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The impact of colectomy and chemotherapy on risk of type 2 diabetes onset in patients with colorectal cancer: Nationwide cohort study in Denmark

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Abstract

Background

Comorbidity with type 2 diabetes (T2D) results in worsening of cancer-specific and overall prognosis in colorectal cancer (CRC) patients. The treatment of CRC *per se* may be diabetogenic. We assessed the impact of different types of surgical cancer resections and oncological treatment on risk of T2D development in CRC patients.

Method

We developed a population-based cohort study including all Danish CRC patients, who had undergone CRC surgery between 2001-2018. Using nationwide register data, we identified and followed patients from date of surgery and until new-onset of T2D, death or end of follow-up.

Results

In total, 46,373 CRC patients were included and divided into six groups according to type of surgical resection: 10,566 Right-No-Chemo (23%), 4,645 Right-Chemo (10%), 10,151 Left-No-

Chemo (22%), 5,257 Left-Chemo (11%), 9,618 Rectal-No-Chemo (21%) and 6,136 Rectal-Chemo (13%). During 245,466 person-years of follow-up 2,556 patients developed T2D. The incidence rate (IR) of T2D was highest in the Left-Chemo group 11.3 (95%CI: 10.4-12.2) per 1,000 person-years and lowest in the Rectal-No-Chemo group 9.6 (95%CI: 8.8-10.4). Between-group unadjusted hazard ratio (HR) of developing T2D was similar and non-significant. In the adjusted analysis, Rectal-No-Chemo was associated with lower T2D risk (HR 0.86 [95%CI 0.75-0.98]) compared to Right-No-Chemo.

For all six groups, an increased level of BMI resulted in a nearly twofold increased risk of developing T2D

Conclusion

This study suggests postoperative T2D screening should be prioritized in CRC survivors with overweight/obesity regardless of type of colorectal cancer treatment applied.

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eLife assessment

This **valuable** study presents findings that suggest the need for postoperative type 2 diabetes screening and that this should be prioritized in colorectal cancer survivors with overweight/obesity regardless of the type of colorectal cancer treatment applied. The evidence supporting the claims of the authors is **solid** and the authors use a population-based cohort study including all Danish colorectal patients who had undergone colorectal cancer surgery between 2001-2018. The work will be of interest to medical biologists, endocrinologists and oncologists working on colorectal cancer.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, [1] and the incidence rate is still increasing. [2] The same applies to the global incidence rate of type 2 diabetes (T2D). The association between CRC and T2D is well-established, as patients with T2D have approximately 30% increased risk of developing CRC,[3] and T2D is known to negatively influence the prognosis of CRC.[4] Furthermore, some studies even show an increased T2D risk in CRC survivors. [5,6] Fortunately, survival after a CRC diagnosis is steadily improving due to early detection, diagnostic precision, and more advanced cancer treatment; and today, more than 70% of non-metastatic CRC patients are alive after 5 years. [7] Accordingly, it becomes increasingly important to identify CRC patients at risk of developing long-term health problems like T2D in order to initiate preventive strategies or treatment. [6] The underlying mechanisms behind the increased T2D risk in CRC survivors are poorly understood. However, shared life-style related risk factors such as obesity, physical inactivity, and unhealthy diet may play a role. [8–10]

Another explanation may be treatment-induced hyperglycemia. Prior studies showed that treatment with adjuvant chemotherapy can induce hyperglycemia and development of T2D in CRC patients. [6,11,12] Moreover, glucocorticoid, administered to alleviate side effects of chemotherapy, may impair glucose homeostasis and thus increase the risk of T2D. [13,14] In addition to the drug-induced metabolic disturbances, a recent study revealed that the type of CRC surgery *per se* is associated with diverging risk of T2D. [15] A previous nationwide Danish study revealed that patients, who had undergone left-sided colon resection for CRC and other colonic illnesses had an increased risk of developing T2D, whereas this risk was unaltered in patients who had undergone right-sided colonic resections compared with a control group. [15] However, this study lacks essential information on the role of potential modifying factors like BMI, treatment with chemotherapy etc. Along the same line, in a population of non-CRC patients, Lee et al. published that patients who had undergone right-sided or transversal colonic resections had a reduced risk of developing T2D compared with a matched non-colectomy control group. [16] These findings raise an intriguing question of whether the risk of developing T2D in CRC survivors may be casually affected by the type of CRC surgery. Possible explanations of this side-specific risk modification include removal of different enteroendocrine cell types resulting in gut changes that is important for insulin secretion and action and for appetite regulation as well as changes in the microbiome, but causality remains to be investigated further. [17–19]

In the present study, we tested the hypothesis whether different types of surgical cancer resection and oncological treatment have an impact on risk of developing diabetes in CRC survivors. For this purpose, we used a nationwide register to compare the frequency of diabetes development in CRC patients who had undergone right-sided colectomy, left-sided colectomy or rectal resection with and without chemotherapy, when adjusting for potential modifying factors like BMI etc.

Methods and material

Study population

The study was based on information from Danish nationwide health registers. All data are recorded with reference to a civil registration number, which is a unique personal identification number assigned to all Danish residents. This number permits accurate linkage of recorded information at the personal level. [20]

The study population was identified through the Danish Colorectal Cancer Group (DCCG) database, which contains prospectively collected and validated data on all patients with CRC since 2001, including data on patient's characteristics, diagnostics and treatment. [21] The degree of patient inclusion in the database is high (>95%) and thus adequately represents the population of Danish CRC patients undergoing anti-cancer resections. [21]

We included all CRC cancer patients undergoing cancer surgery between 1st of May 2001 until 31st of December 2018 (**Figure 1**). Patients with unspecified surgery or total colectomy were excluded as these procedures are not standard treatment for CRC. Additionally, individuals diagnosed with Type 1 diabetes (T1D) either before or after surgery were excluded, along with those diagnosed with T2D preoperatively or within the first 2 weeks postoperatively, as the last group probably represents patients with preoperatively unknown pre-existing prediabetes or diabetes.[22]

Exposure

Patients were subdivided into six groups according to the surgical procedure and whether the patients had received chemotherapy or not. The group "right-sided colonic resection" (Right) included patients with cancer in coecum, ascending colon, or the oral part of colon transversum,

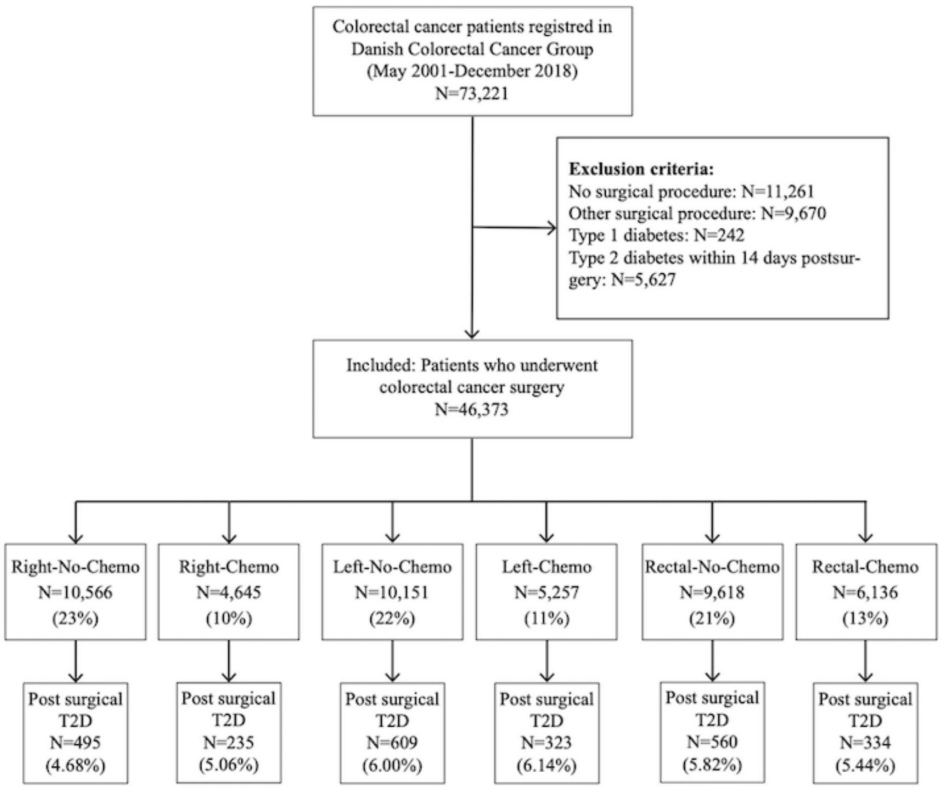

Figure 1

Flowchart of the study.
2D: New-onset of type 2 diabetes
Right: Right-sided colonic resections; Left: Left-sided colonic resections; Rectal: Rectal recestions
No-chemo: No chemotherapy; Chemo: Chemotherapy

the group “left-sided colonic resection” (Left) included patients with cancer in the anal part of colon transversum, descending colon, and sigmoid colon, and the group “rectal resection“ (Rectal) included patients with rectal cancer. Information regarding chemotherapy was limited to whether the patient had received chemotherapy (Chemo) or not (No-Chemo).

Based on the combination of surgical procedures and chemotherapy, the study population was divided into six groups: Right-No-Chemo, Right-Chemo, Left-No-Chemo, Left-Chemo, Rectal-No-Chemo, Rectal-Chemo.

Radiation therapy is only part of standard treatment for rectal cancer, and therefore this oncological modality was restricted to Rectal patients (Rectal-No-Radiation vs. Rectal-Radiation).

Finally, a sub analysis was made comparing all colonic resected patients (All Colon) with all rectal resected (All Rectal)

Outcome

The primary outcome was first-time diagnosis of T2D after different types of CRC cancer surgery and chemotherapy. Patients were followed from date of surgery until time to T2D diagnosis, emigration, death, or the end of follow up (31st of December 2018), whichever came first.

Individuals with T2D were identified from data in the Danish National Patient Register (comprising information on diagnoses during all hospital contacts in Denmark), the National Prescription Registry (comprising information on all prescriptions filled at any pharmacy in Denmark), and the Danish National Health Service Register (comprising information on podiatrist services) as described by Carstensen et al. [22] Diabetes is defined as the second occurrence of any event across three types of inclusion events: 1) Diabetes diagnosed during hospitalisation 2) diabetes-specific services received at podiatrist, 3) purchases of glucose lowering drugs. Thus, if a patient developed transient T2D during chemotherapy treatment, it will only be an inclusion event if they purchase of glucose lowering drugs. Individuals were classified as having T1D if they had received prescriptions for insulin combined with a diagnosis of type 1 from a medical hospital department. Otherwise, diabetes was classified as type 2.[23]

Statistical analysis

Descriptive data was presented as means with standard deviations (SD) for continuous variables and proportions (n, %) for categorical variables. Crude incidence rates (number of T2D diagnoses by person-time at risk) were calculated for the six groups (type of surgery ± chemo), and characterised by preoperative variables (sex, age, body mass index (BMI), smoking, alcohol status, American Society of Anesthesiologists physical status classification score (ASA), and treatment with radiotherapy in Rectal cancer patients). Unadjusted and adjusted Cox regression analyses were used to calculate hazard ratios (HRs) for developing T2D after different types of surgery with and without chemotherapy (using Right-No-Chemo as a reference group), after radiation therapy among Rectal resected (using Rectal-No-Radiation as reference), and after overall type of surgery (All Colon (ref) vs All Rectal). The adjusted analyses were performed stepwise by first adjusting for year of surgery, age at surgery, sex and BMI (Model 1), then further adjusting ASA, smoking and alcohol consumption (Model 2a), and lastly, further adjusting for chemotherapy (Model 2b) in the analyses on radiation therapy and overall type of surgery

Finally, the impact of BMI on the risk of developing of T2D was investigated within each of the six groups. BMI was categorized into 4 subgroups (18.5-24.9, 25-29.9, 30-34.9 and 35-39.9), and underweight (BMI<18.5) or severely obese (BMI ≥ 40) subjects were excluded from these analyses due to low numbers. For each group (type of surgery ± chemotherapy), the HR for developing T2D depending on BMI subgroups was calculated by using Cox regression analysis adjusted for age,

sex, year of surgery, and ASA score using normal weight (BMI:18.5-24.9) as the reference group. A sensitivity analyses was performed restricting the inclusion period of surgery patients from 2001-2018 to 2010-2018, as baseline information was complete from 2010.

All analyzes were conducted using STATA version 16 (STATA Corp., College Station, Tex., USA). P-value of P<0.05 was considered statistically significant. Results were presented with 95% confidence interval (CI) when relevant.

Results

Baseline characteristics

A total of 46,373 CRC patients without preoperatively recorded diabetes were found eligible for the study (**Figure 1**) and were divided into six groups: 10,566 Right-No-Chemo (23%), 4,645 Right-Chemo (10%), 10,151 Left-No-Chemo (22%), 5,257 Left-Chemo (11%), 9,618 Rectal-No-Chemo (21%) and 6,136 Rectal-Chemo (13%).

Compared with the Right, the Left and Rectal groups were younger, more often men, and less often classified as ASA>II (**Table 1**). Those that had received chemotherapy were generally younger, less often classified as ASA>II and as expected more often stage III/IV cancers than No-Chemo.

Incidence rates of diabetes

During the 245,466 person-years of follow up, 2,556 cases of T2D were diagnosed (10.4 per 1000 person-years) (**Table 2**) and the mean time to onset of T2D post-surgery spanned from 4.1-4.7 years across the subgroups. The incidence rate (IR) of T2D was almost similar between the six groups with the highest IR observed in the Left-No-Chemo group (IR 11.3 (95%CI: 10.4-12.2) per 1,000 person-years), and the lowest IR observed in the Rectal-No-Chemo group (IR 9.6 (95%CI: 8.8-10.4) per 1,000 person-years). Across all groups, the T2D IR was consistently higher in males than in females, in patients with BMI ≥25 compared with BMI of 18.5-24.9, and in ASA > I compared with ASA score I (**Table 2**).

Risk of developing T2D after different types of colorectal cancer surgery with and without chemotherapy

When compared with the Right-No-Chemo group, the other groups had similar and non-significant unadjusted hazard ratio (HR) of developing T2D (**Table 3**). In the adjusted analysis Rectal-No-Chemo was associated with a lower risk of T2D (HR 0.86 [95%CI 0.75-0.98]) compared with Right-No-Chemo. In the sub analysis comparing All Colon resected with All Rectal resected, the unadjusted and adjusted HR for developing T2D were significant lower for Rectal resected. Moreover, adjusting for cancer stage did not affect the results (Supplementary table 1).

Risk of developing T2D after radiation therapy among rectal resected patients

Radiation therapy in the rectal resected groups had no impact on the incidence rate of (**Table 2**), and the unadjusted/adjusted HR of developing T2D was non-significant when comparing Rectal-No-Radiation patients with Rectal-Radiation patients (**Table 3**).

	Right-sided resection (Right) (N=15,211)		Left-sided resection (Left) (N=15,408)		Rectum resection (Rectal) (N=15,754)	
	Right-No-Chemo	***Right-Chemo***	***Left-No-Chemo***	***Left-Chemo***	***Rectal-No-Chemo***	***Rectal-Chemo***
All patients, n (%)	10,566 (23%)	4,645 (10%)	10,151 (22%)	5,257 (11%)	9,618 (21%)	6,136 (13%)
Sex, n (%)						
Male	4,338 (41%)	2,126 (46%)	5,450 (54%)	2,834 (54%)	5,743 (60%)	3,745 (61%)
Female	6,228 (59%)	2,519 (54%)	4,701 (46%)	2,423 (46%)	3,875 (40%)	2,391 (39%)
Age, year, mean (SD)	75.2 (10.0)	66.9 (10.1)	72.1 (10.7)	64.8 (10.1)	70.0 (10.7)	64.3 (10.1)
BMI, mean (SD)	25.0 (4.7)	25.4 (4.7)	25.7 (4.6)	25.8 (4.5)	25.6 (4.4)	25.6 (4.4)
BMI subgroups						
<18.5	482 (4.6%)	114 (2.5%)	287 (2.8%)	97 (1.8%)	225 (2.3%)	143 (2.3%)
18.5-24.9	4,183 (40%)	1,907 (41%)	3,638 (36%)	2,004 (38%)	3,693 (38%)	2,570 (42%)
25-29.9	2,671 (25%)	1,347 (29%)	2,945 (29%)	1,641 (31%)	3,021 (31%)	1,993 (32%)
30-34.9	814 (7.7%)	404 (8.7%)	961 (9%)	545 (10%)	889 (9.2%)	611 (10%)
35-39.9	194 (1.8%)	90 (1.9%)	214 (2.1%)	135 (2.6%)	171 (1.8%)	132 (2.2%)
>40	62 (0.6%)	34 (0.7%)	69 (0.7%)	39 (0.7%)	60 (0.6%)	30 (0.5%)
Missing	2,160 (20%)	749 (16%)	2,037 (20%)	796 (15%)	1,559 (16%)	657 (11%)
Smoking, n (%)						
Never	3,132 (30%)	1,533 (33%)	3,030 (30%)	1,804 (34%)	2,828 (29%)	2,014 (33%)
Current	1,671 (16%)	791 (17%)	1,486 (15%)	821 (16%)	1,679 (17%)	1,305 (21%)
Former	3,376 (32%)	1,465 (32%)	3,415 (34%)	1,700 (32%)	3,421 (36%)	2,021(33%)
Missing	2,387 (22%)	856 (18%)	2,220 (21%)	932 (18%)	1,690 (18%)	796 (13%)
Alcohol[a], n (%)						
1-14	4,819 (46%)	2,342 (51%)	4,803 (47%)	2,771 (53%)	4,886 (51%)	3,399 (55%)
14-21	478 (5%)	254 (5%)	618 (6%)	333 (6%)	711 (7%)	494 (8%)
>21	433 (4%)	256 (6%)	593 (6%)	323 (6%)	671 (7%)	412 (7%)
None	2,269 (21%)	889 (19%)	1,722 (17%)	872 (17%)	1,446 (15%)	1,006 (16%)
Missing	2,567 (24%)	895 (19%)	2,415 (24%)	958 (18%)	1,904 (20%)	825 (13%)
ASA score[b], n (%)						
Healthy (=I)	1,633 (15%)	1,331 (29%)	2,185 (22%)	1,735 (33%)	2,541 (26%)	2,082 (34%)
Mild (=II)	5,457 (52%)	2,596 (56%)	5,299 (51%)	2,857 (54%)	5,265 (55%)	3,415 (56%)
Sick (=>II)	3,160 (30%)	613 (13%)	2,442 (24%)	548 (11%)	1,653 (17%)	557 (9%)
Missing	316 (3%)	105 (2%)	295 (3%)	117 (2%)	159 (2%)	82 (1%)
Screening detected tumor, n (%)	770 (7%)	299 (6%)	1,077 (11%)	457 (9%)	664 (7%)	394 (6%)
UICC stage[c], n (%)						
I/II	7,002 (66%)	674 (15%)	7,339 (72%)	745 (14%)	5,940 (62%)	420 (7%)
III/IV	3,330 (32%)	3,504 (75%)	2,506 (25%)	3,989 (76%)	2,246 (23%)	2,471 (40%)
Unknown	234 (2%)	467 (10%)	306 (3%)	523 (10%)	1,432 (15%)	3,245 (53%)
Radiation, n (%)	.	.	.	.	1,157 (12%)	2,983 (49%)

Chemo: Chemotherapy

[a] Alcohol items per week

[b] The American Society of Anesthesiologist score: I: Healthy, but with CRC, III: Mild systemic disease without substantial functional limitations, >II: Severe systemic disease, includes ASA stage III, IV, V, VI

[c] UICC stage, Union of International Cancer Control, Stage I: T1 or T2, Stage II: T3 or T4, Stage III: N1 or N2, Stage IV: Disseminated disease at time of diagnosis

Table 1.

Baseline characteristics

	Right-sided resection (Right) (N=15.211)		Left-sided resection (Left) (N=15.408)		Rectum resection (Rectal) (N=15,754)	
	Right-No-Chemo	*Right-Chemo*	*Left-No-Chemo*	*Left-Chemo*	*Rectal-No-Chemo*	*Rectal-Chemo*
All patients, n	10,566	4,645	10,151	5,257	9,618	6,136
T2D development						
Numbers	495	235	609	323	560	334
Mean time, year (SD)	4.1 (3.4)	4.1 (3.6)	4.1 (3.5)	4.4 (3.6)	4.7 (3.7)	4.3 (3.5)
Person-years	48,039	22,317	53,935	29,301	58,448	33,422
Incidence rates	10.3 (9.4-11.2)	10.5 (9.3-12.0)	11.3 (10.4-12.2)	11.0 (9.9-12.3)	9.6 (8.8-10.4)	10.0 (9.0-11.1)
Sex						
Male	13 (11-15)	14 (12-16)	14 (12-15)	14 (12-16)	11 (10-12)	12 (11-14)
Female	9 (8-10)	8 (7-10)	9 (8-10)	8 (7-10)	8 (7-9)	7 (6-8)
Age						
<50	3 (1-8)	6 (3-11)	7 (5-12)	8 (5-12)	5 (3-8)	6 (4-10)
50-64.9	12 (10-14)	13 (11-16)	11 (9-12)	10 (8-12)	10 (8-12)	10 (9-12)
65-74.9	12 (11-14)	11 (9-14)	12 (11-14)	14 (12-17)	14 (12-17)	11 (10-13)
≥75	9 (8-10)	6 (4-9)	11 (10-13)	8 (6-12)	8 (6-12)	8 (5-11)
BMI subgroups						
18.5-24.9	6 (5-7)	5 (4-7)	6 (5-8)	4 (3-5)	4 (4-5)	4 (3-6)
25-29.9	13 (11-16)	11 (9-14)	13 (11-15)	12 (10-15)	11 (9-12)	12 (10-14)
30-34.9	23 (18-28)	30 (23-40)	21 (17-25)	24 (19-30)	25 (21-30)	24 (19-30)
35-39.9	51 (38-70)	53 (34-84)	32 (23-45)	34 (23-52)	30 (21-44)	31 (20-48)
Missing	7 (6-9)	9 (6-12)	11 (9-12)	12 (10-16)	9 (8-12)	10 (8-14)
Smoking						
Never	9 (8-11)	11 (9-14)	9 (8-11)	8 (7-10)	8 (7-10)	9 (7-11)
Current	13 (10-15)	9 (7-13)	11 (9-14)	12 (10-16)	10 (8-12)	10 (7-12)
Former	11 (10-13)	12 (10-15)	13 (11-15)	13 (11-15)	11 (9-12)	11 (9-13)
Missing	8 (7-10)	9 (6-12)	11 (10-14)	12 (9-15)	9 (8-11)	11 (8-14)
Alcohol[a]						
1-14	11 (9-12)	10 (8-12)	10 (9-12)	10 (9-12)	9 (8-10)	10 (8-11)
14-21	9 (6-14)	7 (3-14)	9 (6-13)	10 (7-16)	8 (6-11)	9 (6-14)
>21	10 (7-16)	16 (11-25)	14 (11-19)	12 (8-18)	11 (9-15)	13 (9-18)
None	12 (10-14)	14 (10-18)	13 (11-16)	12 (9-16)	13 (11-15)	10 (7-13)
Missing	9 (7-10)	10 (7-13)	12 (10-14)	12 (10-16)	10 (9-10)	10 (8-13)
ASA score[b]						
Healthy (=I)	7 (6-9)	5 (3-7)	7 (6-9)	7 (5-9)	5 (4-6)	6 (4-7)
Mild (=II)	10 (9-12)	12 (11-15)	12 (11-13)	13 (11-15)	11 (10-12)	13 (11-14)
Sick (=>II)	14 (12-17)	17 (13-24)	17 (12-17)	18 (14-25)	15 (12-18)	12 (8-17)
Missing	6 (3-11)	15 (7-31)	13 (8-20)	11 (5-23)	9 (5-17)	10 (4-25)
Radiation						
Yes	.	.	.	.	11 (9-13)	11 (9-13)
No	.	.	.	.	9 (9-10)	10 (9-12)

Chemo: Chemotherapy
[a] Alcohol items per week
[b] The American Society of Anesthesiologist score: I: Healthy, but with CRC, III: Mild systemic disease without substantial functional limitations, >II: Severe systemic disease, includes ASA stage III, IV, V, VI

Table 2.

Absolute incidence rates of type 2 diabetes (T2D) per 1000 person-years (95% CI) among colorectal cancer patients treated with different types of colorectal cancer surgery with and without chemotherapy.

	Unadjusted		Model 1		Model 2[(a/b)]	
	HR (95%CI)	*p-value*	HR (95%CI)	*p-value*	HR (95%CI)	*p-value*
Surgery and chemotherapy						
Right-No-Chemo	ref					
Right-Chemo	1.02 (0.87;1.19)	0.799	0.99 (0.83;1.17)	0.880	1.01 (0.85;1.20)[a]	0.884
Left-No-Chemo	1.10 (0.98;1.24)	0.112	0.92 (0.81;1.05)	0.228	0.94 (0.82;1.07)[a]	0.333
Left-Chemo	1.07 (0.93;1.23)	0.339	0.93 (0.79;1.09)	0.366	0.97 (0.83;1.14)[a]	0.708
Rectal-No-Chemo	0.94 (0.83;1.06)	0.317	0.82 (0.72;0.94)	0.004	0.86 (0.75;0.98)[a]	0.028
Rectal-Chemo	0.96 (0.84;1.11)	0.610	0.84 (0.72;0.99)	0.031	0.89 (0.76;1.03)[a]	0.126
Surgery and radiation therapy						
Rectal-No-Radiation	ref					
Rectal-Radiation	1.07 (0.93;1.24)	0.336	0.98 (0.85;1.13)	0.804	0.97 (0.84;1.12)[b]	0.691
Surgery						
All Colon	ref					
All Rectal	0.90 (0.83;0.98)	0.013	0.87 (0.79;0.95)	0.002	0.89 (0.82;0.98)[b]	0.015

Right: Right-sided colonic resections; Left: Left-sided colonic resections; Rectal: Rectal resections
No-Chemo: No chemotherapy; Chemo: Chemotherapy
No-radiation: No radiotherapy; Radiation: Radiation therapy

All Colon: All right- and left-sided colonic resections with and without chemotherapy
All Rectal: All rectal resections with and without chemotherapy, and with and without radiation therapy

Model 1: adjusted for year of surgery, age at surgery, sex, BMI
Model 2a: adjusted like Model 1 and further adjusted for performance status before surgery assessed by American Society of Anesthesiologist physical scale, smoking and alcohol
Model 2b: adjusted like Model 2a and further adjusted for chemotherapy

Table 3.

Likelihood of developing type 2 diabetes after different types of colorectal cancer surgery with and without oncological treatment, unadjusted and adjusted analysis

The impact of BMI on development of T2D

BMI had a strong association with T2D regardless of surgical resection and treatment with chemotherapy (**Figure 2**). The risk of developing T2D increased near twofold every time the BMI group increased one level, for example in the Right-No-Chemo group: HR 2.13 in BMI 25-30, HR 3.63 in BMI 30-35, HR 8.01 in BMI 35-40, compared with the reference BMI of 18.5-25. A similar pattern was observed within each of the other five groups, although a less pronounced impact of BMI was observed in the Left-No-Chemo group: HR 1.85 in 25-30, 2.93 in 30-35, 4.21 in 35-40 BMI group.

Discussion

This national cohort study demonstrated an IR of developing T2D after CRC surgery similar to previous studies. [5,11] Comparing resection types, rectal cancer resected patients had a slightly lower risk of developing T2D when compared to colon cancer resected patients. Treatment with chemotherapy had no impact on T2D risk in any of the resection groups, and radiation therapy did not affect T2D risk either.

Within each of the six groups (different types of surgery with and without chemotherapy), BMI was strongly associated to developing T2D, the risk increased almost twofold every time the BMI group increased one level.

Only few studies have examined the risk of developing T2D after different kinds of colonic- and rectal surgical procedures, and in contrast to the present study the following studies were not able to adjust for several confounders incl. preoperative BMI. Jensen et al. found a higher risk of T2D after the left-sided compared with the right-sided colonic resections, but, in contrast to the current study, patients operated for both non-malignant as well as malignant diseases were included. [15] In support of side-specific effect of colonic resections, Wu et al. investigated a population of non-CRC patients and showed that right-sided and transversal colonic resections were associated with a reduced risk of T2D development compared with patients without colectomy.[16] In contrast to both the abovementioned studies the most recent epidemiological study found an increased T2D risk after colectomy compared with small bowel resection in non-cancer patients, but when stratifying by resection type, they found no difference in T2D risk. [24]

In Denmark, the overall T2D prevalence is 6.9%[25], lower than the global average in 2021 (10.5%) and also falls below the estimate of high-income countries (11.1%).[26] Similarly, the obesity rate of 20% aligns with other Scandinavian countries and is below that of most high-income nations.[27]

Obesity is one of the predominant factors in the development of T2D[28–30], and the linear increase in new onset T2D with increased BMI reported in this study is well described in the literature. [31] It is important to emphasize that only pre-operative BMI was included in the adjustments as post-surgery BMI information was not available and accordingly, weight trajectories after surgery could not be included in the analyses. It's still unknown how body weight and body composition changes after different types of CRC resection, and thus it is not clear whether changes in weight in any groups play a role in diabetes development.

Like our findings, Jensen et al. and Wu et al. found a tendency towards a decreased risk of T2D after rectal resection, although these findings were not statistically significant in the previous studies. [15,16] Further studies are needed to elucidate the potential mechanism behind this finding.

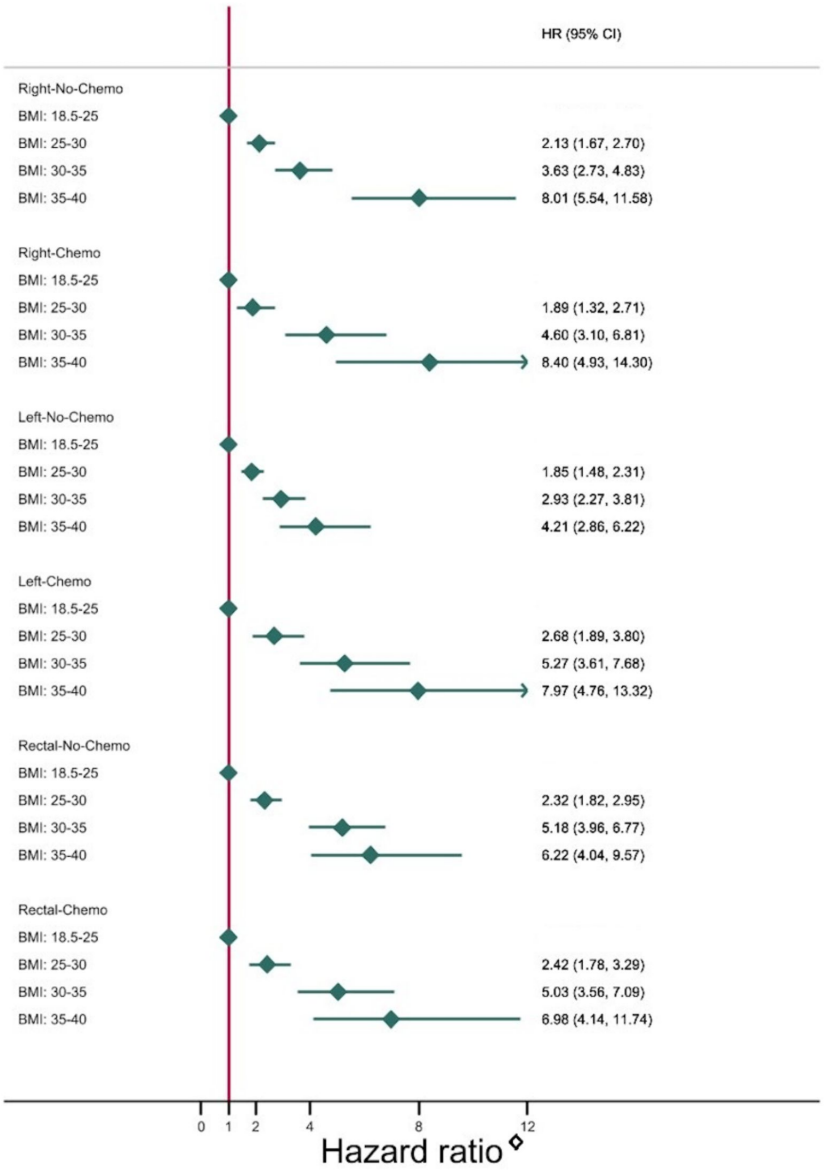

Figure 2

Likelihood of developing type 2 diabetes depending on BMI subgroups (using normal weight, BMI:18.5-25 as reference) after different types of colorectal cancer surgery with and without chemotherapy.
◊Hazard ratios were adjusted for age, sex, year of surgery and ASA score (performance status before surgery assessed by American Society of Anesthesiologist physical scale).

We found no impact of treatment with chemotherapy on T2D risk, which was a bit surprising. Prior studies indicated that treatment with chemotherapy may induce hyperglycemia, and especially the combined use of chemotherapy and glucocorticoid, administered to alleviate side-effects of chemotherapy, may have synergistic effects on later diabetes risk. [32]

In the study period of the present study, different types of chemotherapy have been part of the standard treatment of colon and rectum cancer respectively, and knowledge regarding the specific effects of each drug on glucose homeostasis is sparse.[33] In most cases CRC patients included in the study, will however have been treated with the chemotherapy 5-Flourouracil.[12] In a recent study a significant increase in glycemic variability, a precursor of T2D development, was found in non-diabetic early-stage colon cancer patients during 5-Flourouracil and Capecitabine chemotherapy treatment. [34]. Moreover, Feng et al. showed a 10% increased risk of developing T2D in CRC patients during and after treatment with adjuvant 5-Flourouracil. They argued that 5-Flourouracil could induce toxicity in B-cells leading to hyperglycaemia. [12] Similarly, Lee et al revealed an impairment in glucose homeostasis in both breast cancer and CRC patients treated with chemotherapy and glucocorticoid following treatment.[13] Nonetheless 65% of the newly diagnosed T2D cases remitted 6 months after discontinuation of chemotherapy, suggesting that chemotherapy is a reversible diabetogenic factor. [13] Thus, in summary, treatment with chemotherapy may primarily induce transient effects on glucose homeostasis in CRC patients. In contrast to the lack of influence of chemotherapy treatment, it was not surprising that radiation therapy had no impact on diabetes risk in our study.

Due to the strong negative prognostic effects of comorbidity with T2D on CRC outcomes, identifying CRC patients at increased risk of developing T2D is of great clinical importance. Our study did not support a role of cancer surgery with left-sided colonic resection or treatment with chemotherapy in T2D development in CRC survivors. However, in line with existing literature we found BMI to be strongly associated with T2D development.

A core strength of the present study is the use of a nationwide database, allowing inclusion of large numbers of CRC patients treated with different types of CRC resections, providing valid real-life data regarding with close to complete coverage and long-term follow-up and a register-based approach to identify individuals with T2D. We were able to adjust for several confounders such as BMI, alcohol consumption and smoking, which has been a limitation in previous studies. [15,16]

The limitation of the present study includes that information on BMI and other risk factors for developing T2D were only available preoperatively, eliminating the possibility of exploring an impact of BMI trajectories after cancer treatment until the T2D diagnosis. [35] Secondly, information on dose, length of treatment and type of chemotherapy were not available. Thirdly, information on physical activity, diet, medication, and comorbidities, apart from the ASA score, were not available. In addition, our findings are limited by the register-based data collection method. Clinical well-designed mechanistic investigations are warranted to establish whether left-sided CRC resection *per se* drives metabolic alterations leading to an increased risk of T2D.

In summary, we report a slightly increased risk of developing T2D after CRC treatment with colonic resection compared with rectal resection, whereas chemotherapy had no impact on new onset T2D. Within each surgical subgroup, BMI at time of surgery was strongly associated to developing T2D. This study suggests that postoperative diabetes screening should be prioritized in CRC survivors with overweight/obesity regardless of type of colorectal cancer treatment applied.

Data Availability

All data produced in the present study are available upon reasonable request to the authors

Acknowledgements

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Funding

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Ethics approval

According to Danish law and the Committee on Health Research Ethics in the Central Denmark Region, the study required no ethical approval because it was based on secondary use of register data for research purposes. This committee also waived patient consent for the use of register data. The study was approved by the Central Region Denmark (file no. 1-16-02-304-19).

Patient consent for publication

Not applicable

Contributors

Conceptualization, TL and LLL. Methodology, TL, LLL, CK, TIAS, MSS and JFC. Access to and verified the raw data and formal analysis TL and SBG. Resources, TL, LLL. Writing - Original draft CK, TL, LLL, MSS and SM. Writing – Review and editing, all authors contributed.

All authors approved the final version for publication, and LLL had final responsibility for the decision to submit.

Declaration of interests

The authors disclose no conflicts.

Data sharing

Anonymized data will be made available upon reasonable request for academic use and within the limitations of the informed consent. Requests should be made to last author tinlaurb@rm.dk. Due to the Danish law it is not possible to make national health registers available, but on request we would like to collaborate and discuss reasonable access to data.

	Adjusted for UICC		Model 1 + UICC		Model 2+UICC	
	HR (95%CI)	*p-value*	HR (95%CI)	*p-value*	HR (95%CI)	*p-value*
Surgery and chemotherapy						
Right-No-Chemo	ref					
Right-Chemo	0.98 (0.83;1.15)	0.788	0.93 (0.78;1.11)	0.441	0.97 (0.81;1.16)	0.731
Left-No-Chemo	1.11 (0.98;1.24)	0.097	0.93 (0.81;1.06)	0.269	0.94 (0.83;1.07)	0.374
Left-Chemo	1.03 (0.89;1.19)	0.730	0.88 (0.74;1.03)	0.120	0.93 (0.79;1.09)	0.373
Rectal-No-Chemo	0.93 (0.82;1.05)	0.225	0.81 (0.71;0.93)	0.002	0.85 (0.74;0.97)	0.018
Rectal-Chemo	0.89 (0.76;1.04)	0.139	0.76 (0.64;0.90)	0.002	0.82 (0.69;0.97)	0.022

Right: Right-sided colonic resections; Left: Left-sided colonic resections; Rectal: Rectal resections
No-Chemo: No chemotherapy; Chemo: Chemotherapy

All Colon: All right- and left-sided colonic resections with and without chemotherapy
All Rectal: All rectal resections with and without chemotherapy, and with and without radiation therapy

Model 1: adjusted for year of surgery, age at surgery, sex, BMI
Model 2: adjusted like Model 1 and further adjusted for performance status before surgery assessed by American Society of Anesthesiologist physical scale, smoking and alcohol

Supplementary table 1.

Likelihood of developing type 2 diabetes after different types of colorectal cancer surgery with and without oncological treatment, adjusted for UICC alone and in Model 1 and Model 2

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Reviewer #1 (Public Review):

Summary:
In this study, the authors set out to determine whether colorectal cancer surgery site (right, left, rectal) and chemotherapy impact the subsequent risk of developing T2DM in the Danish national health register.

Strengths:
- The research question is conceptually interesting
- The Danish national health register is a comprehensive health database
- The data analysis was thorough and appropriate
-The findings are interesting, and a little surprising that there was no impact of chemotherapy on the development of T2DM
- The authors have addressed my previous clarifications and questions.

- Regarding the generalizability of this study, as the authors discuss the prevalence of T2DM and obesity are lower in Denmark than in a number of other high income countries. Therefore, similar studies in other populations would be of interest.
- The study includes individuals who filled a prescription for diabetes medication, so likely includes some individuals with transient hyperglycemia/steroid induced diabetes during chemotherapy, rather than those with new onset longterm T2DM.

Overall, the authors achieved their aims, and the conclusions are supported by their results as reported.

The results are unlikely to significantly impact clinical practice or T2DM screening in this population, however are of interest to the community.

https://doi.org/10.7554/eLife.89354.2.sa0

Author Response

The following is the authors' response to the original reviews.

> ***eLife assessment***
>
> *This study presents valuable findings on diabetogenic risk from colorectal cancer (CRC) treatment. The authors claim that postoperative screening for type 2 diabetes should be prioritized in CRC survivors with overweight/obesity, irrespective of the oncological treatment received. The evidence supporting the claims is solid but requires confirmation in different populations. These results have theoretical or practical implications and will be of interest to endocrinologists, oncologists, general practitioners, gastrointestinal surgeons, and policymakers working on CRC and diabetes.*

Author response: We thank you for taking the time to provide constructive feedback on our manuscript and for the useful suggestions. We have provided a point-by-point response to each of the reviewers' comments with clearly marked changes to the manuscript.

> ***Public reviews***
>
> ***Reviewer #1 (Public Review):***
>
> *Summary:*
>
> *In this study, the authors set out to determine whether colorectal cancer surgery site (right, left, rectal) and chemotherapy impact the subsequent risk of developing T2DM in the Danish national health register.*
>
> *Strengths:*
>
> - *The research question is conceptually interesting*
> - *The Danish national health register is a comprehensive health database*
> - *The data analysis was thorough and appropriate*
> - *The findings are interesting, and a little surprising that there was no impact of chemotherapy on the development of T2DM*
>
> *Weaknesses:*
>
> *This is not a weakness as such, but in the discussion, I would consider adding some brief comment on the international generalizability of the findings - e.g. demographic make up of the Danish population health register and background rates of DM and obesity in this population with CRC compared to countries on other continents.*

Author response: We agree that this information would be valuable. It has now been added in the Discussion section.

Changes in manuscript: "In Denmark, the overall T2D prevalence is 6.9%25, lower than the global average in 2021 (10.5%) and also falls below the estimate of high-income countries (11.1%).26 Similarly, the obesity rate of 20% aligns with other Scandinavian countries and is below that of most high-income nations.27" (Page 8, line 256-258)

> *A little more information would be helpful regarding how T2DM was diagnosed in the registry.*

Author response: We have now added a more thorough explanation of how T2D was diagnosed in the Methods section.

Changes in manuscript: "Diabetes is defined as the second occurrence of any event across three types of inclusion events: 1) Diabetes diagnosed during hospitalisation 2) diabetes-specific services received at podiatrist 3) purchases of glucose lowering. Thus, if a patient developed transient T2D during chemotherapy treatment, it will only be an inclusion event if they purchase glucose lowering drugs. Individuals were classified as having T1D if they had received prescriptions for insulin combined with a diagnosis of type 1 from a medical hospital department. Otherwise, diabetes was classified as type 2.22" (Page 5, line 154-160)

> *If someone did develop transient hyperglycemia requiring DM medications during chemotherapy, would the investigators have been able to identify these people?*

Author response: Yes, we have added a sentence in the Methods section.

Changes in manuscript: "Thus, if a patient developed transient T2D during chemotherapy treatment, it will only be an inclusion event if they purchase glucose lowering drugs." (Page 5, line 156-158)

> *Would they have been classified as T2DM based on filling a prescription for DM meds for a period of time? Also, did the authors have information regarding time to development of T2DM after surgery?*

Author response: Yes, if they have 2 (or more) prescriptions of oral glucose lowering drugs. Yes, we have information regarding time to development of T2DM after surgery and found no difference between the groups.

Changes in manuscript: Information on mean time to develop T2D post-surgery has now been added to Table 2.

> *In the adjusted Models, the authors did not adjust for cancer stage, even though cancer stage appears to be very different between the chemo and no chemo groups. It would be interesting to know if it affects the results if the model adjusted for cancer stage*

Author response: We agree that adjustment for cancer stage would be a valuable information and we have performed the analysis and added a sentence in the Result section.

Changes in manuscript: An adjusted analysis of cancer stage now appears in the Supplementary table 1.

"Moreover, adjusting for cancer stage did not affect the results (Supplementary table 1)." (Page 7, line 219-220)

> *It would be worthwhile to report if mortality rates were different between the groups during follow up, and if the authors investigated whether perhaps differences in*

> *mortality rates led to specific groups living longer, and therefore having more time to develop DM*

Author response: This situation is accounted for in the analysis by using Cox-regression analysis. This method accounts for the potential competing effect of mortality.

Changes in manuscript: None.

> *Overall, the authors achieved their aims, and the conclusions are supported by their results as reported.*

The results are unlikely to significantly change patient treatment or T2DM screening in this population. With some additional information, as described above, the results would be of interest to the community.

> ***Reviewer #2 (Public Review):***
>
> *Summary:*
>
> *The study showed the impact of cancer treatment on new onset of diabetes among patients with colorectal cancer using the national database. Findings reported that individuals with rectal cancer without chemotherapy were less likely to develop diabetes but among other groups, treatment didn't show any impact on the development of diabetes. BMI still played a significant role in developing diabetes regardless of treatment types.*
>
> *Strengths:*
>
> *One of the strengths of this study is innovative findings about the prognosis of colorectal cancer treatment stratified by treatment types. Especially, as it examined the impact of treatment on the risk of new chronic disease after diagnosis, it became significant evidence that suggests practical insights in developing a proper monitoring system for patients with colorectal cancer and their outcomes after treatment and diagnosis. It is imperative for providers to guide patients and caregivers to prevent adverse outcomes like new onset of chronic disease based on BMI and types of treatment. The next strength is the national database. As the study used the national database, the generalizability is validated.*
>
> *Weaknesses:*
>
> *Even though the study attempted to examine the impact of each treatment option, the dosage of chemotherapy and the types of chemotherapy were not able to be examined due to the data source.*

Author response: No unfortunately not. We agree that this would have been valuable information. This is stated in the original manuscript as a limitation. Please refer to page 10 line 305-306.

Changes in manuscript: None.

> ***Recommendations for the authors:***
>
> ***Reviewer #1 (Recommendations For The Authors):***
>
> *Minor things:*

> *There are minor inconsistencies in the methods and results regarding BMI. In the methods, the authors state that BMI <18.5 and >/=40 were excluded, but these groups are included in Table 2.*

Author response: This has been corrected

Changes in manuscript: BMI groups <18.5 and >/=40 are now excluded in Table 2. (Page 18)

> *Line 204, I believe should be BMI 18.5-24.9, not 20-24.9.*

Author response: This has been corrected

Changes in manuscript: "For each group (type of surgery ± chemotherapy), the HR for developing T2D depending on BMI subgroups was calculated by using Cox regression analysis adjusted for age, sex, year of surgery, and ASA score using normal weight (BMI:18.5-24.9) as the reference group." (Page 6, line 184-186)

> *Rather than showing the BMI mean in Table 1, it would be interesting to see the BMI breakdown by category.*

Author response: Yes, we agree. This analysis has now been added to Table 1

Changes in manuscript: Please refer to Table 1

> *Re line 215, I would consider rewriting to remove the multiple negatives -e.g. Radiation therapy in rectal resected had did not impact the incidence rate of T2D in the Rectal-No-Chemo group or Rectal-Chemo group*

Author response: This has been corrected. Please refer to the Result section.

Changes in manuscript: "Radiation therapy in the rectal resected groups had no impact on the incidence rate of T2D (Table 2); and the unadjusted/adjusted HR of developing T2D was non-significant when comparing Rectal-No-Radiation patients with Rectal-Radiation patients (Table 3)." (Page 7, 223-225)

> *Consider changing some of the "didn't"s in the discussion to "did not"*

Author response: This has been corrected.

Changes in manuscript: Revised and corrected throughout the discussion.

> ***Reviewer #2 (Recommendations For The Authors):***
>
> *Some points need to be clarified and improved.*
>
> *In the method, patients with Type 1 Diabetes were excluded in the baseline but some patients were diagnosed with Type 1 diabetes after treatment and they were included in your analysis. It is interesting to identify Type 1 Diabetes after the treatment as an outcome, do you think that this diagnosis is caused by the treatment? And incidence rate or other HRs did not seem to include Type 1 Diabetes as stated in the methods. Did you exclude every Type 1 diabetes? If not, It needs to give further explanation about this outcome since the mechanism of Type 1 Diabetes and Type 2 Diabetes is different.*

Author response: This matter has now been clarified in the Methods section.

Changes in manuscript: “Additionally, individuals diagnosed with Type 1 diabetes (T1D) either before or after surgery were excluded, along with those diagnosed with T2D preoperatively or within the first 2 weeks postoperatively, as the last group probably represents patients with preoperatively unknown pre-existing prediabetes or diabetes.22” (Page 4, line: 125-128)

> *Despite limited existing findings, some studies actually reported the incidence rates of Type 2 Diabetes among patients with CRC (Singh S, Earle CC, Bae SJ, et al. Incidence of Diabetes in Colorectal Cancer Survivors. J Natl Cancer Inst. 2016;108(6):djv402. Published 2016 Feb 2. doi:10.1093/jnci/djv402; Khan NF, Mant D, Carpenter L, Forman D, Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. Br J Cancer. 2011;105 Suppl 1(Suppl 1):S29-S37. doi:10.1038/bjc.2011.420; Jo A, Scarton L, O'Neal LJ, et al. New onset of type 2 diabetes as a complication after cancer diagnosis: A systematic review. Cancer Med. 2021;10(2):439-446. doi:10.1002/cam4.3666) whereas your study examined the impact of the different types of treatments.*

Author response: Our findings of T2D rate among CRC patients are now commented on in discussion section, and the abovementioned studies are included as references.

Changes in manuscript: “This national cohort study demonstrated an IR of developing T2D after CRC surgery similar to previous studies.5,11” (Page 8, line 237-238)

> *To strengthen the presentation, some places should be revised.*
>
> - *Line 216: it says that Table 1 showed no impact of radiation therapy on the incidence rate of T2D. However, either the interpretation or the table number seems wrong. Table 1 does not have this information. Correct this statement.*
> - *Line 239: There are typo and incomplete sentence. Check the sentence and correct the sentence.*
> - *Line 257-261: It may be a systematic issue to separate these two paragraphs. But two paragraphs seem related so make them one paragraph.*

Author response: These suggested changes have been made. Regarding line 216 the paragraph has been adjusted to the following:

Changes in manuscript: “Radiation therapy in the rectal resected groups had no impact on the incidence rate of T2D (Table 2); and the unadjusted/adjusted HR of developing T2D was non-significant when comparing Rectal-No-Radiation patients with Rectal-Radiation patients (Table 3).” (Page 7, 223-225)

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