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 1,658 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. 1 Despite the high sensitivity of colonoscopy in detecting CRC, PCCRCs may account for up to 8% of all CRCs. 2-11 Previous studies have consistently reported that PCCRCs represent a high proportion of CRCs diagnosed in patients with inflammatory bowel disease. 12-17 Similarly, diverticular disease, prior colorectal adenomas and hereditary CRC syndromes are suggested as risk factors for a subsequent PCCRC diagnosis. 15-17 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. 1,16,18-20

For at least two reasons, type 2 diabetes (T2D) could be associated with increased risk of PCCRC, but evidence remains limited. 17 First, mounting research suggests that patients with T2D are at particularly high risk of CRC. 21-24 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. Second, T2D is suggested to be associated with inadequate bowel preparation for colonoscopy, possibly due to functional impairment of gastrointestinal motility. Presence of T2D could thus lead to reduced visualisation of the colonic mucosa, in turn elevating the likelihood of overlooking preneoplastic polyps. This subsequently could increase PCCRC risk.

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.

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). 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).

METHODS
Setting
The study setting was the universal, tax-funded Danish healthcare system provided by the National Health Service. 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). 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. 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. 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. 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. 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. 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. 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. 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. 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 the same methodology for each colonoscopy individual. 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 the same methodology for each colonoscopy individual.

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 promitogenic, 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, 34,022 (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 1.78, 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...
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 20594 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 hyper-insulinaemia 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. However, only limited knowledge on the impact of T2D on PCCRC risk exists. 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. 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 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. 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. Endogenous as well as exogenic 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. 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...
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 1  Cumulative incidence proportions (CIPs) in percentages with associated 95% CIs of postcolonoscopy colorectal cancers (PCCRCs) among patients with type 2 diabetes (T2D) who underwent colonoscopy in Denmark during 1995–2012. Death and total colectomy 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. 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 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. Allowing 36 months of follow-up after colonoscopies performed in 2012. Date of total colectomy recorded in the Danish National Patient Registry plus 90 days. DM, diabetes mellitus.
may enhance CRC development.\textsuperscript{24} Accordingly, inflammation is suggested as one reason for increased CRC risk in patients with inflammatory bowel disease.\textsuperscript{57–61} 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.\textsuperscript{37 40 62} The virtually complete follow-up for all patients undergoing colonoscopy is also an important strength.

**Figure 2** Cumulative incidence proportions (CIPs) in percentages with associated 95% CIs of postcolonoscopy colorectal cancers (PCCRCs)\textsuperscript{1} among patients without type 2 diabetes (T2D)\textsuperscript{2} who underwent colonoscopy in Denmark during 1995–2012\textsuperscript{3}. Death and total colectomy\textsuperscript{4} are treated as competing risks. PCCRCs were diagnosed in Denmark during 1995–2015. \textsuperscript{1}Colorectal cancer diagnosed within >6 to 36 months after a negative colonoscopy. \textsuperscript{2}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. \textsuperscript{3}Allowing 36 months of follow-up after colonoscopies performed in 2012. \textsuperscript{4}Date of total colectomy recorded in the Danish National Patient Registry plus 90 days. DM, diabetes mellitus.
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**          |                   |                      |
| 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 2.0)   |
| 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

| Medication§ | Crude HR (95% CI) | Adjusted HR‡ (95% CI) |
|-------------|-------------------|----------------------|
| 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

| Stage       | Crude HR (95% CI) | Adjusted HR‡ (95% CI) |
|-------------|-------------------|----------------------|
| 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.

*Colonorectal 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.
‡‡The first 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.
§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, post-colonoscopy colorectal cancer; T2D, type 2 diabetes.

colono

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. 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.

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

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

| Colonoscopies¶ | False-negative colonoscopies*, n | True-positive colonoscopies†, n | Total, 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.
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.

**Contributors**

FST, HTS, LP and RE contributed to the methodology of the study. HTS, LP and RE acquired the data. FST, HTS, LP and RE directed the analyses, which were carried out by FST. FST wrote the initial draft. All authors contributed to the discussion and interpretation of the results, which determined the intellectual content of the manuscript. All authors reviewed, edited and accepted the final version for submission. FST is the guarantor of the article.

**Funding**

FST is supported by a scholarship from Aarhus University. The study was supported by grants from the Nevo Nordisk Foundation (NNF1900098609) and the Danish Cancer Society (R247-A14719).

**Disclaimer**

The funding sources had no role in the design and conduct of the study, nor the analysis and interpretation of the data.

**Competing interests**

None declared.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

No data are available.

**Supplemental material**

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