoscopies being technically more difficult and with an impaired view of affected mucosal areas [13]. Previous studies provided important evidence on colonoscopies associated with diverticular disease-related PCCRC, emphasizing the need for increased awareness of the risk of overlooking CRC precursors in patients with diverticular disease. However, the absolute risk of PCCRC among all patients with diverticular disease who undergo colonoscopy remains unknown. Such evidence is crucial for guiding clinical decision making, particularly for planning surveillance colonoscopies for patients with diverticular disease.

We therefore conducted a population-based cohort study to investigate the absolute and relative risks of PCCRC in patients with and without diverticular disease who underwent a colonoscopy (Aim I), and to estimate 3-year PCCRC rates according to the World Endoscopy Organization (WEO) recommendations for CRC patients with and without diverticular disease (Aim II).

Methods

Setting

We conducted this study within the setting of universal tax-funded healthcare provided by the National Health Service and offered to all Danish residents [14]. We used existing Danish health and administrative registries to identify patients who underwent at least one colonoscopy in Denmark during the period 1 January 1995 to 31 December 2015. In March 2014, a fecal immunochemical test-based CRC screening program, with colonoscopy as the second-line diagnostic procedure, was introduced nationwide in Denmark [15]. Most colonoscopies included in the present study were thus performed outside the formal CRC screening program among patients with symptoms such as anemia, gastrointestinal bleeding, changing bowel habits etc. Linkage of individual-level data from different registries was enabled by the unique 10-digit identifier assigned to each legal resident of Denmark by the Danish Civil Registration System at the time of birth or upon immigration [16]. These data also allowed us to monitor deaths and emigration from Denmark during the entire study period. The study was reported to the Danish Data Protection Agency by Aarhus University (Record no. 2016–051–000001/1671). Details of all diagnosis and procedure codes used in the study are provided in **Table 1s** and **Table 2s** in the online-only Supplementary material.

Aim I: Absolute and relative risks of PCCRC

Colonoscopy cohort

We searched the Danish National Patient Registry (DNPR) covering all Danish hospitals to identify all patients with a record of at least one colonoscopy during 1995–2012. This approach allowed at least 36 months of follow-up for colonoscopies performed in 2012 to be included in the study. The DNPR contains records of all hospital inpatient stays since 1977 [17]. Since 1995, the DNPR has also included hospital outpatient clinic visits and emergency room contacts. Its data include the unique 10-digit identifier assigned to each resident, dates of hospital admission and discharge, surgical and endoscopic procedures, and up to 20 discharge diagnoses coded according to the International Classification of Diseases (ICD). In 1995, reporting of colonoscopies performed during contacts with public hospital outpatient clinics became mandatory, and the high quality of coding has been documented even prior to 1995 [7, 18]. In Denmark, most colonoscopies are performed at public hospitals, with only a minor proportion taking place in private endoscopy clinics. Reporting to the DNPR became mandatory for all private clinics in 2003 [17].

We defined the first-time colonoscopy recorded in the DNPR as colonoscopy #1. The first subsequent colonoscopy recorded more than 6 months after colonoscopy #1 was considered as colonoscopy #2. Similarly, we required colonoscopy #3, #4, and #5 to be recorded more than 6 months after colonoscopy #2, #3, and #4, respectively.

Assessment of diverticular disease

For all patients included in the colonoscopy cohort, we obtained information from the DNPR on any records of diverticular disease diagnoses. We considered all patients who received a first-time diagnosis of diverticular disease, recorded in the DNPR before or within 90 days after their first-time colonoscopy, to be patients with diverticular disease. The remaining patients were categorized as patients without diverticular disease. As we were unable to distinguish between diverticulosis and diverticulitis using ICD-10 codes [19], and because PCCRC risk may depend on the severity of diverticular disease, we additionally classified patients with diverticular disease in mutually exclusive categories: 1) surgically treated for diverticular disease, 2) conservatively treated for diverticular disease, and as 3) other cases of diverticular disease. This classification functioned as a surrogate measure for disease severity. For surgically treated patients, we required a code for a relevant abdominal surgery to be recorded in the DNPR within 120 days after the diverticular disease diagnosis. We considered patients with diverticular disease as conservatively treated if they received the diagnosis during an inpatient stay and had no records of surgery within 120 days after the first-time diagnosis. The remaining diverticular disease patients (i. e. those with outpatient diverticular disease diagnoses and no surgeries) were categorized as other cases of diverticular disease. Based on clinical experience, we expected the third group to contain patients diagnosed with diverticular disease at a computed tomography scan or colonoscopy performed for other indications (i. e. those with asymptomatic diverticular disease). Patients with and without diverticular disease who had a record of inflammatory bowel disease, CRC, or total colectomy before the date of their first-time colonoscopy were excluded. Patients who received a diagnosis of a hereditary CRC syndrome were included provided they did not receive a CRC diagnosis prior to their first-time colonoscopy (0.3% of patients with diverticular disease and 1.2% of patients without diverticular disease).

PCCRC

The outcome of Aim I was incidence of PCCRC. As recommended by the WEO, we defined PCCRC as a CRC diagnosed beyond 6 months and up to 36 months following a colonoscopy that did not detect a cancer [20]. We categorized PCCRCs by anatomic location as follows: proximal to the splenic flexure, distal to and including the splenic flexure, rectal, or unknown. Data on PCCRCs were obtained from the Danish Cancer Registry. This registry contains records of all incident malignant neoplasms diagnosed in Denmark since 1943 [21].

Comorbidities

We obtained information on conditions included in the Charlson Comorbidity Index (CCI) [22] based on discharge diagnoses recorded in the DNPR from 1977 until a first-time colonoscopy. The CCI comprises a scoring system that assigns 1–6 points to a range of conditions as components of a summed aggregated score (The specific CCI conditions and their corresponding ICD codes are provided in **Table 2s**.).

Aim II: 3-year rates of PCCRC

CRC cohort and assessment of diverticular disease

For Aim II, we obtained information on all CRCs recorded in the Danish Cancer Registry during the study period, as well as specifically within 0–36 months following a colonoscopy. PCCRCs were defined as CRCs diagnosed beyond 6 months and up to 36 months after a prior colonoscopy. Colonoscopies that failed to detect the subsequent PCCRC were denoted as false negatives. We defined CRCs diagnosed within 6 months of a preceding colonoscopy as detected CRCs, with the corresponding colonoscopies denoted as true positives. Of note, we defined PCCRCs as those diagnosed beyond 6 months following a negative colonoscopy to avoid overlapping time intervals with detected CRCs. For all CRCs, we searched the DNPR to obtain information on diverticular disease diagnoses recorded before or within 90 days after a true-positive colonoscopy (for detected CRCs) or false-negative colonoscopy (for PCCRCs). In the likely event that a PCCRC patient had a false-negative colonoscopy followed by a true-positive colonoscopy, diverticular disease status was assessed on the date of their false-negative colonoscopy. As described for Aim 1, patients with diverticular disease were categorized as 1) surgically treated, 2) conservatively treated, or 3) other cases of diverticular disease.

Statistical analyses

Aim I: Absolute and relative risks of PCCRC

We characterized patients with and without diverticular disease according to sex, age at first-time colonoscopy, year of first-time colonoscopy, type of contact (inpatient unit or outpatient clinic) for diverticular disease, region of first-time colonoscopy, CCI score, and severity of diverticular disease.

As a measure of absolute PCCRC risk, we calculated 7–36-month cumulative incidence proportions (CIPs) and associated 95%CIs of PCCRC. We treated death and colectomy as competing risks. Using the Aalen–Johansen estimator, we calculated CIPs as estimates of cause-specific risk, accounting for the impossibility of experiencing a PCCRC if a competing event (i.e. death or colectomy) occurs beforehand [23]. To calculate CIPs, we followed patients with and without diverticular disease from 7 months after the date of their first-time colonoscopy until first occurrence of either PCCRC, death, colectomy, emigration, or 36 months. Patients who received a diagnosis of detected CRC, underwent a colectomy, died, or emigrated within 6 months after their first-time colonoscopy were not included in this portion of the study. For patients with multiple colonoscopies, we applied the same methodology to each colonoscopy individually (i.e. providing risk estimates for colonoscopies #1–5 separately). We stratified CIPs by sex, age group at colonoscopy, years since colonoscopy, severity of diverticular disease, and anatomic location of PCCRC.

As a measure of relative PCCRC risk, comparing patients with and without diverticular disease, we used Cox proportional hazards regression models to compute crude and adjusted hazard ratios (HRs) with associated 95%CIs. The follow-up period was the same as for CIPs. In five separate analyses, we calculated crude and adjusted HRs for colonoscopies #1–5. In the adjusted model, we included age group, sex, year of colonoscopy, and CCI score. We stratified HRs by sex, age group at colonoscopy, severity of diverticular disease, and anatomic location of PCCRC.

Aim II: 3-year rates of PCCRC

For Aim II, we calculated the 3-year rates of PCCRC for patients with and without diverticular disease by dividing the number of false-negative colonoscopies by the total number of true-positive and false-negative colonoscopies, as recommended by the WEO [20]. For individuals who underwent multiple colonoscopies, only the first false-negative and the first-true positive colonoscopy were included in the calculation. We stratified 3-year PCCRC rates by sex, age group at colonoscopy, severity of diverticular disease, and anatomic location of PCCRC.

Sensitivity analyses

In three sensitivity analyses, we assessed the cutoff for the PCCRC definition set by the WEO by extending the PCCRC definition to CRCs diagnosed respectively within: 1) 7–12 months, 2) 7–60 months, and 3) 7–120 months after a preceding colonoscopy that did not detect a cancer. The results of our sensitivity analyses were not materially different from those of our main analysis (data not shown).

Results

Aim I: Absolute and relative risks of PCCRC

Colonoscopy cohort characteristics

The study cohort comprised 56 642 patients with and 306 800 patients without diverticular disease. The group of patients with diverticular disease included 2270 (4.0%) who were surgically treated, 22 210 (39.2%) who were conservatively treated, and 32 162 (56.8%) who were classified as other cases of diverticular disease. The characteristics of patents with and without

diverticular disease are shown in ▶ **Table 1**. Patients with diverticular disease were older (median age 69.2 vs. 60.3 years) and had a slightly higher burden of comorbidities (CCI score = 0, 53.3% vs. 61.4%) than patients without diverticular disease. The remaining characteristics were similar between patients with and without diverticular disease (▶ **Table 1**).

Absolute risks of PCCRC

Within the first 6 months after the first-time colonoscopy, we excluded 1897 (3.3%) patients with diverticular disease who died, 752 (1.3%) who had detected CRC, 61 (0.1%) who underwent colectomy, and 30 (0.05%) who emigrated from Denmark. Among patients without diverticular disease, we excluded 13 002 (4.2%) who died, 13 632 (4.4%) who had detected CRC, 587 (0.2%) who underwent colectomy, and 289 (0.09%) who emigrated from Denmark. The CIPs of competing events (i. e. death and colectomy) are reported in **Table 3s**. Among patients with diverticular disease, we observed 243 cases of PCCRC recorded within 7–36 months after a first-time colonoscopy, yielding a CIP of 0.45% (95%CI 0.40%–0.51%) (▶ **Fig. 1**, **Table 2**). The corresponding number and CIP among patients without diverticular disease were 1015 and 0.36% (95%CI 0.34%–0.38%), respectively (▶ **Fig. 1**, ▶ **Table 2**). Of note, we observed an increasing risk of PCCRC with increasing age in both patients with and without diverticular disease (▶ **Table 2**). The 7–36-month CIPs for subsequent colonoscopies were low and comparable, with estimates of less than 1% for both patients with and without diverticular disease (▶ **Table 2**). Stratification by sex, age group, years since colonoscopy, and severity of diverticular disease for subsequent colonoscopies yielded similar findings so those for first-time colonoscopies (▶ **Table 2**). Finally, stratification by anatomic location of PCCRC showed higher CIPs for proximally located PCCRCs in both groups.

Relative risks of PCCRC

In our regression model, we observed no or only slight differences in PCCRC risk between patients with and without diverticular disease after adjusting for sex, age group, year of colonoscopy, and CCI score (▶ **Table 3**). The differences between our crude and adjusted estimates were primarily driven by the differing age distribution. Stratification by sex indicated a slightly lower relative risk of PCCRC for males, when comparing patients with and without diverticular disease; this finding was evident for colonoscopies #1–3 (▶ **Table 3**). Due to low numbers of PCCRCs among patients who had been surgically treated for diverticular disease, we were unable to conduct a meaningful comparison between these patients and patients without diverticular disease. Stratification by anatomic location of PCCRC yielded slightly increased HRs for proximally located PCCRCs after a first (HR 1.23, 95%CI 1.01–1.50) and second (HR 1.26, 95%CI 0.79–2.03) colonoscopy (▶ **Table 3**).

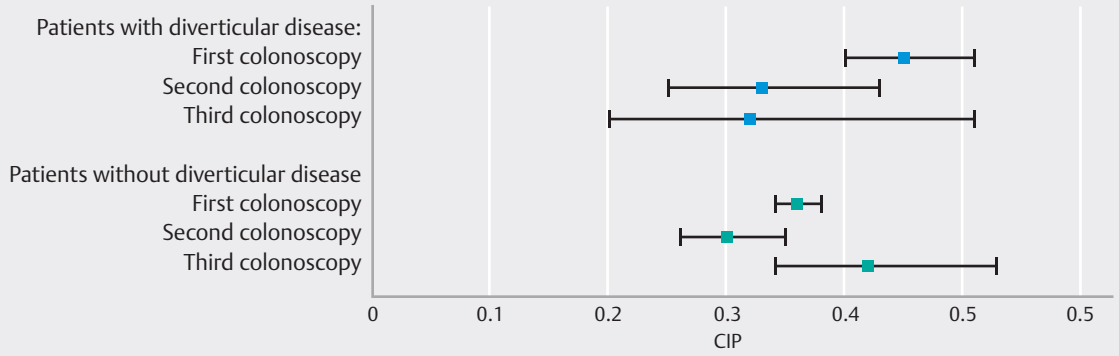
Aim II: 3-year rates of PCCRC

Among 1958 colonoscopies, we categorized 373 (19.0%) as false negative and 1585 (81.0%) as true positive in patients with diverticular disease, yielding a 3-year PCCRC rate of 19.0%

▶ **Table 1** Characteristics of patients undergoing at least one colonoscopy in Denmark during 1995–2012, by presence of coexisting diverticular disease. Patients with inflammatory bowel disease, prior colorectal cancer, or total colectomy were excluded.

	Diverticular disease[1]	No diverticular disease
Total	56 642 (100)	306 800 (100)
▪ Female	31 534 (55.7)	169 340 (55.2)
▪ Male	25 108 (44.3)	137 460 (44.8)
Age at first-time colonoscopy, years		
▪ Median age at diagnosis (IQR)	69.2 (59.7–77.7)	60.3 (48.1–70.9)
▪ 0–59	14 520 (25.6)	151 505 (49.4)
▪ 60–69	15 043 (26.6)	72 739 (23.7)
▪ 70+	27 079 (47.8)	82 556 (26.9)
Year of first-time colonoscopy		
▪ 1995–2000	9135 (16.1)	47 993 (15.6)
▪ 2001–2006	17 881 (31.6)	103 625 (33.8)
▪ 2007–2012	29 626 (52.3)	155 182 (50.6)
Type of admission[2]		
▪ Inpatient unit	18 530 (32.7)	88 884 (29.0)
▪ Outpatient clinic	38 112 (67.3)	217 916 (71.0)
Region of first-time colonoscopy		
▪ Capital	9090 (16.0)	59 748 (19.5)
▪ Zealand	7911 (14.0)	37 421 (12.2)
▪ Southern	17 081 (30.2)	83 702 (27.3)
▪ Central	12 852 (22.7)	86 021 (28.0)
▪ North	8512 (15.0)	33 741 (11.0)
▪ Unknown	1195 (2.1)	6167 (2.0)
CCI score[3]		
▪ 0 points: no comorbidity	30 194 (53.3)	188 301 (61.4)
▪ 1–2 points: low comorbidity	18 994 (33.5)	85 126 (27.8)
▪ 3 or more points: high comorbidity	7454 (13.2)	33 336 (10.9)
Severity of diverticular disease		
▪ Surgically treated	2270 (4.0)	N/A
▪ Conservatively treated	22 210 (39.2)	N/A
▪ Other cases	32 162 (56.8)	N/A

Data are n (%) unless otherwise stated.
IQR, interquartile range; CCI, Charlson Comorbidity Index; N/A, not applicable.
[1]Diagnosed before or within 90 days after the first-time colonoscopy.
[2]Treatment setting (i. e. either hospitalized or treated as an outpatient without hospitalization).
[3]Calculated based on discharge diagnoses recorded before the first-time colonoscopy.



▶ **Fig. 1** Cumulative incidence proportions in percentages with associated 95%CIs of post-colonoscopy colorectal cancer[1] among patients with[2] and without diverticular disease undergoing colonoscopy (treating death and colectomy as competing risks),[3] Denmark, 1995–2015. Patients with inflammatory bowel disease, prior colorectal cancer, or total colectomy were excluded. [1]Colorectal cancer diagnosed 7–36 months after a negative colonoscopy. Colonoscopies performed during 1995–2012 were included. [2]Recorded in the Danish National Patient Registry before or within 90 days after a given colonoscopy. [3]Date of colectomy recorded in the Danish National Patient Registry plus 90 days to avoid ambiguities in coding of dates.

▶ **Table 2** Cumulative incidence proportions in percentages with associated 95%CIs of post-colonoscopy colorectal cancer among patients undergoing a second to fifth colonoscopy (treating death and colectomy as competing risks), by presence of coexisting diverticular disease, Denmark, 1995–2015. Patients with inflammatory bowel disease, prior colorectal cancer, and total colectomy were excluded.

	PCCRC[1]		CIP,[2] % (95%CI)	
	Diverticular disease[3]	No diverticular disease	Diverticular disease[3]	No diverticular disease
First colonoscopy	243 (100)	1.015 (100)	0.45 (0.40–0.51)	0.36 (0.34–0.38)
Sex				
▪ Female	138 (56.8)	501 (49.4)	0.46 (0.39–0.54)	0.32 (0.29–0.35)
▪ Male	105 (43.2)	514 (50.6)	0.44 (0.36–0.53)	0.42 (0.38–0.45)
Age at colonoscopy, years				
▪ 0–59	15 (6.2)	165 (16.3)	0.10 (0.06–0.17)	0.11 (0.10–0.13)
▪ 60–69	44 (18.1)	283 (27.9)	0.30 (0.22–0.40)	0.43 (0.38–0.48)
▪ 70 +	184 (75.7)	567 (55.9)	0.73 (0.63–0.85)	0.83 (0.77–0.90)
Time since first colonoscopy				
▪ 1 year	61 (25.1)	285 (28.1)	0.11 (0.09–0.14)	0.10 (0.09–0.11)
▪ 2 years	105 (43.2)	391 (38.5)	0.31 (0.26–0.36)	0.24 (0.22–0.26)
▪ 3 years	77 (31.7)	339 (33.4)	0.45 (0.40–0.51)	0.36 (0.34–0.38)
Severity of diverticular disease				
▪ Surgically treated	5 (2.1)	N/A	0.22 (0.09–0.50)	N/A
▪ Conservatively treated	103 (42.4)	N/A	0.50 (0.41–0.60)	N/A
▪ Other cases	135 (55.6)	N/A	0.33 (0.22–0.48)	N/A
CRC site				
▪ Proximal colon	130 (53.5)	469 (46.2)	0.24 (0.20–0.28)	0.17 (0.15–0.18)
▪ Distal colon	51 (21.0)	209 (20.6)	0.09 (0.07–0.12)	0.07 (0.06–0.08)
▪ Rectal	32 (13.2)	229 (22.6)	0.06 (0.04–0.08)	0.08 (0.07–0.09)
▪ Unknown	30 (12.3)	108 (10.6)	0.06 (0.04–0.08)	0.04 (0.03–0.05)
Second colonoscopy[4]	53 (100)	160 (100)	0.33 (0.25–0.43)	0.30 (0.26–0.35)

▶ **Table 2** (Continuation)

	PCCRC[1]		CIP,[2] % (95%CI)	
	Diverticular disease[3]	No diverticular disease	Diverticular disease[3]	No diverticular disease
Sex				
▪ Female	34 (64.2)	81 (50.1)	0.38 (0.27–0.53)	0.28 (0.23–0.35)
▪ Male	19 (35.8)	79 (49.4)	0.27 (0.17–0.41)	0.32 (0.26–0.40)
Age at colonoscopy, years				
▪ 0–59	N/A	N/A	0.06 (0.10–0.20)	0.14 (0.10–0.20)
▪ 60–69	N/A	N/A	0.37 (0.23–0.58)	0.29 (0.22–0.39)
▪ 70+	33 (62.3)	81 (50.6)	0.42 (0.29–0.58)	0.56 (0.45–0.69)
Time since second colonoscopy				
▪ 1 year	6 (11.3)	15 (9.4)	0.04 (0.02–0.08)	0.03 (0.02–0.04)
▪ 2 years	22 (41.5)	55 (34.4)	0.18 (0.12–0.25)	0.13 (0.10–0.16)
▪ 3 years	25 (47.2)	91 (8.6)	0.33 (0.25–0.43)	0.30 (0.26–0.35)
Severity of diverticular disease				
▪ Surgically treated	N/A	N/A	N/A	N/A
▪ Conservatively treated	26 (49.1)	N/A	0.36 (0.24–0.52)	N/A
▪ Other cases	27 (50.9)	N/A	0.33 (0.22–0.48)	N/A
CRC site				
▪ Proximal colon	26 (49.1)	72 (45.0)	0.16 (0.11–0.24)	0.13 (0.11–0.17)
▪ Distal colon	9 (17.0)	30 (18.8)	0.06 (0.03–0.11)	0.06 (0.04–0.08)
▪ Rectal	10 (18.9)	42 (26.3)	0.06 (0.03–0.11)	0.08 (0.06–0.11)
▪ Unknown	8 (15.1)	16 (10.0)	0.05 (0.02–0.10)	0.03 (0.02–0.05)
Third colonoscopy[5]	17 (100)	74 (100)	0.32 (0.20–0.51)	0.42 (0.34–0.53)
Sex				
▪ Female	10 (58.8)	28 (37.8)	0.36 (0.19–0.64)	0.31 (0.21–0.45)
▪ Male	7 (41.2)	46 (62.2)	0.28 (0.13–0.56)	0.54 (0.40–0.72)
Age at colonoscopy, years				
▪ 0–59	N/A	14 (18.9)	0.10 (0.01–0.57)	0.20 (0.12–0.34)
▪ 60–69	N/A	24 (32.4)	0.36 (0.15–0.75)	0.42 (0.27–0.61)
▪ 70+	10 (58.8)	36 (48.6)	0.38 (0.20–0.68)	0.75 (0.53–1.02)
Time since third colonoscopy				
▪ 1 year	N/A	10 (13.5)	0.02 (0.00–0.11)	0.06 (0.03–0.10)
▪ 2 years	N/A	32 (43.2)	0.13 (0.06–0.27)	0.24 (0.18–0.32)
▪ 3 years	10 (58.8)	32 (43.2)	0.32 (0.20–0.51)	0.42 (0.34–0.53)
Severity of diverticular disease				
▪ Surgically treated	N/A	N/A	0.60 (0.06–3.06)	N/A
▪ Conservatively treated	11 (64.7)	N/A	0.43 (0.23–0.76)	N/A
▪ Other cases	N/A	N/A	0.19 (0.08–0.44)	N/A
CRC site				
▪ Proximal colon	7 (41.2)	46 (62.2)	0.13 (0.06–0.27)	0.27 (0.20–0.36)
▪ Distal colon	N/A	16 (21.6)	0.06 (0.02–0.16)	0.09 (0.06–0.15)

▶ **Table 2** (Continuation)

	PCCRC[1]		CIP,[2] % (95%CI)	
	Diverticular disease[3]	No diverticular disease	Diverticular disease[3]	No diverticular disease
▪ Rectal	N/A	7 (9.5)	0.08 (0.03–0.19)	0.04 (0.02–0.08)
▪ Unknown	N/A	5 (6.8)	0.06 (0.02–0.16)	0.03 (0.01–0.07)
Fourth colonoscopy[6]	9 (100)	23 (100)	0.47 (0.24–0.88)	0.32 (0.21–0.48)
Fifth colonoscopy[7]	N/A	14 (100)	0.41 (0.12–1.14)	0.44 (0.26–0.73)

N/A, not applicable (n < 5); PCCRC, post-colonoscopy colorectal cancer; CIP, cumulative incidence proportion; CRC, colorectal cancer.
[1]CRC diagnosed 7–36 months after a negative colonoscopy. Colonoscopies performed during 1995–2012 were included.
[2]Death and colectomy treated as competing risks. Date of colectomy recorded in the Danish National Patient Registry plus 90 days to avoid ambiguities in coding of dates.
[3]Recorded in the Danish National Patient Registry before or within 90 days after a given colonoscopy.
[4]The first subsequent colonoscopy recorded >6 months after a first-time colonoscopy.
[5]The first subsequent colonoscopy recorded >6 months after the second colonoscopy.
[6]The first subsequent colonoscopy recorded >6 months after the third colonoscopy.
[7]The first subsequent colonoscopy recorded >6 months after the fourth colonoscopy.

(▶ **Table 4**). The diverticular disease-related 3-year PCCRC rates were 21.3% for females and 16.7% for males and increased with age, from 14.0% for patients aged 0–59 years to 20.8% for patients aged 70 + years. The 3-year PCCRC rate was markedly higher for patients with surgically treated diverticular disease (53.3%) than for the two other groups of patients with diverticular disease, and modestly elevated for proximally located CRCs (22.3%). Among patients without diverticular disease, we identified 1536 false-negative (6.5%) and 21 970 (93.5%) true-positive colonoscopies, yielding a 3-year PCCRC rate of 6.5%. The 3-year PCCRC rates were virtually equal across all strata of sex and age groups among patients without diverticular disease (▶ **Table 4**).

Discussion

In this population-based cohort study, we found that less than 1% of patients with and without diverticular disease who underwent colonoscopy developed a subsequent PCCRC. The relative risk of PCCRC and 3-year PCCRC rate were slightly elevated for proximally located CRCs in patients with diverticular disease compared with those without the disease.

To the best of our knowledge, our study is the first to investigate the absolute risk of PCCRC among patients with and without diverticular disease who undergo colonoscopy. Our results align with those of the few prior studies that investigated the absolute risk of PCCRC in patients undergoing colonoscopy regardless of presence of diverticular disease. Previous studies from Spain [24, 25], Denmark [8, 9, 26], and Australia [10] showed CIPs of PCCRC ranging from 0.2% to 1% in patients undergoing colonoscopy. Therefore, despite different study cohorts, our current study and previous studies all point toward a low absolute risk of PCCRC among patients with and without diverticular disease who undergo colonoscopy. This detail is important to keep in mind when considering the increased 3-year PCCRC rates for diverticular disease suggested by our current study and previous studies.

Our results indicated a slightly increased relative risk of proximal PCCRC in patients with diverticular disease. This is a novel finding that somehow aligns with previous evidence concerning location of PCCRC. Hence, previous studies consistently reported the rectum and proximal colon as major contributors to PCCRC [1, 27, 28, 29, 30, 31, 32, 33]. The novelty in our findings is therefore that the risk of a proximally located PCCRC may be further increased among patients with diverticular disease. Generally, the most plausible explanation for PCCRCs diagnosed within 36 months after a negative colonoscopy is missed or incompletely resected colorectal lesions rather than rapidly growing lesions appearing in the interval between two colonoscopies. Therefore, it is conceivable that our findings reflect missed colorectal lesions in the proximal colon owing to a higher number of incomplete colonoscopies (i. e. not reaching the cecum) due to diverticular disease-related inflammation in the distal colon. Finally, it should be recognized that the number of proximally located PCCRCs in our study was low, which hampered the robustness of our results and highlights the need for further studies investigating this topic. Furthermore, we found higher 3-year PCCRC rates for proximal CRCs than for distal CRCs among both patients with and without diverticular disease. Our relative risk estimates and 3-year PCCRC rates together suggest an association between diverticular disease and proximal PCCRC. However, the 3-year PCCRC rates were substantially higher for patients with diverticular disease compared with those without the disease across all strata of PCCRC site, sex, age, and diverticular disease severity. Therefore, diverticular disease-related CRCs, to a greater extent than non-diverticular disease-related CRCs, could be categorized as a PCCRC regardless of PCCRC site. It may seem counterintuitive that the relative risk of PCCRC was elevated for proximal PCCRC only, while 3-year PCCRC rates were elevated for all PCCRC sites. However, the HRs reflect rate ratios of PCCRC occurring in patients undergoing colonoscopy. In contrast, the 3-year PCCRC rates reflect the proportion of colonoscopy-diagnosed CRCs that could be classified as PCCRC within a 36-month period, without considering the total number of colonoscopies per-

▶ **Table 3** Crude and adjusted hazard ratios and associated 95%CIs of post-colonoscopy colorectal cancer[1] after one, two, three, four, or five colonoscopies, comparing patients with diverticular disease[2] with those without diverticular disease, Denmark, 1995–2015. Patients with inflammatory bowel disease, prior colorectal cancer, or total colectomy were excluded.

	Crude HR (95%CI)	Adjusted HR[3] (95%CI)
First colonoscopy	1.26 (1.09–1.44)	0.84 (0.73–0.97)
Sex		
▪ Female	1.45 (1.21–1.75)	0.89 (0.74–1.08)
▪ Male	1.06 (0.86–1.31)	0.78 (0.64–0.97)
Age at colonoscopy		
▪ 0–59	0.93 (0.54–1.57)	0.91 (0.54–1.55)
▪ 60–69	0.69 (0.50–0.95)	0.71 (0.51–0.97)
▪ 70+	0.87 (0.73–1.02)	0.88 (0.74–1.04)
Severity of diverticular disease		
▪ Surgically treated	N/A	N/A
▪ Conservatively treated	1.47 (1.23–1.74)	0.89 (0.75–1.01)
▪ Other cases	1.03 (0.84–1.27)	0.78 (0.64–0.97)
CRC site		
▪ Proximal colon	1.34 (1.10–1.63)	1.23 (1.01–1.50)
▪ Distal colon	1.15 (0.85–1.56)	1.07 (0.79–1.46)
▪ Rectal	0.72 (0.50–1.05)	0.67 (0.46–1.00)
▪ Unknown	1.30 (0.87–1.95)	1.09 (0.71–1.67)
Second colonoscopy[4]	1.11 (0.81–1.51)	0.86 (0.62–1.17)
Sex		
▪ Female	1.38 (0.92–2.06)	0.97 (0.64–1.46)
▪ Male	0.82 (0.50–1.36)	0.69 (0.41–1.55)
Age at colonoscopy		
▪ 0–59	0.47 (0.11–1.98)	0.46 (0.11–1.92)
▪ 60–69	1.25 (0.72–2.15)	1.29 (0.75–2.23)
▪ 70+	0.72 (0.48–1.08)	0.73 (0.49–1.10)
Severity of diverticular disease		
▪ Surgically treated	N/A	N/A
▪ Conservatively treated	1.25 (0.85–1.84)	0.90 (0.61–1.33)
▪ Other cases	0.96 (0.62–1.51)	0.79 (0.50–1.24)
CRC site		
▪ Proximal colon	1.58 (1.00–2.51)	1.26 (0.79–2.03)
▪ Distal colon	1.25 (0.57–2.72)	1.22 (0.54–2.73)
▪ Rectal	0.88 (0.4–1.85)	0.62 (0.27–1.43)
▪ Unknown	2.18 (0.81–5.88)	2.10 (0.59–7.54)
Third colonoscopy[5]	0.79 (0.46–1.34)	0.62 (0.36–1.07)
Sex		
▪ Female	1.16 (0.56–2.41)	0.88 (0.41–1.86)
▪ Male	0.55 (0.25–1.22)	0.44 (0.20–0.99)
Age at colonoscopy		
▪ 0–59	0.54 (0.07–4.17)	0.53 (0.07–4.08)
▪ 60–69	0.92 (0.37–2.25)	0.93 (0.38–2.31)
▪ 70+	0.52 (0.26–1.05)	0.53 (0.26–1.07)
Severity of diverticular disease		
▪ Surgically treated	N/A	N/A
▪ Conservatively treated	1.06 (0.56–2.00)	0.81 (0.42–1.54)
▪ Other cases	0.45 (0.18–1.12)	0.37 (0.16–0.93)
CRC site		
▪ Proximal colon	0.78 (0.35–1.77)	0.57 (0.25–1.33)
▪ Distal colon	1.18 (0.33–4.24)	1.43 (0.32–6.38)
▪ Rectal	1.34 (0.31–5.70)	24.8 (0.75–817.5)
▪ Unknown	1.34 (0.22–8.21)	N/A
Fourth colonoscopy[6]	1.41 (0.65–3.02)	1.16 (0.51–2.57)
Fifth colonoscopy[7]	0.97 (0.28–3.42)	0.82 (0.22–2.97)

HR, hazard ratio; N/A, not applicable; CRC, colorectal cancer.
[1]CRC diagnosed 7–36 months after a negative colonoscopy. Colonoscopies performed during 1995–2012 were included.
[2]Recorded before or within 90 days after a given colonoscopy.
[3]Adjusted for age group, sex, year of colonoscopy, and Charlson Comorbidity Index score.
[4]The first subsequent colonoscopy recorded >6 months after the first-time colonoscopy.
[5]The first subsequent colonoscopy recorded >6 months after the second colonoscopy.
[6]The first subsequent colonoscopy recorded >6 months after the third colonoscopy.
[7]The first subsequent colonoscopy recorded >6 months after the fourth colonoscopy.

formed. Thus, the two risk estimates are calculated using different methods, as well as different study populations (i.e. HRs in patients undergoing colonoscopy and 3-year PCCRC rates in patients with CRC). This could result in estimates indicating opposite directions of the association and explain why the 3-year PCCRC rates were elevated for patients with diverticular disease across all strata of PCCRC sites, while the PCCRC relative risks were not.

We observed increasing 3-year PCCRC rates with older age groups among patients with diverticular disease. Again, this could be due to more complicated colonoscopies performed among older patients and a higher tendency of endoscopists to cut short the colonoscopy.

The strengths of our study include its population-based design and the availability of high quality and continuously upda-

▶ **Table 4** Colonoscopies categorized as false-negatives or true-positives and post-colonoscopy colorectal cancer 3-year rates, stratified by presence of diverticular disease, Denmark, 1995–2015. Patients with inflammatory bowel disease, prior colorectal cancer, or total colectomy were excluded.

	Colonoscopies[1]			3-year PCCRC rate,[4] %
	False-negative colonoscopies,[2] n	True-positive colonoscopies,[3] n	Total, n	
Patients with diverticular disease[5]	373	1585	1958	19.0
Sex				
▪ Female	214	792	1006	21.3
▪ Male	159	793	952	16.7
Age at colonoscopy				
▪ 0–59	23	141	164	14.2
▪ 60–69	85	378	463	18.3
▪ 70+	265	1066	1271	20.8
Severity of diverticular disease				
▪ Surgically treated	8	7	15	53.3
▪ Conservatively treated	161	590	751	21.4
▪ Other cases	204	988	1192	17.1
CRC site				
▪ Proximal colon	194	676	870	22.3
▪ Distal colon	75	561	636	11.8
▪ Rectal	59	277	336	17.6
▪ Unknown	45	71	116	38.8
Patients without diverticular disease	1536	21 970	23 506	6.5
Sex				
▪ Female	744	10 169	10 913	6.8
▪ Male	792	11 801	12 593	6.3
Age at colonoscopy				
▪ 0–59	258	3703	3961	6.5
▪ 60–69	441	6432	6873	6.4
▪ 70+	837	11 835	12 672	6.6
CRC site				
▪ Proximal colon	733	7966	8699	8.4
▪ Distal colon	318	6542	6860	4.6
▪ Rectal	334	6333	6667	5.0
▪ Unknown	151	1129	1280	11.8

PCCRC, post-colonoscopy colorectal cancer; CRC, colorectal cancer.
[1]Each individual was allowed more than one colonoscopy; however, only the first false-negative and first true-positive colonoscopy were included in the absolute numbers and the calculated 3-year PCCRC rates.
[2]Colonoscopies in which a CRC was diagnosed within 7–36 months after the procedure.
[3]Colonoscopies in which a CRC was detected within 6 months after the procedure.
[4]False-negative colonoscopies/(true-positive colonoscopies + false-negative colonoscopies) ×100.
[5]Diagnosed before or within 90 days after a false-negative or true-positive colonoscopy.

ted data on colonoscopies [7, 8], diverticular disease [19], and CRC [21] diagnoses. Our study also has several limitations. First, the DNPR lacks detailed data on the characteristics of colonoscopies, including completeness, indication, quality of bowel preparation, and endoscopists' detection rates. Missing information on completeness prevented us from initiating follow-up exactly 7 months after the first complete colonoscopy. To deal with this issue, we considered all colonoscopies performed within 6 months of a preceding colonoscopy as part of the same diagnostic window. Considering this approach together with the alignment of our results with those of previous studies, and our large sample size, we do not expect that this issue had a substantial impact on our findings. Nevertheless, the missing information on completeness prevented investigation of the proportion of diverticular disease- and non-diverticular disease-related colonoscopies that were cut short due to inflammation in the distal colon. With respect to the missing data on indication, we assumed that all colonoscopies, regardless of indication, were able to detect a CRC. Detection rates for adenomas and serrated polyps are thought to be inversely associated with PCCRC and are therefore important variables [34, 35]. Lack of data on these measures is a limitation of the current study. However, we find it unlikely that more patients with diverticular disease, compared with patients without diverticular disease, underwent colonoscopies performed by endoscopists with low detection rates.

Second, due to the asymptomatic nature of simple diverticular disease, our study is likely to have missed a substantial number of these cases. However, it should be noted that our study cohort only included individuals who underwent colonoscopy and thereby had a possibility of receiving a diagnosis of diverticular disease.

Third, our study was based on patients undergoing colonoscopy during 1995–2012. The introduction of screening for CRC in many Western countries and the increased awareness of colonoscopy quality in recent years increase the need for future studies based on more updated data.

In conclusion, our findings may indicate an increased relative risk of proximally located PCCRCs in patients with diverticular disease who undergo colonoscopy compared with patients without diverticular disease. Similarly, the proportion of colonoscopy-detected diverticular disease-related CRCs that could be categorized as PCCRCs was elevated, particularly for proximally located CRCs. These findings could reflect that some colonoscopies in patients with diverticular disease may be cut short due to inflammation in the left colon, leaving the right colon unexamined. Nevertheless, less than 1% of patients with and without diverticular disease who underwent a colonoscopy developed a subsequent PCCRC. This low absolute number should be kept in mind when interpreting the elevated relative risk and diverticular disease-related 3-year PCCRC rates. The robustness of our stratified results highlights the need for further evidence regarding diverticular disease as a risk factor for PCCRC.

Conflict of Interest

The authors declare that they have no conflict of interest.

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