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Incidence and Classification of Postcolonoscopy Colorectal Cancers in Inflammatory Bowel Disease: A Dutch Population-Based Cohort Study

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Abstract

Background and Aims: Patients with inflammatory bowel disease [IBD] colitis are at increased risk for colorectal cancer [CRC]. We examined the proportion and most likely aetiology of potentially preventable postcolonoscopy CRCs [PCCRCs] in a population-based cohort. Furthermore, adherence to IBD surveillance guidelines was evaluated in both PCCRCs and the remainder of prevalent CRCs.

Methods: All IBD patients diagnosed from 1991 to 2011 in the South Limburg region of The Netherlands [*i.e.* IBDSL cohort] were included. CRC cases were cross-checked with the Dutch pathology database and cancer registry. PCCRCs were defined as cancers diagnosed within 6–60 months after a colonoscopy and were classified as attributable to 'inappropriate surveillance interval', 'inadequate bowel examination', 'incomplete resection', 'missed lesion' or 'newly developed cancer'.

Results: Twenty CRC cases were identified during 25,931 patient years of follow-up in 2,801 patients. The proportion of PCCRCs was 45.0%. Of these, 55.6% could be considered a 'missed

Abbreviations: CD, Crohn's disease; CRC, Colorectal cancer; ECCO, European Crohn's and Colitis Organisation; IBD, Inflammatory bowel disease; IQR, Interquartile range; IKNL, "Integraal Kankercentrum Nederland"; Montreal A, Age according to Montreal classification; Montreal L, Disease localisation according to Montreal classification; Montreal B, Disease behaviour according to Montreal classification; PALGA, "Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief"; PCCRC, Postcolonoscopy colorectal cancer; PSC, Primary sclerosing cholangitis; PYAR, Patient year at risk; SD, Standard deviation; TNM, Tumour-node-metastasis; UC, Ulcerative colitis.

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lesion', while other possible aetiologies occurred only once. Considering both PCCRCs [n=9] and prevalent CRCs [n=11], ten were detected after publication of the surveillance guideline, but only three patients were enrolled. Moreover, 6 CRCs [30.0%] were detected before the recommended start of surveillance.

Conclusions: In the IBDSL cohort, 45.0% of all CRCs were considered to be PCCRCs, mainly classified as missed lesions. Additionally, a large proportion of CRCs in our cohort were observed before a surveillance endoscopy was performed. Therefore, stringent adherence to IBD surveillance guidelines, improving endoscopy techniques and adjusting the surveillance program may lead to a decrease in CRC incidence.

Key Words: Epidemiology; endoscopy

1. Introduction

Over the past decades, the incidence of colorectal cancer [CRC] in patients with inflammatory bowel disease [IBD] appears to have decreased in many countries.[1,2] Recent accurate population-based studies indicating a lower incidence have been published, and this decrease may partly be attributed to improved disease control and the implementation of international surveillance guidelines.[3] However, patients with Crohn's disease [CD] with colonic involvement, and patients with ulcerative colitis [UC] with left-sided or extensive colitis, remain at increased risk of developing CRC.[1,2,4–7]

An upcoming area of interest is the incidence of potentially preventable postcolonoscopy CRCs [PCCRCs]. These comprise all CRCs arising within 6–60 months after a full colonoscopy that was negative for CRC. In the general population, PCCRCs consititute 2.9–3.7% of all CRCs.[8,9] However, in patients with CD and UC, *Wang et al.* found much higher rates of 15.1% and 15.8%, respectively.[10] Apart from a limited number of studies using hospital-based or selected populations, data on PCCRC incidence from population-based cohorts are lacking.[10–12]

Several studies in the general population found missed lesions to be a major contributor to PCCRCs.[9,13,14] In IBD, missed lesions are thought to occur even more frequently.[10] This may be due to the large proportion of flat lesions in IBD and technical difficulties in the detection of dysplasia when mucosal inflammation is present.[15] Besides missed lesions, inappropriate surveillance intervals, incomplete resection of polyps and incomplete colonoscopies are important contributors to PCCRCs.[9,14]

In this study, we evaluated the proportion of PCCRCs in the population-based IBDSL cohort and determined the most likely aetiology for their occurrence. In addition, for both PCCRCs and prevalent CRCs, adherence to IBD surveillance guidelines was evaluated.

2. Materials and Methods

2.1. Setting and data collection

All IBD patients included in the population-based IBDSL cohort were eligible for this study. This cohort has previously been described in detail.[16] In brief, all patients diagnosed with IBD between January 1991 and June 2011, of at least 18 years of age at diagnosis and living in the region of South Limburg, were included. IBD was diagnosed by certified gastroenterologists based on the combination of endoscopic, radiological and/or histological findings. A multifaceted identification strategy, involving hospitals, the nationwide Dutch Pathology Database [PALGA][17] and general practitioners, resulted in 93% completeness of our cohort. As the remaining patients were unlikely to be biased towards a specific phenotype, an unselected population was assured. The IBDSL study design has been approved by the Ethics Committee of the Maastricht University Medical Centre [NL31636.068.10], is registered in ClinicalTrial.gov [NCT02130349] and meets the ethical standards of the revised version of the Declaration of Helsinki.[18]

Cancer-related data were obtained in order to study the overall cancer risk in the IBDSL cohort.[7] In short, cancer data were collected through medical chart review and cross-checked with PALGA as well as the Dutch Cancer Registry [IKNL].[17,19] All IBDSL patients were followed until 2013, or until lost to follow-up [i.e. death or permanent migration].

In this study, all of the observed CRC cases from the IBDSL cohort were included and additional data were retrieved from patients' medical files. Since both the algorithm for classifying PCCRCs and the IBD surveillance guidelines are not designed for neuro-endocrine tumours [NETs], we excluded these malignancies from the dataset. In addition to the previously collected tumour–node–metastasis stage [TNM], differentiation stage, location of metastases, and IBD to CRC interval, all colonoscopy findings prior to CRC diagnosis were gathered. Each patient's eligibility for the IBD surveillance program according to the then applicable Dutch IBD guidelines, regardless of whether they actually received surveillance, was also assessed. It should be noted that the first guideline on IBD surveillance in the Netherlands was published in the year 2008 and that this Dutch guideline was to a large extent in line with the European ECCO guidelines. This guideline advised surveillance from 8 years after IBD onset in the case of colonic involvement, except for UC patients with only ulcerative proctitis [Montreal classification E1[20]] and patients with only one inflamed colonic segment in CD. Surveillance endoscopies should have been scheduled once every 3 years during the first decade of surveillance, followed by a surveillance endoscopy once every 2 years in the second decade and once every year in the third decade. A surveillance endoscopy should have been performed by either taking four random biopsies every 10 cm at least at nine different locations or by screening using chromoendoscopy. Patients with a concurrent diagnosis of primary sclerosing cholangitis [PSC] should have been enrolled immediately after diagnosis for annual surveillance endoscopies.[21] Enrolment status in the surveillance program of all patients who were diagnosed with CRC was retrieved from patients' medical files and colonoscopy reports. Also, the applied IBD surveillance method [i.e. either multiple random biopsies or the use of chromoendoscopy] was retrieved from the latter.

2.2. Definitions

Colorectal cancers were classified according to the time of occurrence with respect to the index colonoscopy [i.e. the last colonoscopy in which

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no cancer was detected]. In line with previous studies, we defined a CRC that occurred between 6 and 60 months after the index colonoscopy as a 'PCCRC'.[9,22–25] When a PCCRC occurred during a surveillance period [i.e. according to the Dutch IBD surveillance guidelines or Dutch post-polypectomy surveillance guidelines[21,26–28]] and before the date of the next recommended exam, it was considered an 'interval CRC', in agreement with the consensus of the Colorectal Cancer Screening Committee of the World Endoscopy Organization.[29] CRCs that could not be classified as PCCRCs were regarded as 'prevalent CRCs'. Sigmoidoscopies were not regarded as full endoscopies and therefore neglected.

For each PCCRC, the most likely aetiology [i.e. procedural factors or tumour biology] was determined according to a previously described algorithm [Figure 1].[9,24,30] PCCRCs were classified as [i] 'inappropriate surveillance interval' when detected after the index colonoscopy without receiving adequate follow-up according to previously mentioned surveillance guidelines. It should be noted that these Dutch post-polypectomy surveillance guidelines have not been designed for IBD patients. However, since the IBD guidelines do not specify surveillance intervals after occurrence of dysplasia, we used these regular guidelines for the algorithm. [ii] 'Inadequate bowel examination' was defined as inadequate bowel preparation or incomplete intubation [i.e. caecum not visualized] during the index colonoscopy. [iii] 'Incomplete resection' was defined as the development of a CRC in the same anatomic segment as a previously resected advanced adenoma [i.e. villous component, adenoma >10 mm or high-grade dysplasia]. [iv] PCCRCs detected between 6 and 36 months after the index colonoscopy as well as advanced PCCRCs [i.e. > T1N0M0] between 6 and 60 months were defined as 'missed lesions'. [v] If a non-advanced PCCRC was observed after 36 months, it was considered to be a 'newly developed cancer'.

2.3. Statistics

Statistical analyses were performed with SPSS [version 20.0, SPSS Inc., Chicago, IL, USA] to describe cohort characteristics. Incidence rates were calculated per 1000 patient-years at risk [PYAR]. To correct for overestimation of the PYAR, the years after a colectomy were censored and the year of diagnosis and the year follow-up ended only counted as half patient-years, as described before.[7] Due to low number of CRCs, further statistical analysis was not performed.

3. Results

In total, 2801 IBD patients were included in the IBDSL cohort, of which 1644 had UC and 1157 had CD. Baseline characteristics of the patients are shown in Table 1. The median follow-up was 8.8 (interquartile range [IQR] 4.9–14.8]) and 8.1 [IQR 4.3–13.6] years for UC and CD, respectively. As shown in our previous study, CRC incidence could be evaluated in 25 931 PYAR.[7] After exclusion of NETs, 11 CRCs were observed in UC patients and 9 CRCs were observed in CD patients. The total incidence rate of CRC in our cohort was 0.77/1000 patient-years. A general description of all CRCs is published elsewhere.[7]

Of all CRCs, 9 [45.0%] were considered to be PCCRCs. The PCCRC incidence rate was 0.39/1000 PYAR. Characteristics of the observed PCCRCs are provided in Table 2. Of the PCCRCs, 55.6% was observed in males and the mean age at CRC diagnosis was 71.6 years [range 34–83]. Six [54.5%] PCCRCs were observed in UC and 3 [33.3%] in CD patients. All UC patients with a PCCRC had at least a left-sided colitis [Montreal E2], and all CD patients with a PCCRC had colonic or ileocolonic disease [Montreal L2/3] during follow-up. PCCRCs were diagnosed on average 36.1 months [SD 17.2] after the index colonoscopy. Seven [77.8%] patients had active disease on the index colonoscopy. One PCCRC was discovered during surgery, whereas all other PCCRCs were detected by endoscopy. Four [44.4%] PCCRCs were located in the proximal colon, and 3 [33.3%] were detected in an early stage [T1N0M0]. Most of the PCCRCs were characterized as regular adenocarcinoma, except for two mucinous adenocarcinomas. TNM-stages and cell differentiation

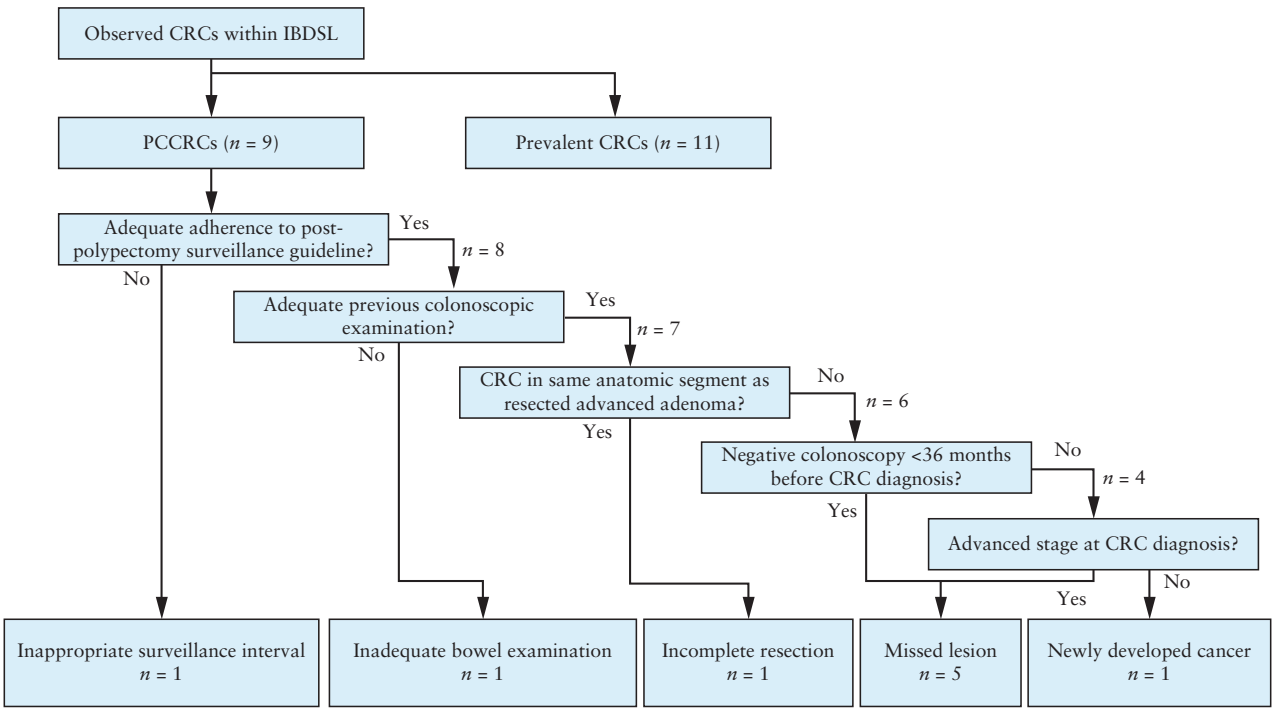

Figure 1. Algorithm to classify CRCs according to procedural factors or tumour biology.

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Table 1. Baseline characteristics of the total study population.

	Ulcerative colitis	Crohn's disease
Patients, *n*	1644	1157
Male, *n* [%]	891 [54]	430 [37]
Age at diagnosis, median [IQR]	45.0 [32.2–59.1]	34.3 [24.3–46.9]
Follow-up, median [IQR]	8.8 [4.9–14.8]	8.1 [4.3–13.6]
Total number of PSC cases, *n* [%]	13 [0.8]	6 [0.5]
Total number of CRC, *n*	11	9
Total number of PCCRC, *n* [%]	6 [55]	3 [33]
Phenotype at diagnosis[a]		
E1, *n* [%]	556 [34]	
E2, *n* [%]	777 [48]	
E3, *n* [%]	296 [18]	
L1, *n* [%]		496 [43]
L2, *n* [%]		369 [32]
L3, *n* [%]		266 [23]
L4, *n* [%]		123 [11]
B1, *n* [%]		894 [78]
B2, *n* [%]		177 [15]
B3, *n* [%]		84 [7]
P, *n* [%]		92 [8]

n, number of patients; IQR, interquartile range; PSC, primary sclerosing cholangitis; CRC, colorectal cancer; PCCRC, postcolonoscopy colorectal cancer. [a]Phenotype according to Montreal Classification. Disease extent of UC was defined as ulcerative proctitis [E1], left-sided UC [E2] and extensive UC [E3]. Disease location of CD was defined as ileal involvement [L1], exclusive colonic involvement [L2], ileocolonic involvement [L3] or isolated upper disease [L4]. L4 is a modifier, added to L1–3 when concomitant upper gastrointestinal disease is present. Disease behaviour of CD was defined as non-stricturing/non-penetrating [B1], stricturing [B2] or penetrating [B3]. Perianal disease [P] is a modifier, added to B1–3 when perianal disease is present.

can also be found in Table 2. None of the patients with a PCCRC was diagnosed with PSC at diagnosis or during follow-up.

The most likely aetiology of the PCCRCs according to the algorithm is shown in Figure 1. Of all PCCRCs, 5 [55.6%] could be considered as 'missed lesions'. 'Inappropriate surveillance interval', 'inadequate bowel examination', 'incomplete resection' and 'newly developed cancers' only occurred once, and therefore each of them contributed to 11.1% of the PCCRCs.

Since guideline adherence is applicable to both PCCRCs and prevalent CRCs, we analysed the adherence in all 20 CRC cases of the IBDSL cohort. All patients with CRC had at least a left-sided colitis [UC] or colonic involvement [CD] during follow-up and were eligible for surveillance. Ten out of the 20 CRCs [50.0%] were found within the recommended surveillance time window and after the Dutch guideline for IBD patients was published [i.e. after 2008]. Only three patients received adequate surveillance with chromoendoscopy or random biopsies, and only one of these received the first surveillance endoscopy within 8 years after diagnosis. Notably, 6 [30.0%] CRCs were observed in eligible IBD patients before the recommended start of surveillance according to the current ECCO guidelines.

4. Discussion

This is the first population-based analysis of PCCRC incidence in IBD, in which we observed that 45.0% of all incident CRCs were considered to be PCCRCs. Regarding their aetiology, missed lesions attributed to 55.6% of the PCCRCs. Poor adherence to surveillance intervals, inadequate bowel examination, incomplete resection and newly developed cancer each accounted for one PCCRC. Ten [50.0%] CRCs were found within the recommended surveillance time window, but only three patients had been enrolled at the time of CRC detection. Moreover, according to the current ECCO guidelines, six [30.0%] CRCs in the IBDSL cohort were detected before surveillance was recommended.

Although the overall CRC incidence in our cohort was low [i.e. 0.77/1000 patient-years],[7] a relatively large proportion of PCCRCs [45.0% of all CRCs in our cohort] was found. The proportion of PCCRCs in a population-based cohort study in the general population of the same region, using the same definitions, was only 2.9%.[9] The high rate of PCCRCs in our cohort may in part be explained by the frequent use of routine endoscopies to detect disease activity. These endoscopies are inferior in detecting dysplasia compared with chromoendoscopy or a random biopsy procedure [i.e. required methods for adequate IBD surveillance]. Furthermore, disease activity may disguise dysplasia and hinder resection. As a consequence, poor dysplasia detection may occur during the performance of colonoscopies for other indications [e.g. follow-up of disease activity] and a false sense of safety can remain. So far, only a few studies have investigated PCCRC incidence in IBD. *Wang et al.* reported a proportion of PCCRCs of 15.1% and 15.8% in UC and CD, respectively, in an elderly [i.e. >67 years old] IBD population in the USA.[10] These lower proportions of PCCRCs may be due to the more stringent definition [i.e. only CRCs within 36 months after a colonoscopy were considered to be PCCRCs]; though, 20% of the CRCs in our cohort would still have been classified as PCCRCs using the same definition. However, differences in guidelines, definitions and populations hinder a direct comparison. In surveillance cohorts, although different definitions have been used, the proportion of true interval CRCs, which is a subset of PCCRCs, still ranges from 21 to 29%.[11,12] Notably, six PCCRCs in this study, and one additional prevalent CRC in the remainder of cases, were diagnosed above the age of 75. The current ECCO guideline does not make any recommendation on when to stop surveillance in IBD patients.[3] Also, the Dutch guideline, which was available during the follow-up of this study, did not include such recommendation.[21] However, as stated in an update of this guideline in 2015 [i.e. after our follow-up ended], clinicians are advised to 'discuss further surveillance strategies with the patient when he/she reaches the age of 75'.[31] Since we observed a lot of PCCRCs in the elderly, we agree that continuation of surveillance, if no contra-indications exist, may be worthwhile and should be discussed by future guideline committees.

Fifty-six percent of the PCCRCs were defined as 'missed lesions' due to their rapid occurrence after an index colonoscopy, or advanced stage at diagnosis. Based on the dwell time between a newly developed neoplasm and an invasive carcinoma, we assume that neoplasia must have been present during the index colonoscopy.[32,33] However, the turnover time from dysplasia to carcinoma in IBD may be shorter than in the general population, given the frequent detection of advanced CRCs in IBD.[34] This may be related to specific molecular pathways and differences in polyp morphology.[35,36] Taking these factors into account, some PCCRCs classified as missed lesions by the algorithm may actually be newly developed CRCs. The rate of missed lesions in the present study is in line with a large study performed in the general population in the same region as our cohort.[9] However, due to the increased occurrence of easily missed flat lesions in IBD,[13] we expected the percentage of missed lesions in the present study to be even larger. Next to a possible rapid turnover time from dysplasia to carcinoma, and the increased occurrence of flat lesions in IBD, the high number of missed lesions may again be a consequence of

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Table 2. Characteristics of PCCRCs detected in the IBDSL cohort.

Pt	Gender	IBD				PCCRC									
		Type	Age [years]	Montreal[c] [diag/max]	Risk factors for CRC [FH/Sm/P/St]	Age	IBD-CRC interval [months]	Time since last colono-scopy [months]	Disease activity/ dysplasia index colonoscopy	Endoscopic technique index colonoscopy	IBD surveillance program applicable/ enrolled	Location	Type	TNM-stage	Differentiation
1[a]	M	UC	60	E2/E2	FH-/Sm-/P-/St-	75	178	20	Moderate/LGD	WLE	Y/N	Rectum	Adenocarcinoma	T1N0M0	Moderate
2	F	UC	65	E3/E3	FH[b]/Sm+/P-/St-	69	51	22	Mild/LGD	WLE	N/N	Rectum	Adenocarcinoma	T1N0M0	Moderate–Poor
3	M	UC	76	E2/E2	FH-/Sm+/P-/St-	77	8	8	Mild/No	WLE	N/N	Rectum	Adenocarcinoma	T3N1M0	Unknown
4	F	UC	68	E1/E2	FH+/Sm+/P-/St-	83	181	29	No/No	HD	Y/N	Ascending colon	Mucinous adenocarcinoma	T3N0M0	Poor
5	F	UC	60	E2/E2	FH-/Sm+/P-/St-	69	104	52	Mild/No	WLE	Y/N	Ascending colon	Adenocarcinoma	T1N0M0	Well
6[a]	M	UC	65	E2/E3	FH[b]/Sm+/P-/St-	78	155	45	Mild/No	WLE + RB [×10]	Y/Y	Ascending colon	Mucinous adenocarcinoma	T2N1M0	Poor
7	M	CD	64	L1/L3	FH-/Sm-/P-/St-	78	178	59	Mild/No	WLE	Y/N	Rectum	Adenocarcinoma	T3N0M0	Moderate
8	F	CD	28	L3/L3	FH[b]/Sm+/P-/St-	34	69	41	Mild/No	WLE	N/N	Transverse colon	Adenocarcinoma	TxNxM1	Unknown
9[a]	M	CD	71	L2/L2	FH-/Sm+/P-/St-	81	116	49	No/LGD	WLE	Y/N	Rectum	Adenocarcinoma	T3N0M0	Moderate

Pt, patient number; [a]interval CRC; 'M', male; 'F', female; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; FH, first-degree relative with CRC (yes [+], no [–], or unknown [b]); Sm, current or past smoker (yes [+], no [–], or unknown [b]); P, presence of PSC (yes [+], no [–], or unknown [b]); St, presence of strictures in the past (yes [+], no [–], or unknown [b]); LGD, low-grade dysplasia; WLE, white light endoscopy; HD, high-definition endoscopy; RB, random biopsy procedure [number of jars obtained]; [c]phenotype according to Montreal Classification at diagnosis [diag] and at maximum during follow-up [max]. Disease extent of UC was defined as ulcerative proctitis [E1], left-sided UC [E] or extensive UC [E3]. Disease location of CD was defined as ileal involvement [L1], exclusive colonic involvement [L2] or ileocolonic involvement [L3].

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the increased difficulty of dysplasia detection when mucosal inflammation is present. In addition, almost every index colonoscopy was performed using white light endoscopy [standard definition], which is considered to be inferior to high-definition endoscopy and chromoendoscopy. Since procedural explanations for PCCRC incidence has only been scarcely investigated in IBD populations, and different definitions are used, direct comparisons cannot be made. *Mooiweer et al.* studied the incidence of CRCs in a surveillance cohort and found 24% to be related to inadequate colonoscopies, 53% to be related to inadequate surveillance intervals and 12% to be related to inadequate management of dysplasia.[12]

Notably, 30.0% of all CRC cases in our cohort were found in IBD patients with at least left-sided or segmental colitis before the recommended start of IBD surveillance [i.e. 8 years after IBD onset], which is in line with a previous nationwide study.[37] Since current guidelines still advise the first surveillance endoscopy at 8 years after IBD onset, these findings raise the question of whether the surveillance guidelines in IBD are optimal. Since disease activity at diagnosis impairs the chance of CRC/dysplasia detection, inclusion of a first surveillance endoscopy after diagnosis, when remission is achieved, should be taken into account and discussed by future guideline committees. Only when absence of dysplasia is guaranteed can a patient be safely enrolled in the present IBD surveillance program. Since surveillance status was only available for patients with a history of CRC and not for the entire IBDSL cohort, adherence to IBD surveillance guidelines could not be completely assessed. As the overall incidence of CRC in our cohort was rather low,[7] we assumed that IBD surveillance was not inferior compared with other countries. According to the previous Dutch [applicable during our study period] and current ECCO guidelines, 10 out of the 20 CRCs [50.0%] were found within the recommended surveillance time window and after the Dutch guideline for IBD patients was published [i.e. after 2008]. Only three patients received adequate surveillance with chromoendoscopy or random biopsies, and only one of these received the first surveillance endoscopy within 8 years after diagnosis. Therefore, nine patients with CRC could potentially have avoided CRC through more stringent adherence to IBD surveillance guidelines by medical practitioners. Although tight surveillance in UC was an international problem in the previous era,[38] *van Rijn et al.* performed a questionnaire-based study on guideline adherence in the Netherlands in which 95% of all UC patients and 65% of all CD patients appeared to receive some type of surveillance.[39] However, only 27% of the Dutch gastroenterologists adhered to the international guidelines.[39] Since the Dutch IBD guideline was introduced in 2008 and the study of *van Rijn et al.* was performed earlier, the current adherence in the Netherlands may have improved. Although the actual guideline adherence cannot be assessed from our dataset, the present study suggests that there is still room for improvement. Closer adherence by gastroenterologists may lead to improvement in this area, and general practitioners should also adhere to the guidelines more closely because patients with longstanding clinical remission might no longer be under the care of gastroenterologists.

The major strength of this study is the assessment of PCCRC incidence in a population-based IBD cohort, thereby reflecting the full disease spectrum from mild to severe cases. Moreover, the IBDSL cohort includes detailed medical data from patients with IBD gathered through extensive manual exploration of patient files since 1991. This ensures very accurate data and a real-time estimation of the true incidence of CRC; therefore, the proportion of PCCRCs we have determined is reliable. Several limitations should be addressed. Most importantly, the algorithm used has been developed for sporadic CRCs and makes certain assumptions. For example, rectal cancer that is found 20 months after an index colonoscopy with incomplete caecal intubation is regarded as due to 'inadequate bowel examination' instead of 'missed lesion' due to the algorithm. However, neglecting these assumptions in our study will only lead to more 'missed lesions' and, therefore, to the same conclusion. In addition, we did observe a low number of CRCs and therefore a low absolute number of PCCRCs in our cohort. Therefore, minor changes in the number of incident cases would have had a large impact on the percentages of the different aetiologies and incidence rates. Furthermore, some of the patients in this cohort had a relatively short follow-up time. As the risk of CRC is higher in patients with longstanding IBD, both CRC and PCCRC rates may be higher after a longer time period of follow-up. Finally, sigmoidoscopies were excluded in the algorithm we used. Since patients with UC are screened frequently for disease activity using a sigmoidoscopy, PCCRC rates may have been even higher if these endoscopies had been taken into account.

Since PCCRC rates were much higher for IBD patients in this population-based study compared with the rates in the general population, it is important that we continue to improve adherence to the IBD surveillance guidelines for patients under the care of gastroenterologists and also for patients being cared for by general practitioners. Also, the guideline could be adapted to prevent CRCs between the IBD diagnosis and the start of CRC screening. Because most of the PCCRCs were regarded as missed lesions, there is some room for improvement in dysplasia detection during endoscopy. The increasing awareness and appraisal of the IBD surveillance guideline and improvement of endoscopy techniques may lead to better results and, hopefully, a further decrease in the incidence of CRC, and of PCCRC in particular, in future studies.

In conclusion, this first population-based cohort study on PCCRC incidence in IBD shows that 45.0% of all CRCs were considered to be PCCRCs. Most of the PCCRCs were classified as missed lesions. Additionally, a large proportion of CRCs in our cohort were observed before an IBD surveillance endoscopy was performed, either due to lack of enrolment in the surveillance program or due to development of a CRC before the recommended start of surveillance. Therefore, stringent adherence to IBD surveillance guidelines, improving endoscopy techniques, and adjusting the surveillance program may help to decrease both CRC incidence and the proportion of PCCRCs in IBD.

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Conflict of Interest

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Author Contributions

SS-D and MJP conceived the study. DSJW, RMMB, TRAvdH, CMClC, MJLR-C and LEO collected the data. DSJW, RMMB, SS-D and MJP analysed

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and interpreted the data. DSJW, RMMB, SS-D and MJP drafted the manuscript. JS, DMAEJ, LPSS and AAMM critically reviewed the data and first drafts. All authors critically reviewed and approved the final manuscript. MJP is guarantor of this article.

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