

# Risk of a post-colonoscopy colorectal cancer in patients with type 2 diabetes: a Danish population-based cohort study

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## ABSTRACT

**Objective** Prevalent type 2 diabetes (T2D) is associated with an increased risk of colorectal cancer and could impair the quality of bowel preparation for colonoscopy. This may in turn increase the risk of overlooked precancerous polyps and subsequent risk of post-colonoscopy colorectal cancer (PCCRC). We investigated whether patients with T2D are at increased risk of PCCRC compared with patients without T2D.

**Design** We conducted a population-based cohort study of patients with T2D and without T2D undergoing colonoscopy in Denmark (1995–2015). We investigated the risk of PCCRC by calculating >6 to 36 months cumulative incidence proportions (CIPs) treating death and colectomy as competing risks. Using Cox proportional-hazards regression analyses, we also computed HRs of PCCRC, comparing patients with T2D and non-T2D. According to the World Endoscopy Organization guidelines, we calculated PCCRC 3-year rates to estimate the proportions of T2D and non-T2D CRC patients experiencing PCCRC.

**Results** We identified 29 031 patients with T2D and 333 232 patients without T2D undergoing colonoscopy. We observed 250 PCCRCs among patients with T2D and 1658 PCCRCs among patients without T2D. The >6 to 36 months CIP after a first-time colonoscopy was 0.64% (95% CI 0.55% to 0.74%) for T2D and 0.36% (95% CI 0.34% to 0.38%) for patients without T2D. The HRs of PCCRC were 1.43 (95% CI 1.21 to 1.72) after a first-time colonoscopy and 1.18 (95% CI 0.75 to 1.85) after a second-time colonoscopy. The PCCRC 3-year rate was 7.9% for patients with T2D and 7.4% for patients without T2D.

**Conclusion** T2D may be associated with an increased HR of PCCRC.

## INTRODUCTION

Post-colonoscopy colorectal cancer (PCCRC), a term endorsed by the World Endoscopy Organization (WEO), refers to colorectal cancers (CRCs) diagnosed after a negative colonoscopy.<sup>1</sup> Despite the high sensitivity of colonoscopy in detecting CRC, PCCRCs may account for up to 8% of all CRCs.<sup>2–11</sup> Previous studies have consistently reported that PCCRCs represent a high proportion of CRCs diagnosed in patients

## Summary box

### What is already known about this subject?

- Post-colonoscopy colorectal cancers account for up to 8% of all colorectal cancers.
- The majority is assumed to arise from colorectal lesions that were missed or insufficiently resected at initial colonoscopy.

### What are the new findings?

- We found that patients with type 2 diabetes (T2D) had an increased relative risk of post-colonoscopy colorectal cancers compared with patients without T2D.
- These findings could reflect an association between T2D/metabolic syndrome and post-colonoscopy colorectal cancer development and growth or technically challenging colonoscopies and polypectomies.

### How might it impact on clinical practice in the foreseeable future?

- Our findings advocate for increased awareness on colorectal lesions when conducting colonoscopies among patients with T2D.

with inflammatory bowel disease.<sup>12–17</sup> Similarly, diverticular disease, prior colorectal adenomas and hereditary CRC syndromes are suggested as risk factors for a subsequent PCCRC diagnosis.<sup>15–17</sup> This elevated PCCRC risk is presumably caused primarily by impaired colonoscopy quality, but potentially also by aggressive CRC biology leading to rapid cancer development in the interval between two colonoscopies.<sup>1 16 18–20</sup>

For at least two reasons, type 2 diabetes (T2D) could be associated with increased risk of PCCRC, but evidence remains limited.<sup>17</sup> First, mounting research suggests that patients with T2D are at particularly high risk of CRC.<sup>21–24</sup> The T2D-CRC link may be due in part to presence of shared risk factors, such as obesity, sedentary lifestyle and a high-calorie diet. However, the link could also reflect T2D-associated conditions such as hyperinsulinaemia, hyperglycaemic and microbiota



alterations promoting gastrointestinal inflammation and colorectal carcinogenesis.<sup>25–31</sup> Second, T2D is suggested to be associated with inadequate bowel preparation for colonoscopy, possibly due to functional impairment of gastrointestinal motility.<sup>32–34</sup> Presence of T2D could thus lead to reduced visualisation of the colonic mucosa, in turn elevating the likelihood of overlooking precancerous polyps. This subsequently could increase PCCRC risk.<sup>35 36</sup>

Evidence regarding the impact of T2D on risk of PCCRC is needed to improve the overall colonoscopy quality and to guide clinical decision making, particularly for planning surveillance colonoscopies for patients with T2D within CRC screening programmes. The increasing need for colonoscopies in Denmark during past decades, the rapidly ageing population, and the increasing prevalence of T2D all point to the need for evidence on T2D-related PCCRC risk.<sup>16 18 32</sup>

We, therefore, conducted the present population-based cohort study to investigate the absolute and relative risk of PCCRC in patients with T2D and without T2D (aim 1) and to estimate the proportion of PCCRCs among all CRCs diagnosed in patients with T2D and without T2D (aim 2).<sup>1</sup>

## METHODS

### Setting

The study setting was the universal, tax-funded Danish healthcare system provided by the National Health Service.<sup>37</sup> We used existing Danish registries to conduct our population-based cohort study within the period 1 January 1995 to 31 December 2015. Individual-level data were linked using the unique 10-digit civil registration number issued to each Danish resident at birth or on emigration by the Danish Civil Registration System (CRS).<sup>38 39</sup> In addition, CRS data allowed for monitoring of deaths and emigration from Denmark. The study was reported to the Danish Data Protection Agency by Aarhus University (Record no. 2016-051-000001/1671).

### Aim 1: risk of a PCCRC

#### Colonoscopy cohort

We included all individuals with at least one colonoscopy performed during the study period as recorded in the Danish National Patient Registry (DNPR). The DNPR contains medical records on all in-hospital stays since 1977 and, since 1995, records on all hospital outpatient visits and contacts with emergency rooms.<sup>40</sup> Data include civil registration number, dates of hospital admission and discharge, surgical procedures (including colonoscopies), and up to 20 discharge diagnoses coded according to the International Classification of Diseases (ICD), 8th Revision until the end of 1993 and 10th Revision (ICD-10) thereafter. Since 1995, reporting of colonoscopies performed during outpatient visits has been mandatory. The quality of coding for colonoscopies in the DNPR is well documented, also before 1995 for colonoscopies

conducted during in-hospital stays.<sup>16</sup> Of note, the majority of all Danish colonoscopies are performed at public hospitals. Private endoscopy clinics conduct only a small proportion of colonoscopies, and even at these clinics, experts perform the exams.

For all patients included in the colonoscopy cohort, data from the DNPR and the Danish National Health Service Prescription Database (DNHSPD) were used to categorise them into patients with T2D and without T2D. The DNHSPD contains data on all drug prescriptions redeemed in Danish community pharmacies since 2004.<sup>41</sup> According to a previously validated algorithm, we defined patients with T2D as individuals who redeemed a prescription for a glucose-lowering drug, and/or received a hospital discharge or outpatient diagnosis of T2D before or within 90 days after their first-time colonoscopy.<sup>42</sup> In line with previous research, we considered type 1 diabetes as a first-time diagnosis of diabetes recorded in the DNPR before age 30 or at least one redeemed prescription for a glucose-lowering drug recorded in the DNHSPD before age 30 in our main analysis.<sup>42</sup> The remaining patients with diabetes mellitus were considered to represent patients with T2D.

In line with our previous study on risk of PCCRC among patients with inflammatory bowel disease, we defined the initial colonoscopy recorded in the DNPR as colonoscopy #1.<sup>43</sup> The first subsequent colonoscopy recorded more than 6 months after colonoscopy #1 was considered colonoscopy #2. In the same manner, we required colonoscopies #3, #4, and #5 to be recorded more than 6 months after colonoscopies number #2, #3, and #4, respectively. Patients with T2D and without T2D with a record of CRC, total colectomy or diagnosis of type 1 diabetes and/or inflammatory bowel disease before the date of their first-time colonoscopy were excluded. For patients with multiple colonoscopies recorded in the DNPR, we reassessed T2D status and exclusion criteria for each colonoscopy separately, permitting patients without T2D to join the T2D cohort if they received a T2D diagnosis or redeemed a prescription for a glucose-lowering drug within 90 days after a subsequent follow-up colonoscopy.

### Pos-tcolonoscopy colorectal cancers

We obtained data from the Danish Cancer Registry (DCR) on incident CRCs recorded after the first-time colonoscopy. The DCR contains records on all incident malignant neoplasms diagnosed in Denmark since 1943, including diagnosis date, tumour location and tumour stage at diagnosis.<sup>44</sup> Cancers are currently coded according to ICD-10. We categorised CRCs by stage at diagnosis into: localised, regional, metastatic and unknown in accordance with the Tumor, Node, and Metastasis (TNM) classification system. In line with the WEO, we defined PCCRC as CRC diagnosed within >6 to 36 months following a colonoscopy in which no cancer was detected.<sup>1</sup>

### Comorbidities

Data on potential cofounders (ie, factors that directly or indirectly through associated lifestyle factors could be associated

with both T2D and CRC) were collected from the DNPR and included atrial fibrillation/flutter, cardiovascular diseases including hypertension, chronic obstructive pulmonary disease, renal disease, alcohol-related diseases, diverticular diseases, obesity and familial hereditary CRC syndromes recorded since 1977.

## Aim 2: PCCRC 3-year rates

### CRC cohort

We used the DNPR and the DCR to identify all CRCs recorded within 0–36 months after a preceding colonoscopy. PCCRCs were defined as CRCs occurring >6 to 36 months after the previous colonoscopy. Colonoscopies that failed to detect a later-diagnosed CRC were defined as 'false-negative'. We defined CRCs diagnosed within 6 months after a preceding colonoscopy as detected CRCs (dCRCs). The colonoscopies during which dCRCs were detected were denoted as 'true-positive'. For all CRCs, we searched the DNPR and DNHSPD to obtain information on potential presence of T2D recorded before or within 90 days after a true-positive (for dCRCs) or false-negative colonoscopy (for PCCRCs). If a PCCRC patient had a false-negative followed by a true-positive colonoscopy, their T2D status was assessed around the time of the false-negative colonoscopy.

## Statistical analyses

### Aim 1: risk of PCCRC

We followed patients with T2D and without T2D from >6 months after the date of their first-time colonoscopy until first occurrence of PCCRC, death, total colectomy, emigration or 36 months. Patients who received a diagnosis of dCRC, underwent a total colectomy, died or emigrated within 6 months after the colonoscopy were excluded from this part of our study. For patients with multiple colonoscopies, we applied the same methodology for each colonoscopy individually. As an absolute risk measure, we computed >6 to 36 month cumulative incidence proportions (CIPs) of PCCRC with associated 95% CIs in patients with T2D and without T2D after first-time and subsequently performed colonoscopies (up to five colonoscopies). Death and total colectomy were treated as competing risks of PCCRC. The CIPs were modelled using the 'stcompet' command for Stata statistical software package introduced in 2004 by Coviello and Bogges.<sup>45</sup> This user-written command calculates non-parametric estimates of the cause-specific CIPs, accounting for the fact that it is impossible to experience the event (ie, PCCRC) if a competing event is occurring before (ie, death or total colectomy). We stratified CIPs by sex, age at colonoscopy, and time since previous colonoscopy. In addition, we used Cox proportional-hazards regression analyses to compute crude and HRs and associated 95% CIs as a measure of relative risks. The adjusted model included sex, age at colonoscopy, year of colonoscopy and presence of

the comorbidities mentioned above recorded before or on the date of colonoscopy (first-time and subsequent). Patients without T2D served as the reference group. Time elapsed since first-time colonoscopy was considered the underlying time scale. We stratified HRs by sex, age at colonoscopy, diabetes medication before colonoscopy and cancer stage at diagnosis.

### Aim 2: PCCRC 3-year rates

According to the WEO guidelines, we calculated PCCRC 3-year rates in patients with T2D and without T2D by dividing the number of false-negative colonoscopies by the total number of true-positive and false-negative colonoscopies.<sup>1</sup> For individuals who underwent multiple colonoscopies, only the first false-negative and the first true-positive colonoscopy were included in the PCCRC 3-year rate calculation. We stratified PCCRC 3-year rates by sex, age at colonoscopy and year of colonoscopy among patients with T2D and without T2D.

## Sensitivity analyses

Due to varying data availability over the study period, we identified patients with T2D using both ICD codes in the DNPR during 1977–2013 and prescription redemptions recorded in the DNHSPD during 2004–2013. We evaluated the impact of our identification method by conducting a sensitivity analysis restricting the study cohort to patients who underwent colonoscopies during 2005–2012 (allowing 1 year of prescription records prior to colonoscopies performed in 2005). Additionally, this restricted analysis evaluated the potential impact of left truncation for colonoscopies performed during outpatient visits before 1995 without records captured in the DNPR.

Furthermore, we assessed the >6 to 36 months cut-off for the PCCRC definition set by the WEO by extending the PCCRC definition to CRCs diagnosed within >6 to 60 months after a preceding colonoscopy. To permit at least 60 months of postcolonoscopy follow-up, we restricted this analysis to colonoscopies performed during 1995–2010. This allowed us to calculate CIPs and HRs as described above. PCCRC 5-year rates were calculated including colonoscopies performed during 1995–2015, but with the extended definitions.

Finally, hyperinsulinaemia may be promotogenic, which in turn could increase the risk of PCCRC in patients with T2D. The hyperinsulinaemia is usually followed by insulin supplementation, and we, therefore, evaluated the impact of insulin treatment comparing the risk of PCCRC in patients with T2D needing insulin versus those not needing insulin. Data management and statistical analyses were performed using the Stata statistical software package V.15.1 (StataCorp). All diagnosis and procedure codes are listed in online supplemental table 1).

## RESULTS

### Aim 1: colonoscopy cohort characteristics

We identified 29 031 patients with T2D and 333 232 patients with without T2D who underwent a first-time colonoscopy during 1995–2012 (table 1).

In total, 3402 (1%) patients without T2D were diagnosed with T2D or redeemed a prescription for a glucose-lowering drug prior to a subsequent colonoscopy and then joined the T2D cohort.

Compared with patients without T2D, patients with T2D were more likely to be male (52.8% vs 44.0%), older at first-time colonoscopy (median age at colonoscopy: 69.0 vs 61.0 years), and to have a higher burden of chronic obstructive pulmonary disease, atrial fibrillation/flutter, cardiovascular diseases including hypertension, renal diseases, alcohol-related diagnoses, obesity and diverticular diseases. The proportion of cardiovascular diseases was particularly elevated for patients with T2D (56.4% vs 20.9%). Remaining characteristics were quite equally distributed among patients with and without T2D (table 1).

### Cumulative incidence proportions of PCCRC

We observed 160 cases of T2D-related PCCRC recorded after a first-time colonoscopy, yielding the >6 to 36 months CIP of 0.64% (95% CI 0.55% to 0.74%) (figure 1). In the group of patients without T2D, 1099 cases of PCCRC were observed, yielding a CIP of 0.36 (95% CI 0.34 to 0.38) (figure 2). Stratification by age at first-time colonoscopy revealed a slightly increased risk of PCCRC with increasing age (figures 1 and 2). Stratification by sex and time since colonoscopy yielded no material differences in risk of PCCRC between patients with and without T2D (figures 1 and 2). The >6 to 36 months CIPs after subsequent colonoscopies were comparably low in both groups. Estimates were less than 1% for virtually all follow-up colonoscopies in T2D as well as patients without T2D (figures 1 and 2). The small number of PCCRCs recorded after colonoscopies #4 and #5 impaired possibilities for stratifications (figures 1 and 2).

### HRs of PCCRC

Table 2 shows crude and adjusted HRs of PCCRC in patients with T2D compared with patients without T2D.

Patients with T2D had an elevated HR of PCCRC after colonoscopy #1 (HR 1.44, 95% CI 1.21 to 1.72) and #2 (HR 1.18, 95% CI 0.75 to 1.85). Stratification by sex and age at colonoscopy revealed no clear patterns while stratification by cancer stage at diagnosis showed a particularly elevated risk of metastatic cancers after the first colonoscopy (HR 1.73, 95% CI 1.22 to 2.47). Prescriptions for insulin recorded before colonoscopy #1 and #2 were associated with a particularly elevated HR of PCCRC. Likewise, prescriptions for metformin were associated with an increased HR after colonoscopy #1 and #2 while

**Table 1** Characteristics of patients undergoing at least one colonoscopy\* in Denmark during 1995–2012, by presence/absence of type 2 diabetes (T2D)†

	Patients with T2D, n (%)	Patients with outT2D, n (%)
Total	29031 (100)	333232 (100)
Female	13474 (46.4)	186602 (56.0)
Male	15557 (53.6)	146630 (44.0)
Age at first-time colonoscopy, years		
Median age at first-time colonoscopy (IQR)	69.0 (61.0–76.5)	61.0 (49.0–71.8)
0–59	6537 (22.5)	158339 (47.5)
60–69	8906 (30.7)	78846 (23.7)
70+	13588 (46.8)	96047 (28.8)
Year of first-time colonoscopy		
1995–2000	2366 (8.2)	54667 (16.4)
2001–2006	8137 (28.0)	113059 (33.9)
2007–2012	18528 (63.8)	165506 (49.7)
Type of admission for colonoscopy		
Inpatient unit	11002 (37.9)	96036 (28.8)
Outpatient clinic	18029 (62.1)	237196 (71.2)
Region of first-time colonoscopy		
Capital	6741 (23.2)	61853 (18.6)
Zealand	4110 (14.2)	41091 (12.3)
Southern	7935 (27.3)	92580 (27.8)
Central	6846 (23.6)	91630 (27.5)
Northern	3132 (10.8)	38993 (11.7)
Unknown	267 (0.9)	7085 (2.1)
Comorbidities‡		
Chronic obstructive pulmonary disease	2837 (9.8)	14637 (4.4)
Atrial fibrillation/flutter	3977 (13.7)	16944 (5.1)
Cardiovascular diseases	16749 (57.9)	69713 (20.9)
Renal disease	1836 (6.3)	5997 (1.8)
Alcohol-related diagnoses	1842 (6.3)	9953 (3.0)
Obesity	4159 (14.3)	7599 (2.3)
Diverticular disease	3504 (12.1)	33048 (9.9)
Familial hereditary colorectal cancer syndromes	108 (0.4)	3624 (1.1)
Year of first-time T2D diagnosis/prescription for a glucose-lowering drug		
1977–1986	1745 (6.0)	N/A
1987–1996	4511 (15.5)	N/A
1997–2006	15852 (54.6)	N/A

Continued

**Table 1** Continued

	Patients with T2D, n (%)	Patients with outT2D, n (%)
2007–2013	6923 (23.8)	N/A

Numbers below 5 are marked with <5 to ensure anonymity according to Danish legislation.

\*Patients with a diagnosis of colorectal cancer or inflammatory bowel disease and patients who underwent a total colectomy before their first-time colonoscopy are not included.

†Diagnosis of T2D recorded in the Danish National Patient Registry before or within 90 days after a first-time colonoscopy and/or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before or within 90 days after a first-time colonoscopy. Patients with a first-time diagnosis of diabetes in the Danish National Patient Registry or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before age 30 were considered as having type 1 diabetes and were not included.

‡Recorded before the date of first-time colonoscopy in the Danish National Patient Registry.

prescriptions for sulfonylureas were associated with an increased HR after colonoscopy #1.

### Aim 2: PCCRC 3-year rates

We identified 250 false-negative and 2938 true-positive colonoscopies in patients with T2D, yielding a PCCRC 3-year rate of 7.9% for patients with T2D (table 3). Among patients without T2D, we observed 1658 false-negative and 20 594 true-positive colonoscopies, yielding a PCCRC 3-year rate of 7.4% (table 3). The PCCRC 3-year rates were elevated among women for both patients with and without T2D.

### Sensitivity analyses

Restriction to a cohort comprising colonoscopies performed during 2005–2012 revealed the same pattern as observed in our main analysis. However, we found a more pronounced increase in the HRs of PCCRC comparing patients with T2D with patients without T2D than observed in our main analysis. Estimates of >6 to 36 months CIPs were less than 1% for both patients with and without T2D (online supplemental table 2). Comparing patients with T2D with patients without T2D, the HRs of PCCRC were 1.57 (95% CI 1.28 to 1.93) after colonoscopy #1 and 1.74 (95% CI 0.95 to 3.16) after colonoscopy #2 (online supplemental table 3). The PCCRC 3-year rate was slightly higher in patients with T2D than in patients without T2D (7.0% vs 5.4%) (online supplemental table 4). Rates for both groups were slightly decreased compared with our main analysis.

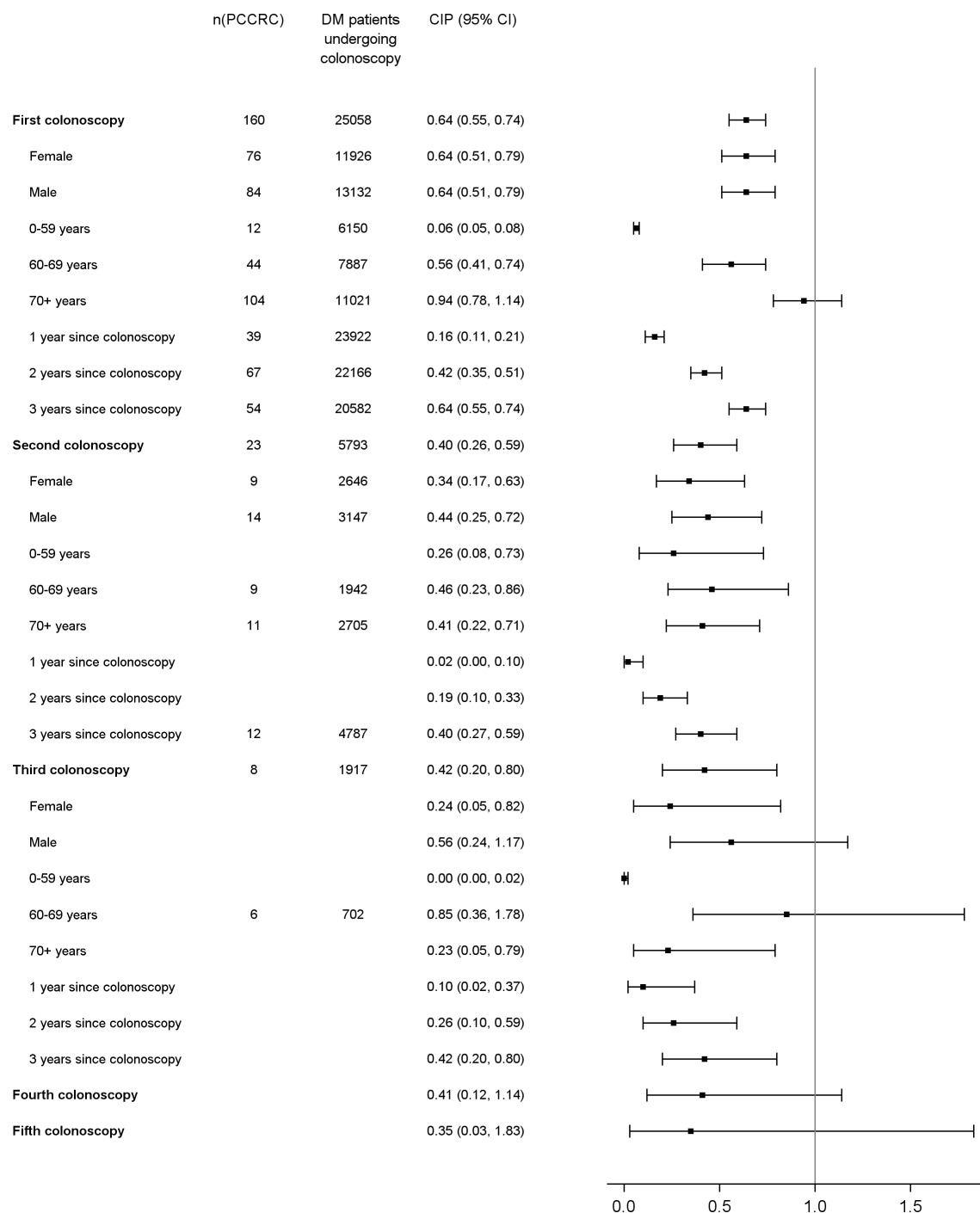
The sensitivity analysis evaluating the PCCRC cut-off set by the WEO showed low CIPs of PCCRC for patients with and without T2D (online supplemental table 5) and slightly elevated HRs of PCCRC after colonoscopy #1 and #2 (online supplemental table 6). Not surprisingly, expanding the PCCRC definition resulted in increased PCCRC 5-year rates for both patients with and without

T2D, but without material differences between the two groups (9.9% vs 10.2%) (online supplemental table 7). Our analysis investigating the impact of potential hyperinsulinaemia showed that patients with T2D requiring insulin had a higher risk of PCCRC after a first and second-time colonoscopy (online supplemental table 8).

### DISCUSSION

In this population-based cohort study including virtually all patients undergoing colonoscopy in Denmark during 1995–2015, we observed a 44% increased HR of PCCRC after a first-time colonoscopy when comparing patients with T2D with patients without T2Ds. However, the corresponding CIPs after first-time and subsequent colonoscopies were below 1% for patients with as well as without T2D. The proportion of CRC diagnoses that could be categorised as PCCRC was only marginally elevated for patients with T2D.

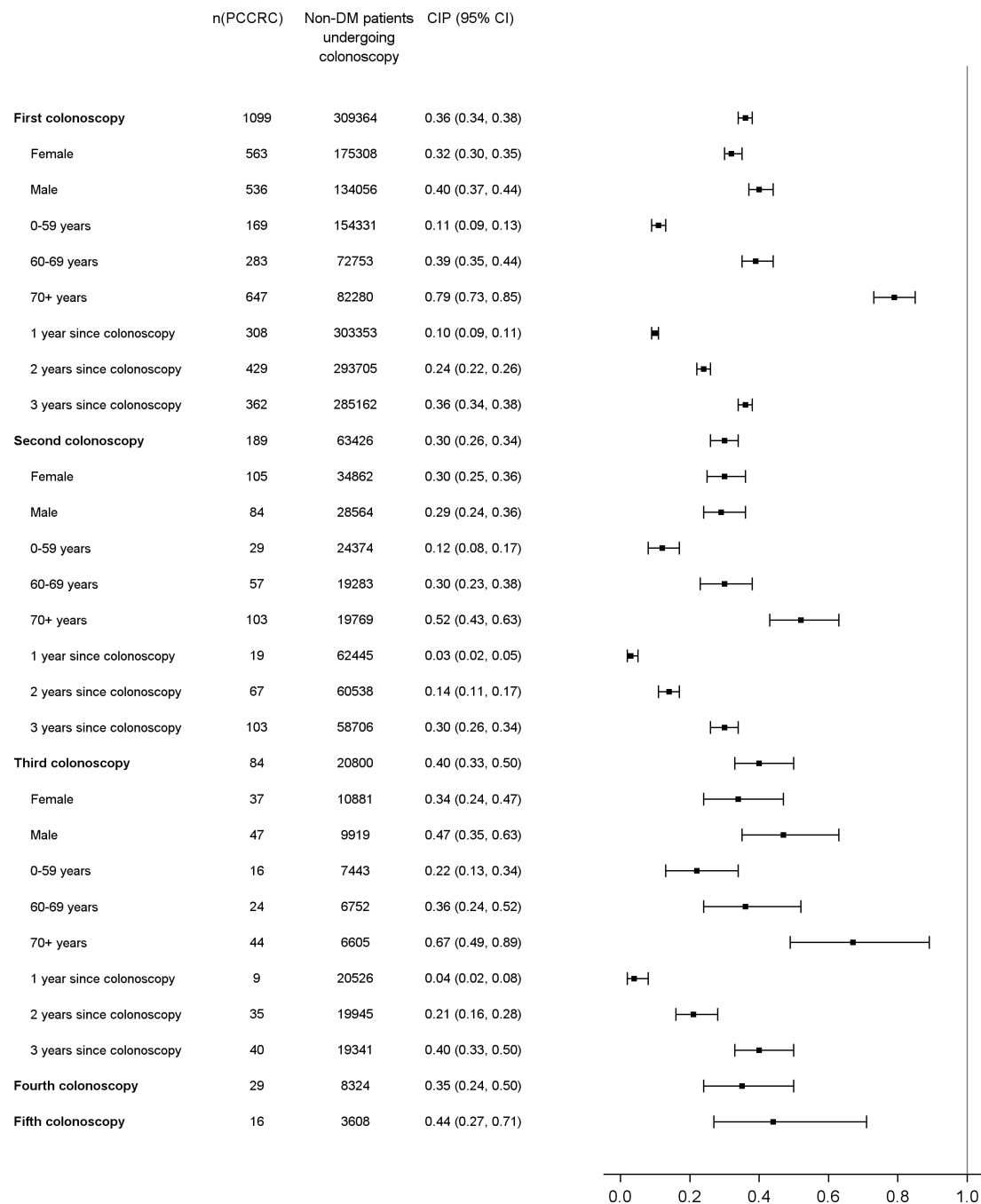
Several previous studies have reported an increased risk of CRC in patients with T2D.<sup>21–24 46–51</sup> However, only limited knowledge on the impact of T2D on PCCRC risk exists.<sup>17</sup> In line with our findings, a Swedish study by Forsberg *et al* suggested a slightly increased relative risk of PCCRC in diabetic patients (1.13, 95% CI 0.99 to 1.30). Overall, most PCCRCs are thought to arise from overlooked lesions, while the proportion of PCCRC appearing as rapidly growing lesions is probably low.<sup>1</sup> Although our study was unable to address the reason for the increased HRs, we speculate that presence of T2D might be associated with an elevated risk of inadequate bowel preparation for colonoscopy, in turn impairing the detection of both small and large adenomas and even cancers. Our finding of decreasing HRs with increasing numbers of colonoscopies supports for the hypothesis as repeated colonoscopies would lower the number of potential missed or incompletely resected polyps with the potential to progress to invasive CRC. The elevated HR of metastatic PCCRC after a first-time colonoscopy indicates that missed precursors could be the predominant origin for T2D-related PCCRC as these polyps or even cancers would have a prolonged time to diagnosis and thereby a higher likelihood of progression to advance stage disease.<sup>33 52 53</sup> Concurrently, it is necessary to consider that the effects of long-standing T2D might affect the molecular pathways driving CRC initiation. The progressive impairment of insulin sensitivity among patients with T2D could lead to chronic compensatory hyperinsulinaemia.<sup>54–56</sup> Endogenous as well as exogenous insulin may promote colorectal carcinogenesis through enhanced stimulation of the insulin-like growth factor-1 receptor, in turn increasing cell proliferation and prolonging their survival.<sup>25</sup> Accordingly, our analysis investigating the potential impact of hyperinsulinaemia showed that patients with T2D requiring insulin supplementation may have a higher risk of PCCRC than those not requiring insulin. In addition, patients with T2D with prescriptions for insulin had a particularly increased risk



**Figure 1** Cumulative incidence proportions (CIPs) in percentages with associated 95% CIs of postcolonoscopy colorectal cancers (PCCRCs)<sup>1</sup> among patients with type 2 diabetes (T2D)<sup>2</sup> who underwent colonoscopy in Denmark during 1995–2012<sup>3</sup>. Death and total colectomy<sup>4</sup> are treated as competing risks. PCCRCs were diagnosed in Denmark during 1995–2015. Numbers below 5 are not included to ensure anonymity according to Danish legislation. <sup>1</sup>Colorectal cancer diagnosed within >6 to 36 months after a negative colonoscopy. <sup>2</sup>Diagnosis of T2D recorded in the Danish National Patient Registry before or within 90 days after a first-time colonoscopy and/or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before or within 90 days after the first-time colonoscopy. Patients with diabetes diagnoses and prescriptions recorded before age 30 not included as these were considered to represent patients with type 1 diabetes. <sup>3</sup>Allowing 36 months of follow-up after colonoscopies performed in 2012. <sup>4</sup>Date of total colectomy recorded in the Danish National Patient Registry plus 90 days. DM, diabetes mellitus.

of PCCRC compared with patients with non-T2D. Use of insulin among patients with T2D may, therefore, serve as a 'red flag' that could indicate a potential increased risk of PCCRC. These findings could, however, also be

explained by other factors such as differences in T2D disease severity and should be interpreted with caution. In addition, inflammation is a crucial component of T2D-induced organ injury and long-standing inflammation



**Figure 2** Cumulative incidence proportions (CIPs) in percentages with associated 95% CIs of postcolonoscopy colorectal cancers (PCCRCs)<sup>1</sup> among patients without type 2 diabetes (T2D)<sup>2</sup> who underwent colonoscopy in Denmark during 1995–2012<sup>3</sup>. Death and total colectomy<sup>4</sup> are treated as competing risks. PCCRCs were diagnosed in Denmark during 1995–2015. <sup>1</sup>Colorectal cancer diagnosed within >6 to 36 months after a negative colonoscopy. <sup>2</sup>Diagnosis of T2D recorded in the Danish National Patient Registry before or within 90 days after first-time colonoscopy and/or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before or within 90 days after the first-time colonoscopy. <sup>3</sup>Allowing 36 months of follow-up after colonoscopies performed in 2012. <sup>4</sup>Date of total colectomy recorded in the Danish National Patient Registry plus 90 days. DM, diabetes mellitus.

may enhance CRC development.<sup>24</sup> Accordingly, inflammation is suggested as one reason for increased CRC risk in patients with inflammatory bowel disease.<sup>57–61</sup> A different or particularly aggressive CRC biology could therefore also play an important role for PCCRC pathogenesis in patients with T2D. We consider, however, it beyond the scope of this study to investigate the exact

impact of T2D on molecular PCCRC features. Future research is needed to provide the necessary answers.

The strengths of our study include its population-based design, its setting within a universal, tax-funded healthcare system, and use of high-quality, prospectively collected data on colonoscopies and other diagnoses.<sup>37 40 62</sup> The virtually complete follow-up for all patients undergoing

**Table 2** Crude and adjusted HRs and associated 95% CIs of PCCRC\* after one, two, three, four and five colonoscopies, comparing patients with type 2 diabetes (T2D)† with non-T2D

	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
First colonoscopy	1.89 (1.60 to 2.24)	1.44 (1.21 to 1.72)
Sex		
Female	2.07 (1.63 to 2.63)	1.52 (1.18 to 1.95)
Male	1.69 (1.34 to 2.13)	1.38 (1.08 to 1.76)
Age at colonoscopy		
0–59	1.83 (1.02 to 3.28)	1.77 (0.95 to 3.30)
60–69	1.49 (1.08 to 2.04)	1.80 (1.29 to 2.52)
70+	1.25 (1.02 to 1.54)	1.29 (1.04 to 1.60)
Medication§		
Insulin	2.42 (1.81 to 3.24)	2.15 (1.58 to 2.92)
Metformin	1.64 (1.30 to 2.06)	1.46 (1.14 to 1.87)
Sulfonylureas	1.98 (1.51 to 2.60)	1.53 (1.15 to 2.03)
Other antidiabetic drugs	N/A	N/A
PCCRC stage at diagnosis		
Localised	1.52 (1.14 to 2.03)	1.21 (0.89 to 1.64)
Regional	1.47 (0.98 to 2.21)	1.22 (0.80 to 1.87)
Metastatic	2.24 (1.60 to 3.13)	1.73 (1.22 to 2.47)
Unknown	2.81 (2.01 to 3.92)	1.78 (1.25 to 2.53)
Second colonoscopy¶	1.45 (0.94 to 2.23)	1.18 (0.75 to 1.85)
Sex		
Female	1.20 (0.61 to 2.38)	0.95 (0.47 to 1.92)
Male	1.66 (0.94 to 2.93)	1.44 (0.80 to 2.60)
Age at colonoscopy		
0–59	2.44 (0.74 to 8.03)	3.12 (0.91 to 10.69)
60–69	1.69 (0.83 to 3.41)	1.55 (0.74 to 3.24)
70+	0.85 (0.4 to 1.58)	0.85 (0.45 to 1.62)
Medication§		
Insulin	1.84 (0.90 to 3.74)	1.63 (0.79 to 3.39)
Metformin	1.69 (1.00 to 2.86)	1.47 (0.85 to 2.55)
Sulfonylureas	1.19 (0.56 to 2.54)	0.95 (0.44 to 2.06)
Other antidiabetic drugs	N/A	N/A
PCCRC stage at diagnosis		
Localised	1.08 (0.50 to 2.35)	1.02 (0.46 to 2.26)
Regional	1.51 (0.53 to 4.27)	1.24 (0.41 to 3.71)
Metastatic	0.95 (0.29 to 3.09)	0.79 (0.23 to 2.68)
Unknown	2.49 (1.21 to 5.11)	1.62 (0.77 to 3.42)
Third colonoscopy**	1.12 (0.54 to 2.31)	0.78 (0.37 to 1.67)
Sex		
Female	0.75 (0.18 to 3.13)	0.68 (0.16 to 2.93)
Male	1.27 (0.55 to 2.99)	0.83 (0.34 to 2.)
Age at colonoscopy		
0–59	N/A	N/A
60–69	2.59 (1.06 to 6.34)	1.92 (0.71 to 5.20)
70+	0.37 (0.09 to 1.52)	0.32 (0.07 to 1.34)

Continued



Table 2 Continued

	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Medication§		
Insulin	1.02 (0.25 to 4.15)	0.66 (0.16 to 2.81)
Metformin	1.31 (0.53 to 3.23)	0.99 (0.38 to 2.56)
Sulfonylureas	0.74 (0.18 to 2.98)	0.54 (0.13 to 2.25)
Other antidiabetic drugs	N/A	N/A
PCCRC stage at diagnosis		
Localised	0.54 (0.13 to 2.23)	0.51 (0.12 to 2.14)
Regional	1.46 (0.18 to 11.71)	1.23 (0.15 to 10.29)
Metastatic	1.20 (0.28 to 5.15)	0.61 (0.13 to 2.80)
Unknown	2.72 (0.77 to 9.56)	1.62 (0.43 to 6.02)
Fourth colonoscopy††	1.19 (0.36 to 3.91)	1.18 (0.35 to 3.98)
Fifth colonoscopy‡‡	0.83 (0.11 to 6.32)	0.81 (0.10 to 6.41)

Denmark, 1995–2015.

\*Colorectal cancer diagnosed within >6 to 36 months after a negative colonoscopy.

†Diagnosis of T2D recorded in the Danish National Patient Registry before or within 90 days after a first-time colonoscopy and/or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before or within 90 days a first-time colonoscopy. Patients with diabetes diagnoses and prescriptions recorded before age 30 not included as these were considered to represent patients with type 1 diabetes.

‡Adjusted for age group, sex, year of colonoscopy and presence of chronic obstructive pulmonary disease, atrial fibrillation/flutter, cardiovascular diseases, renal diseases, alcohol-related diseases diverticular diseases, obesity and familial hereditary colorectal cancer syndromes.

§Comparing patients with T2D with prescriptions for the given medication before the relevant colonoscopy with patients with non-T2D.

¶Patients T2D are allowed to be included in multiple medication groups.

¶¶The first subsequent colonoscopy recorded more than 6 months after the first-time colonoscopy.

\*\*The first colonoscopy recorded more than 6 months after the second colonoscopy.

††The first colonoscopy recorded more than 6 months after the third colonoscopy.

‡‡The first colonoscopy recorded more than 6 months after the fourth colonoscopy.

PCCRC, postcolonoscopy colorectal cancer; T2D, type 2 diabetes.

colonoscopy in Denmark allowed us to calculate PCCRC 3-year rates, as suggested by the WEO, as well as the absolute risk of PCCRC after colonoscopy.

However, our study also has limitations. First, due to differing data availability over the study period, the cohort of patients without T2D may have included patients with T2D treated solely by general practitioners during 1995–2003. Accordingly, our sensitivity analysis restricted to colonoscopies performed during 2005–2012 indicated that our main analysis might have underestimated the HR of PCCRC in patients with T2D. This is most likely due to misclassification of patients considered as patients without T2D in our study who were actually treated for T2D by their general practitioner. In addition, the PCCRC 3-year rates for T2D as well as patients without T2D were lower than in our main analysis. This may be explained by the overall decreasing trend for PCCRC 3-year rates in Denmark (ranging from 22.1% in 2001 to 7.7% in 2012) as previously described by Pedersen *et al.*<sup>15</sup> Although the rates were generally lower, we observed an increased difference in the PCCRC 3-year rates among patients with and without T2D with PCCRCs accounting for a higher proportion of all CRCs diagnosed in patients with T2D. The elevation in PCCRC 3-year rates for T2D

patients can likely be explained by the misclassification bias described above.

Second, the DNPR lacks detailed data on colonoscopy quality (including completeness, quality of bowel preparation, and withdrawal time), on polypectomies, and on the indication for colonoscopy. Thus, we were unable to directly explore causes of PCCRC in patients with T2D. A detailed case review investigating the causes of PCCRC in patients with T2D would be needed. Such knowledge would have profound implications for patients, endoscopists, and those writing surveillance guidelines. Of note, the Danish CRC screening programme was introduced nationwide in March 2014.<sup>63</sup> Therefore, most patients included in the colonoscopy cohort underwent colonoscopy due to symptoms of CRC or other gastrointestinal diseases, rather than due to a positive faecal occult blood test performed in the later CRC screening programme.

Third, the quality of PCCRC categorization is highly dependent on the validity of coding of dates in the DNPR and the DCR. Hence, dCRCs can be misclassified as PCCRCs if dates of colonoscopies or CRCs are coded ambiguously. However, expansion of the PCCRC definition in our sensitivity analysis did not yield findings that differed from the pattern seen on our main analysis.

**Table 3** Colonoscopies categorised as false-negative\* or true-positive† and PCCRC 3-year rates‡ stratified by presence of type 2 diabetes (T2D)

	Colonoscopies‡		Total, n	PCCRC 3-year rate‡
	False-negative colonoscopies*, n	True-positive colonoscopies†, n		%
Patients with T2D	250	2938	3188	7.90
Sex				
Female	113	1134	1247	9.10
Male	137	1806	1943	7.00
Age at colonoscopy				
0–59	21	257	378	7.60
60–69	73	834	907	8.00
70+	156	1847	2003	7.80
Year of colonoscopy				
1995–2001	28	75	103	27.20
2002–2008	81	788	869	9.30
2009–2015	141	2075	2216	6.40
Patients without T2D	1,658	20 594	22 252	7.40
Sex				
Female	844	9,819	10 663	7.90
Male	814	10 775	11 589	7.00
Age at colonoscopy				
0–59	259	3565	3824	6.80
60–69	453	5975	6428	7.00
70+	946	11 054	12 000	7.90
Year of colonoscopy				
1995–2001	382	1198	1580	24.20
2002–2008	664	6508	7172	9.20
2009–2015	612	12 888	13 500	4.50

Denmark, 1995–2015.

\*Colonoscopies in which a CRC was diagnosed within >6 to 36 months after the procedure.

†Colonoscopies in which a CRC was detected within the following 6 months.

‡False-negative colonoscopies/ (true-positive colonoscopies+false-negative colonoscopies) × 100.

§Diagnosis of T2D recorded in the Danish National Patient Registry before or within 90 days after the first false-negative or true-positive colonoscopy and/or at least one redeemed prescription for a glucose-lowering drug recorded in the Danish National Health Service Prescription Database before or within 90 days after the first false-negative or true-positive colonoscopy. Patients with diabetes diagnoses and prescriptions recorded before age 30 not included as these were considered to represent patients with type 1 diabetes.

¶Each individual was allowed one or more colonoscopy; however, only the first false-negative and true-positive colonoscopies were included in these numbers and the calculated PCCRC 3-year rates.

CRC, colorectal cancer; PCCRC, postcolonoscopy colorectal cancer.

Thus, such misclassification likely accounts for an insignificant source of bias.

Fourth, our identification of patients with diabetes requires consideration. Due to small numbers of patients with type 1 diabetes undergoing colonoscopy, our main focus was on patients with T2D. Thus, our results are only applicable for patients with T2D. In addition, the ICD coding of diabetes in the DNPR did not allow us to distinguish type 1 diabetes from T2D. We, therefore, considered patients with type 1 diabetes as those with relevant diagnoses and prescriptions recorded before age 30. Our

approach was based on prior research; unfortunately, no validation study exists. Furthermore, the use of prescriptions to identify patients with diabetes has its limitations as metformin is prescribed for other diseases such as polycystic ovary syndrome. Finally, our cohort of non-exposed patients might contain individuals with asymptomatic and undiagnosed T2D. Occurrence of polycystic ovary syndrome in our exposed group as well as occurrence of undiagnosed cases of T2D in our reference group could have introduced a conservative bias.

In conclusion, we found that patients with T2D had an increased HR of PCCRC compared with patients without T2D. These findings could indicate that impaired quality of bowel preparation for colonoscopy among patients with T2D may increase the risk of overlooked precancerous polyps, thereby increasing the risk of PCCRC.

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