Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer

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Conclusions This prospective study showed an increased risk of proximal colon cancer in women with T2DM compared with non-T2DM women. Eur J Gastroenterol Hepatol 28:896–903
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Colorectal cancer (CRC) is a major health problem worldwide. Evidence on the risk factors for CRC has accumulated considerably in the past decades. Type 2 diabetes mellitus (T2DM), which shares several risk factors with CRC such as an increased BMI, abdominal fat, low levels of physical activity and a Western diet (e.g. high consumption of red and processed meat) [1,2], has been associated with an increased risk of CRC [3]. The main

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Materials and methods

The Netherlands Cohort Study on diet and cancer (NLCS) was initiated in 1986 [9]. The study protocol was approved by the Medical Ethics Committee of the Maastricht University and TNO Nutrition Zeist, the Netherlands. The design is briefly explained below and a more detailed description of the design of the NLCS is available elsewhere [9]. For reasons of efficiency, a case-cohort approach is used for processing and analysing data within the NLCS. This approach entails that incident cancer cases are enumerated from the entire cohort, whereas a random subcohort ($n=5000$), selected immediately after baseline, is followed for vital status to estimate the accumulated person-time at risk but also to estimate the exposure within the entire cohort. The NLCS includes 58 279 men and 62 573 women who were between 55 and 69 years old at baseline. Each participant completed a self-administered questionnaire with questions on dietary habits, lifestyle, chronic conditions and demographic factors at baseline. The questionnaire consisted of 11 pages, of which only the first page was scanned and processed digitally for each cohort participant. The remaining pages had to be key-entered manually, which was done for cancer cases and subcohort members for reasons of efficiency. Processing occurred blinded with respect to case/(sub)cohort status to minimize observer bias in coding and interpretation of the data. Incident CRC cases are identified by record linkage to the Netherlands Cancer Registry and the Dutch national pathology registry (PALGA) (>96% completeness). Follow-up of vital status is performed by linkage to the Central Bureau of Genealogy and the municipal registries (~100% completeness). NLCS participants reporting a history of cancer at baseline other than nonmelanoma skin cancer were excluded from follow-up, leaving a total of 4774 subcohort members. After 17.3 years of follow-up, 3056 CRC cases were available for analyses. Among these, 1044 were proximal colon cancer cases (International Classification of Diseases for Oncology first edition codes 153.0, 153.1, 153.4, 153.5 and 153.6), 970 were distal colon cancer cases (codes 153.2, 153.3 and 153.7), 678 were rectal cancer cases (code 154.1), 73 were colon cancers that could not be classified as proximally or distally located and 291 were rectosigmoid cancers, which comprised a group that was too small for separate analyses. Unclassified colon cancers and rectosigmoid cancers were included when analysing overall CRC.

Case-cohort versus full-cohort analyses

Primarily, analyses were carried out using the case-cohort approach. Complete questionnaire data for cases and subcohort members were available for 17.3 years of follow-up (as stated above). In addition, information on chronic conditions [e.g. diabetes mellitus (DM) status] and demographics (e.g. age, sex) from the first page of the baseline questionnaire was available for the entire cohort for 20.3 years of follow-up, enabling full-cohort analyses for 20.3 years of follow-up. Full-cohort data for 20.3 years of follow-up were available at the time of this study because of the digital processing of the first page of the questionnaire. Although the unavailability of the remaining pages meant limited possibilities for adjustment for

potential confounders in the full-cohort analysis, the advantage in the full-cohort analysis was a gain in power because a higher number of incident CRC cases had occurred after 20.3 years of follow-up ($n=4593$). Any gain in power is important, considering that the prevalence of diabetes is low in the NLCS. In total, after the exclusion of prevalent cancer cases other than those with non-melanoma skin cancer, the full cohort includes 4292 participants who reported T2DM at baseline (3.7%) and 110 211 participants who did not (96.3%). Analyses in which T2DM patients were subdivided into smaller groups, that is, according to the duration of T2DM or the age at diagnosis, were carried out using full-cohort data only because of power considerations.

Assessment of DM status and relevant confounders

DM status and age at diagnosis (classified in 5-year age groups) were derived from the first page of the baseline questionnaire on the basis of the following question: 'Has a physician ever diagnosed you with diabetes mellitus and what was your age at that time?' Participants could indicate age categories ranging from 'younger than 30 years of age', and then 5-year age categories, for example, '30 to 34 years' and '35 to 39 years', up until the category '65 to 69 years'. Individuals who reported to have been diagnosed with DM after 30 years of age were classified as having T2DM. This cut-off point was based on epidemiological data on the prevalence of DM and the previous literature [10–12]. Individuals with a diagnosis of DM before the age of 30 years ($n=11$) were considered non-T2DM in this study. The duration of DM was calculated by subtracting the median age at diagnosis of DM from the age at baseline.

The covariates used in the analyses were also derived from the baseline questionnaire. These covariates included age, sex, BMI, trouser/skirt size, nonoccupational physical activity, family history of CRC (yes or no), smoking, intake of alcohol and dietary habits (total meat, fruit and vegetables, fish, sweets, added sugar, saturated fats, fibre intake and energy). BMI (kg/m^2) was calculated using self-reported weight and height. Trouser or skirt size was reported from individuals' clothing label. Trouser/skirt size has been shown to correlate with hip and waist measurements in a subset of weight-stable individuals and was associated with endometrial and renal cell cancer risk in a manner as would be expected for waist circumference, rendering trouser/skirt size as a good proxy for waist circumference [13]. Nonoccupational physical activity was a sum measure of several activities: daily walking/cycling (min/day), weekly recreational walking/cycling, weekly engagement in gardening/odd jobs and weekly participation in sports/gymnastics (categories: never, 1, 1–2 and >2 h/week). Nonoccupational physical activity was classified as low (≤ 30 min/day), low-intermediate (>30–60 min/day), high-intermediate (>60–90 min/day) and high (>90 min/day). Dietary and alcohol intake were assessed using a semi-quantitative food-frequency questionnaire, which was part of the baseline questionnaire and which included 150 food items. Nutrient intake was calculated using the Dutch food composition table 1986–1987 [14]. The food-frequency questionnaire was found to rank individuals adequately according to dietary intake compared with a 9-day dietary

record [15] and was shown to be a good indicator of intake for at least 5 years [16].

Statistical analyses

We carried out sex-specific and subsite-specific analyses using Stata (version 12; Statacorp., College Station, Texas, USA). Baseline characteristics were compared between diabetic subcohort members and nondiabetic subcohort members using Student's *t*-test, Mann–Whitney *U*, Fisher's exact test and χ^2 -tests, where appropriate. Age-adjusted and multivariable-adjusted hazard ratios (HRs) for CRC were calculated using Cox regression with 'time-on-study' in years as the timescale. The time of origin was identical for all NLCS participants. Confounders were selected a priori on the basis of the literature and checked for their potential to alter HRs by more than 10% using a backward procedure. Although none altered HRs by more than 10%, all were included in multivariable-adjusted models. For all analyses, the proportional hazards assumption was tested using the scaled Schoenfeld residuals and by visual inspection of the $-\log$ to $\log$ -transformed hazard curves. In addition, analyses were repeated by splitting up the follow-up time at half point into two equal periods. To account for the additional variance introduced in case-cohort analyses, SEs were estimated using the robust Huber–White sandwich estimator option [17]. Statistical significance was tested at the 0.05 level using two-sided tests. In the analyses, individuals reporting a diagnosis of DM before 30 years of age were included in the nonexposed group. To assess the impact of the potential presence of type 1 DM patients in the unexposed population, a sensitivity analysis was carried out excluding individuals reporting a diagnosis of DM before the age of 30 years ($n = 11$). To assess the impact of BMI as an effect modifier, a sensitivity analysis was carried out in which the results were stratified according to BMI status (≤ 25 vs. > 25 kg/m²).

Results

Case-cohort analyses using 17.3 years of follow-up

After 17.3 years of follow-up and after exclusion of individuals with incomplete/inconsistent questionnaires and missing values on variables included in the multivariable-adjusted analysis, a total of 3919 subcohort members, which included 122 subcohort members with T2DM (3.1%) and 130 subcohort members with CRC (3.3%), and 3056 CRC cases, of whom 92 had T2DM (3.0%), were available for analyses. Baseline characteristics of the subcohort members are presented in Table 1. Compared with men without T2DM, men with T2DM were older ($P < 0.01$), had a significantly lower intake of 'sweets' and 'added sugar' ($P < 0.001$ for both) and had a slightly lower but nonsignificant ($P = 0.071$) total energy intake. Women with T2DM were significantly older ($P = 0.01$), had a significantly higher BMI ($P < 0.01$) and a borderline significantly larger trouser/skirt size ($P = 0.052$) compared with women without T2DM. With respect to dietary factors, women with T2DM on average had a higher meat intake ($P < 0.01$) and a lower intake of 'sweets' and 'added sugar' ($P < 0.001$ for both). CRC cases were older, had a higher BMI and more often a family history of CRC compared with subcohort members [18] (data not shown).

Overall and subsite-specific associations between T2DM and CRC are presented in Table 2 for men and women separately. In multivariable-adjusted models, T2DM was not associated with the risk of overall CRC in men and women [HR = 0.98, 95% confidence interval (CI): 0.63–1.49 and HR = 1.24, 95% CI: 0.83–1.86, respectively]. The subsite-specific analyses showed that T2DM was associated with a statistically significant increased risk of proximal colon cancer in women (HR = 1.82, 95% CI: 1.11–2.98), but not men (HR = 1.37, 95% CI: 0.77–2.42). No association was observed between T2DM and distal colon cancer and rectal cancer risk in both men and women. There were no essential differences in HRs between the age-adjusted and multivariable-adjusted analyses.

Patients with DM diagnosed before the age of 30 years ($n = 11$) were included in analyses as non-T2DM patients. In sensitivity analyses, exclusion of these patients did not alter the results (data not shown). Stratification according to BMI marginally attenuated effect sizes and did not result in significant new findings (data not shown).

Full-cohort analyses using 20.3 years of follow-up

For the full-cohort analyses, we had available a total of 110 211 cohort members, of whom 4292 were T2DM patients (3.8%), and 4593 CRC cases after the exclusion of 5975 prevalent cancer cases (excluding nonmelanoma skin cancers). Age-adjusted analyses showed a significantly increased risk of proximal colon cancer in women with T2DM compared with women without T2DM (HR = 1.44, 95% CI: 1.05–1.99). The results of the full-cohort analyses, in which the duration of T2DM and the age at self-reported diagnosis of T2DM were modelled, are shown in Table 3. Table 3 also shows the results of analyses in the full cohort according to short and long follow-up durations. The majority of the patients with T2DM had been diagnosed with DM 0–10 years before baseline and after the age of 50 years. In men, an increased duration appeared to be associated with an increasing risk of proximal colon cancer [HR (0–10 years) = 0.82; HR (10–15 years) = 1.60; HR (>15 years) = 1.83], although the number of cases in subgroups was small and the HRs did not reach statistical significance, nor was there a statistically significant test for trend across categories. In women, a short duration of T2DM (0–10 years) and a self-reported diagnosis of T2DM after 50 years of age versus long T2DM duration and a diagnosis of T2DM before 50 years of age were both associated with a significantly increased risk of proximal colon cancer (HR = 1.89, 95% CI: 1.32–2.69 and HR = 1.64, 95% CI: 1.17–2.32, respectively). In both men and women, the duration since the diagnosis of T2DM and the age at diagnosis of T2DM were not associated with the risk of distal colon cancer and rectal cancer. Analyses according to the follow-up duration generally showed no essential differences in estimates between short (0–10 years) and long (10–20.3 years) durations of follow-up. Associations in relation to proximal colon cancer in men seemed stronger after longer follow-up duration than a shorter follow-up duration, but caution is warranted in interpreting the results because the number of cancer cases was small in these analyses.

Table 1. Baseline characteristics of nondiabetic individuals and patients with type 2 diabetes mellitus within the subcohort of the Netherlands Cohort Study

Characteristic	Men			Women		
	No T2DM [N=1835 (97.1%)]	T2DM [N=55 (2.9%)]	P-value	No T2DM [N=1962 (96.7%)]	T2DM [N=67 (3.3%)]	P-value
Age at baseline (years) ^a	61.2 (4.2)	62.9 (4.4)	0.003	61.3 (4.3)	62.7 (4.2)	0.001
BMI (kg/m ²) ^a	24.9 (2.5)	25.1 (2.8)	0.631	25.0 (3.5)	26.4 (3.9)	0.005
Pants/skirt size (≥ large size) (%)	63	66	0.668	55	67	0.052
Age at diagnosis of T2DM (years) ^a	NA	53.7 (7.7)		NA	56.3 (7.5)	
Exposure time T2DM (years) ^a	NA	9.0 (7.5)		NA	6.8 (6.4)	
Family history of CRC (yes) (%)	5.5	3.0	0.363	5.9	4.5	0.795
Smoking status (%)			0.701			0.133
Never	13	11		57	69	
Exsmoker	52	58		21	18	
Current smoker	35	31		22	13	
Alcohol intake (%)			0.151			0.085
0 (g/day)	14	18		32	42	
0.1–30 (g/day)	72	60		64	58	
>30 (g/day)	14	22		3.7	0.0	
Dietary habits (g/day)						
Total meat ^{a,b}	123 (48)	123 (41)	0.893	104 (43)	119 (49)	0.004
Fruit and vegetables ^a	358 (159)	377 (152)	0.370	401 (161)	407 (168)	0.760
Fish ^a	14 (17)	11 (12)	0.122	11 (14)	15 (19)	0.513
Sweets ^{a,c}	41 (26)	30 (30)	<0.001	42 (26)	27 (22)	<0.001
Added sugar ^a	31 (33)	6 (18)	<0.001	12 (20)	2 (9)	<0.001
Saturated fats ^a	37 (12)	35 (13)	0.131	30 (10)	29 (9)	0.263
Fibre intake ^a	29 (9)	30 (8)	0.513	25 (7)	24 (7)	0.625
Energy (kcal/day) ^a	2176 (509)	2050 (475)	0.071	1690 (397)	1629 (343)	0.215
Physical activity (%)			0.196			0.080
≤30 (min/day)	17	26		23	30	
>30 to ≤60 (min/day)	31	20		31	36	
>60 to ≤90 (min/day)	20	18		24	10	
>90 (min/day)	32	36		22	24	

CRC, colorectal cancer; NA, not available; T2DM, type 2 diabetes mellitus.

^aValues presented as: mean (SD from the mean).^bConsisting of the sum of pork, beef, poultry, game and processed meat.^cConsisting of the sum of sweet sandwich filling, cookies, cake and candy.**Table 2.** Case-cohort and full-cohort analysis on the association between type 2 diabetes mellitus and colorectal cancer in the Netherlands Cohort Study

	Case-cohort analyses (0–17.3 years follow-up)				Full-cohort analyses (0–20.3 years follow-up) ^c		
	PY (non-T2DM/T2DM ^b)	Cases (non-T2DM/T2DM)	HR (95% CI) age-adjusted	HR ^a (95% CI)	PY (non-T2DM/T2DM)	Cases (non-T2DM/T2DM)	HR (95% CI) age-adjusted
Men							
Overall CRC	26 131/670	1690/45	0.98 (0.64–1.50)	0.97 (0.63–1.49)	844 054/26 416	2492/72	0.95 (0.75–1.20)
Proximal colon cancer	26 131/670	477/18	1.34 (0.76–2.36)	1.37 (0.77–2.42)	844 054/26 416	730/25	1.13 (0.76–1.68)
Distal colon cancer	26 131/670	562/12	0.78 (0.41–1.50)	0.78 (0.40–1.51)	844 054/26 416	818/19	0.77 (0.49–1.21)
Rectal cancer	26 131/670	432/5	0.44 (0.17–1.12)	0.41 (0.16–1.05)	844 054/26 416	618/14	0.50 (0.21–1.22)
Women							
Overall CRC	30 593/943	1274/47	1.16 (0.78–1.71)	1.24 (0.83–1.86)	1 002 024/33 165	1959/70	1.08 (0.85–1.37)
Proximal colon cancer	30 593/943	523/26	1.54 (0.96–2.48)	1.82 (1.11–2.98)	1 002 024/33 165	820/39	1.44 (1.05–1.99)
Distal colon cancer	30 593/943	386/10	0.83 (0.42–1.63)	0.81 (0.40–1.61)	1 002 024/33 165	570/14	0.75 (0.44–1.27)
Rectal cancer	30 593/943	232/9	1.23 (0.60–2.52)	1.18 (0.56–2.48)	1 002 024/33 165	368/13	1.16 (0.54–2.48)

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PY, person-years; T2DM, type 2 diabetes mellitus.

^aHazard ratios adjusted for age, BMI, pants/skirt size, family history of CRC, smoking status, alcohol intake, dietary habits and nonoccupational physical activity.^bType 2 diabetes mellitus (age of onset ≥ 30 years) determined by self-report at baseline.^cBecause of the limited number of patients with T2DM at baseline in case-cohort analyses, additional full-cohort analyses were carried out with restriction to confounder adjustment.

Discussion

In this large population-based cohort study, we found that T2DM was associated with an 82% increased risk of proximal colon cancer, but not distal colon and rectal cancer in women. An increased risk of proximal colon cancer was particularly observed in women with a T2DM diagnosis after 50 years of age and in women with a short duration of T2DM (0–10 years). In men, T2DM was not

significantly associated with the risk of overall CRC or CRC at any subsite.

Our results appear to be consistent with other large cohort studies that investigated the subsite-specific CRC risk in diabetic women. The Nurses' Health Study [19] found T2DM to be associated with an increased risk of proximal colon cancer in women (HR=1.64, 95% CI 1.04–2.60) and found no association with distal colon cancer (HR=1.38, 95% CI 0.88–2.15) and rectal cancer

Table 3. Full-cohort analyses on associations between duration of type 2 diabetes mellitus, age at diagnosis of type 2 DM, follow-up duration and colorectal cancer risk in the Netherlands cohort study

	Colorectal cancer			Proximal		Distal		Rectal	
	PY at risk	N cases	Age-adjusted HR (95% CI)	N cases	Age-adjusted HR (95% CI)	N cases	Age-adjusted HR (95% CI)	N cases	Age-adjusted HR (95% CI)
Men									
Duration of T2DM ^{a,b}									
No T2DM	844,054	2492	1	730	1	818	1	618	1
T2DM (0–10 years)	16,437	44	0.95 (0.71–1.28)	11	0.82 (0.45–1.49)	15	0.99 (0.60–1.66)	10	0.86 (0.46–1.61)
T2DM (10–15 years)	4,385	11	0.86 (0.48–1.56)	6	1.60 (0.72–3.57)	2	0.48 (0.12–1.92)	1	0.32 (0.04–2.24)
T2DM (>15 years)	4,858	17	1.16 (0.72–1.87)	8	1.83 (0.91–3.67)	2	0.42 (0.10–1.68)	3	0.84 (0.27–2.60)
<i>P</i> _{trend}			0.923		0.117		0.145		0.313
Age at diagnosis of T2DM ^b									
No T2DM	844,054	2492	1	730	1	818	1	618	1
T2DM (diagnosed <50 years)	6,978	19	1.00 (0.63–1.57)	8	1.47 (0.73–2.96)	3	0.48 (0.15–1.49)	3	0.62 (0.20–1.92)
T2DM (diagnosed ≥50 years)	19,438	53	0.94 (0.71–1.23)	17	1.02 (0.63–1.65)	16	0.87 (0.53–1.42)	11	0.78 (0.43–1.42)
Follow-up time									
0–10 years (no T2DM vs. T2DM)	493 177/17 110	1041/34	0.91 (0.65–1.28)	284/9	0.87 (0.45–1.70)	456/19	1.17 (0.74–1.86)	277/5	0.50 (0.21–1.22)
10–20.3 years (no T2DM vs. T2DM)	350 878/9306	1451/38	0.98 (0.71–1.36)	446/16	1.35 (0.82–2.22)	634/12	0.71 (0.40–1.26)	341/9	0.99 (0.51–1.92)
Women									
Duration of T2DM ^b									
No T2DM	1 002 024	1959	1	820	1	570	1	368	1
T2DM (0–10 years)	20,959	53	1.30 (0.99–1.71)	32	1.89 (1.32–2.69)	7	0.60 (0.41–1.33)	10	1.31 (0.70–2.46)
T2DM (10–15 years)	5,005	6	0.61 (0.27–1.36)	3	0.73 (0.24–2.28)	2	0.71 (0.14–2.22)	1	0.55 (0.08–3.88)
T2DM (>15 years)	6,383	10	0.79 (0.43–1.47)	4	0.76 (0.28–2.02)	5	1.38 (0.45–2.61)	1	0.42 (0.06–3.03)
<i>P</i> _{trend}			0.794		0.353		0.773		0.573
Age at diagnosis of T2DM ^b									
No T2DM	1 002 024	1959	1	820	1	570	1	368	1
T2DM (diagnosed <50 years)	8,628	12	0.77 (0.44–1.36)	5	0.79 (0.33–1.90)	4	0.86 (0.32–2.30)	3	1.01 (0.32–3.14)
T2DM (diagnosed ≥50 years)	24,536	58	1.18 (0.91–1.53)	34	1.64 (1.17–2.32)	10	0.71 (0.38–1.33)	10	1.10 (0.58–2.06)
Follow-up duration									
0–10 years (no T2DM vs. T2DM)	541 028/20 142	794/35	1.09 (0.78–1.53)	295/19	1.55 (0.97–2.47)	325/9	0.71 (0.36–1.37)	151/7	1.16 (0.54–2.48)
10–20.3 years (no T2DM vs. T2DM)	460 996/13 023	1165/35	1.06 (0.75–1.48)	525/20	1.33 (0.85–2.09)	400/9	0.79 (0.41–1.54)	217/6	0.98 (0.43–2.20)

CI, confidence interval; FU, follow-up; HR, hazard ratio; PY, person-years; T2DM, type 2 diabetes mellitus.

^aT2DM (age of onset ≥30 years), T2DM status, T2DM duration and age of diagnosis determined by self-report at baseline.^bSome counts do not add up to totals because patients could not be classified on the basis of age of diagnosis of diabetes mellitus.^c

risk (HR = 1.11, 95% CI 0.56–2.21) in a model adjusted for age, BMI and levels of physical activity. Participants of the Nurses' Health Study were younger compared with participants of the NLCS, with a mean age of 42–45 years at baseline. DM status and other variables were reassessed biennially and the follow-up duration was 18 years. In the Iowa Women's Health Study, women with T2DM compared with nondiabetic women were also at an increased risk of proximal colon cancer (HR = 1.9, 95% CI: 1.3–2.6), but not distal colon cancer (HR = 1.1, 95% CI 0.6–1.8) and rectal cancer (HR = 0.8, 95% CI 0.4–1.6). In a cohort study carried out by Weiderpass *et al.* [20], standardized incidence ratios were calculated according to the CRC subsite. In both men and women, T2DM appeared to be more strongly associated with proximal colon cancer than with distal colon and rectal cancer. In contrast to these results, in a cohort study by Flood *et al.* [21], a borderline significant positive association was observed of T2DM with cancer in the distal colon and rectum [HR 1.65 (95% CI 0.98–2.78)] and a non-significant association with proximal colon cancer (RR 1.46 [95% CI 0.85–2.49]) in women in a multivariable-adjusted model similar to our study. Despite the efforts made towards obtaining CRC cases and characteristics in the latter study, about 25% of CRC cases could not be classified by location, which could partly explain the differences in the subsite distribution of CRC cases and the nonsignificant RRs because of the lower power in subsite-specific analyses compared with our study. In a cohort of Swedish men [12], who were between 45 and 79 years old at baseline, a multivariable-adjusted increased risk was observed for overall CRC [RR 1.49 (95% CI 1.14–1.96)], particularly rectal cancer [RR 1.79 (95% CI 1.18–2.73)], when comparing diabetic men with nondiabetic men; the risk of proximal and distal colon cancer appeared to be increased, although this was not statistically significant. It should be noted that there was a markedly higher percentage of rectal cancer cases in this Swedish cohort (43%) compared with ours (20%) and others (27%) [22], which could partly explain the difference in the results found. Other more recent studies found a modestly increased risk of CRC in diabetic individuals compared with nondiabetic individuals. Although sex-specific and subsite-specific risk estimates were not always presented [22–25], the authors reported that the results were similar for proximal and distal cancers. Finally, in a recent meta-analysis, 24 cohort studies were combined. The authors found that the risk of CRC was increased in diabetic individuals and that the risk of proximal colon cancer appeared to be higher than the risk of distal colon cancer, although not statistically significantly different [26].

There are several potential explanations for the increased risk of proximal colon cancer that was found in diabetic women compared with nondiabetic women, especially those diagnosed with DM after 50 years of age, in this study. Most of these explanations apply to men as well, in whom diabetes was observed to be borderline significantly associated with an increased risk of proximal colon cancer. First, in postmenopausal women, low levels of oestrogen may result in loss of the protective effect of oestrogen on insulin resistance and CRC [27,28]. Second, high age of onset strongly coincides with a short duration of DM exposure in our cohort and could reflect the period

closest to exposure to high levels of serum-insulin in which colorectal neoplasms develop. Third, individuals diagnosed with DM at an older age are possibly less motivated to adjust their lifestyle, resulting in an increased risk of CRC compared with diabetic patients diagnosed early who may be more likely to adjust their lifestyle [29]. Fourth, as age of onset increases, type 1 DM and latent autoimmune diabetes in adults are less likely. Thus, selection of T2DM patients on the basis of higher age minimizes potential misclassification of T2DM, resulting in stronger associations with outcome.

The literature remains inconsistent on the potentially differing effects of CRC risk factors (e.g. T2DM, physical activity) on specific subsites of the colorectal tract. The biological mechanisms that explain the differences in subsite-specific associations are yet to be elucidated. Studies have indicated different responses of proximal colon cells and more distally localized cells to growth-stimulating hormones such as gastrin, leptin and IGF [30, 31]. For example, a pilot study in rodents showed that a 50–75% reduction in circulating IGF-1 levels resulted in a reduction in azoxymethane-induced colon tumours in the proximal colon, but not in the distal colon [32]. A higher sensitivity to IGF-1 of proximal colon cells compared with cells in the distal colon could partly explain the findings in this and possibly our study.

The interpretation of results on the associations between the onset of T2DM and duration of exposure to T2DM on the one hand and the risk of CRC on the other is complex when considering a dynamic underlying pathway that involves varying degrees of insulin resistance and hyperinsulinaemia, and associated alterations in IGF levels. First, intrinsic insulin levels vary from increased levels in the prediabetic stage to decreased levels in well-established T2DM as pancreatic β cells become more dysfunctional [33]. Second, from the time of DM diagnosis, various other factors such as medication [34–36] and changes in lifestyle (dietary changes, weight loss, increased physical activity) may influence the degree of insulin resistance and consequently serum levels of insulin. Taking into consideration this dynamic nature of the degree of insulin resistance, a history of T2DM may be viewed as a proxy for a temporary exposure to increased insulin and IGF levels and thus colonic cell growth promotion, which could increase the risk of CRC.

The association between T2DM and proximal colon cancer found in our cohort was present in women who were between 55 and 69 years old at baseline, which was similar to the age range of other cohort studies in which the same association was observed as mentioned above [11,19]. This age range largely overlaps that of the screening population in the Netherlands (55–75 years) and other international cancer screening network countries. As interval colon cancers, liberally defined as colon cancers that occur between two colonoscopies, are frequently located proximally [37] and women with T2DM are less likely to take part in screening programmes [38], future studies could perhaps investigate whether or not more tailored screening strategies (e.g. shortening the screening interval) are useful in women with T2DM.

Factors that contribute to the strength of this study are its prospective design, the large study population including men and women, the long period of follow-up with a high

number and nearly complete follow-up of histologically confirmed colorectal cancers as well as the extensive baseline questionnaire. There are some limitations to our study. Classification of T2DM was performed on the basis of self-reports, which could have resulted in some misclassification as there may have been undiagnosed diabetic patients in our cohort. However, previous studies within large cohorts have shown that the self-report of treated diabetes is an accurate proxy to use in epidemiologic studies [22,28,39]. Any misclassification is also likely to have been independent of disease and will have most likely resulted in an attenuation of HRs. Another limitation may have been that there were no repeated measurements with respect to DM and covariates during the follow-up period in the NLCS. Especially with a longer follow-up duration, the probability of misclassification of DM (unidentified T2DM patient in the non-T2DM population), using one baseline measurement, increases. Considering this misclassification, together with a relatively low proportion of patients with T2DM at baseline, especially in men, associations are likely to be underestimated in this study.

Conclusion

In conclusion, after 17.3 years of follow-up, we found a moderate increase in the risk of proximal colon cancer in women, but not men with T2DM compared with those without T2DM. Future studies are needed to determine whether a more tailored screening strategy could be useful in this subgroup of patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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