# The Risk of Colorectal Cancer in Patients With Type 2 Diabetes: Associations With Treatment Stage and Obesity

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## OBJECTIVE

**To assess the risk of colorectal cancer associated with type 2 diabetes, as compared with a nondiabetic reference population, and to study additional associations between treatment stage and duration of obesity and colorectal cancer risk.**

## RESEARCH DESIGN AND METHODS

**We conducted an observational population-based cohort study within the Clinical Practice Research Datalink (1987–2012). All patients (≥18 years) with at least one prescription for an antidiabetic drug (*n* = 300,039) were matched (1:1) by birth year, sex, and practice to a comparison cohort without diabetes. Cox proportional hazards models were used to derive adjusted hazard ratios (HRs) for colorectal cancer associated with type 2 diabetes. Within the diabetic cohort, associations of colorectal cancer with treatment stages and duration of obesity (BMI ≥30 kg/m$^2$) were studied.**

## RESULTS

**After a median follow-up of 4.5 years, 2,759 cases of colorectal cancer were observed among the diabetic study population. Type 2 diabetes was associated with a 1.3-fold increased risk of colorectal cancer (HR 1.26 [95% CI 1.18–1.33]). Among diabetic patients, no association was found with treatment stages. A trend of increased colorectal cancer risk was observed with longer duration of obesity. Risk of colorectal cancer was significantly increased for patients with recorded duration of obesity of 4–8 years (HR 1.19 [1.06–1.34]) and >8 years (1.28 [1.11–1.49]).**

## CONCLUSIONS

**Type 2 diabetes is associated with a moderately increased risk of colorectal cancer. Among diabetic patients, an increased risk was observed for patients who suffered from obesity for a total duration of 4 years or more.**


Colorectal cancer is the third most common cancer in men and the second in women (1). Individuals with type 2 diabetes appear to have an increased risk of developing colorectal cancer compared with their nondiabetic counterparts (2). The global increase in incidence of type 2 diabetes, with an estimated total of 347 million adults suffering from type 2 diabetes in 2008 (3), warrants further examination of the potential link between type 2 diabetes and colorectal cancer.

Observational cohort studies have found that colorectal cancer is more common in people with metabolic disturbances (4,5). Shared risk factors for colorectal cancer

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and type 2 diabetes include obesity, sedentary lifestyle, and high caloric diet. Studies reported a fairly consistent, albeit moderate, increased risk of colorectal cancer associated with both type 2 diabetes (2) and obesity (6). This may, at least in part, be due to a progressive decrease in insulin sensitivity in diabetic patients (7,8), leading to chronic compensatory hyperinsulinemia (8–10). Hyperinsulinemia was shown to have a strong association with increased body weight, in particular abdominal body fat (11). Mechanistically, insulin (both endogenic or exogenic) may promote colorectal carcinogenesis through a cross-talk with the insulin-like growth factor-1 (IGF-1) receptor, which stimulates proliferation and prolongs cell survival (12). A stimulatory effect on cell growth of intestinal epithelial and colon cancer cells was shown in preclinical studies (13,14). In addition, dietary hyperinsulinemia was associated with increased tumor growth in in vivo experiments (15). Moreover, several nested case-control studies have found positive associations between increased blood insulin levels and colorectal cancer incidence (16,17).

If hyperinsulinemia is considered a major causal factor for cancer, hypotheses should focus on insulin resistance status (as the main cause of required hyperinsulinemia) rather than specific medications that increase insulin levels. The type(s) of hypoglycemic agent(s) used could, however, be indicative of overall insulin resistance status, with more intensive treatment indicating higher overall insulin resistance.

Therefore, we first quantified the risk of colorectal cancer associated with type 2 diabetes as compared with a nondiabetic reference population. Second, among type 2 diabetic patients, we evaluated additional associations between colorectal cancer risk and treatment stage and duration of obesity as indicators of chronic hyperinsulinemia.

## RESEARCH DESIGN AND METHODS

### Data Source

Data were obtained from the Clinical Practice Research Datalink (CPRD), which comprises electronic medical records from British general practitioners since 1987 (18). The accuracy and completeness of CPRD data have been well validated in previous studies (19,20). Currently, CPRD includes ~8% of the total U.K. population. The period of valid data collection varies between practices, depending on the date at which they are considered up to standard. In April 2004, the Quality of Outcomes Framework (QOF) was implemented in the U.K., which stimulates payments to general practices based on quality indicators that focus on specific aspects of care (e.g., registration of BMI). The protocol of this study was approved by CPRD's Independent Scientific Advisory Committee.

### Study Design and Population

For this retrospective cohort study, we identified men and women (≥18 years) treated with at least one prescription for a hypoglycemic agent. The date of cohort entry was the date of the first recorded prescription for a hypoglycemic agent during up-to-standard data collection. Subjects aged 30 years or younger with a first recorded prescription for insulin at cohort entry, without a concomitant prescription for a noninsulin antidiabetic drug (NIAD), were considered type 1 diabetic patients and excluded from the cohort. In addition, we excluded all patients with a diagnostic code for type 1 diabetes in CPRD prior to cohort entry (Fig. 1).

At the date of cohort entry, a reference patient without any past recorded prescriptions for hypoglycemic agents was matched to each subject in the diabetic cohort by sex, year of birth, and practice. The comparison cohort was selected using incidence density sampling; if a reference subject received a prescription for a hypoglycemic agent during follow-up, this person was censored as a reference at that time and became a diabetic patient. A patient was excluded from the cohort if no suitable reference subject was found.

All participants were followed from the index date until the outcome of interest, end of data collection (December 2012), date of migration out of the CPRD population, or death, whichever came first. Patients with a history of any type of cancer prior to the index date (except

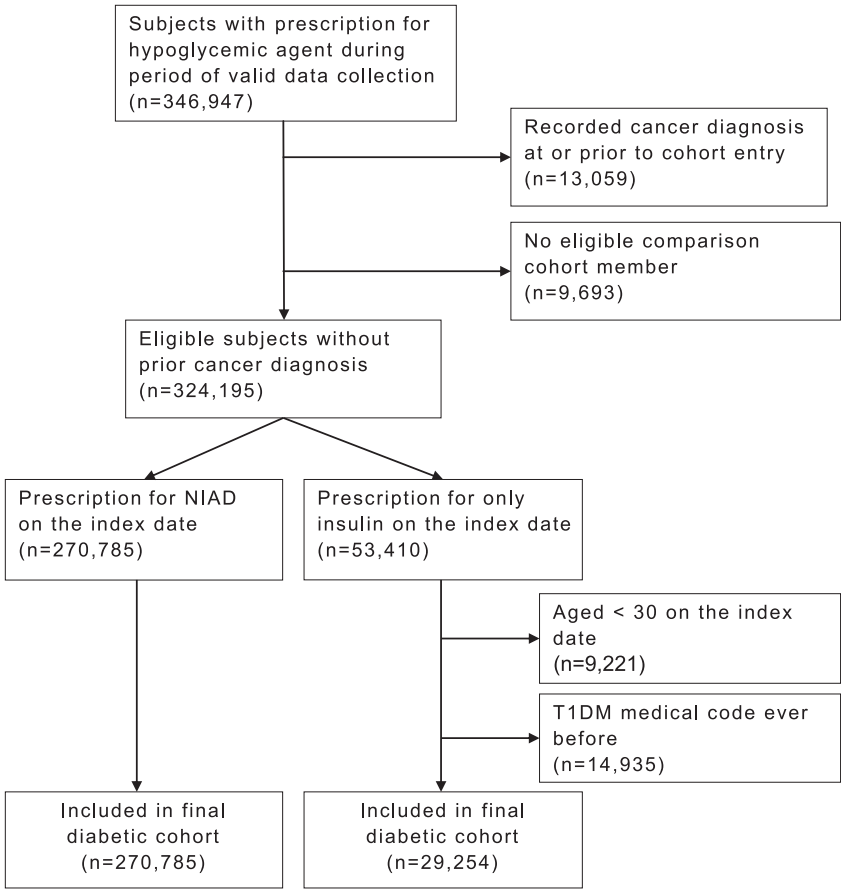


**Figure 1**—Flowchart for patient inclusion and exclusion in the diabetes study cohort. T1DM, type 1 diabetes mellitus.

nonmelanoma skin cancer) were excluded together with their matched counterpart (see Fig. 1).

### Exposure

Individual follow-up for all subjects was divided into fixed time periods of 90 days. In the primary analysis, patients treated with hypoglycemic agents were considered type 2 diabetic patients and retained this status throughout follow-up (time fixed).

Since factors influencing the degree of insulin resistance can change throughout the years, we evaluated two time-varying approaches to estimate the effect of insulin resistance on the colorectal cancer risk among diabetic patients. First, a previously applied proxy indicator for type 2 diabetes severity was adapted (21), using prescribed antidiabetic medication to construct treatment stages. We used recent guidelines to define treatment stages, based on the stepwise approach in diabetes treatment (22). Although guidelines have changed over time, the general medicinal approach has remained fairly consistent (23). We determined current exposure to hypoglycemic agents time dependently at the start of each 90-day interval as a prescription on the start date or in the 90 days before. The following classes of NIADs were defined: biguanides, sulfonylureas, glinides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, $\alpha$-glucosidase inhibitors, GLP-1 agonists, and a separate category for all remaining NIADs. We constructed five mutually exclusive treatment stages: *1*) current use of a single NIAD, *2*) simultaneous use of two or *3*) more than two NIADs from different classes, *4*) current use of NIAD(s) combined with insulin, and *5*) current insulin monotherapy. Treatment intensity (and hence treatment stage) may be reduced as a result of reduced insulin resistance due to, for example, weight loss (24), use of insulin sensitizers (25), or lifestyle intervention (26).

Second, we used BMI as an indicator for insulin resistance, given its strong association with body fat content (11). Obesity (BMI $\geq$30 kg/m$^2$) was then determined from BMI measurement recorded in CPRD. The most recent BMI measurement before the start of follow-up was used to determine obesity at baseline. Individuals without a recorded BMI prior to baseline were categorized as "unknown BMI" at cohort entry. Subsequently, obesity status was updated time dependently during follow-up, using the most recent measurement recorded at the start of each 90-day interval. The cumulative number of years with mapped obesity was then calculated at the start of each interval. A categorical variable was created with mutually exclusive duration categories, where person-time with unknown BMI was included in the reference group (nonobese). We performed a sensitivity analysis to evaluate the influence of the potential difference in quality of data on BMI following the implementation of the QOF in April 2004 (see statistical analyses).

### Study Outcome

Patients were followed up for the occurrence of colorectal cancer, measured as a first medical record in CPRD (see Supplementary Data for a list of the medical codes), stratified by anatomical region (i.e., distal colon, proximal colon, and rectal cancer).

### Potential Confounders

Estimated risks were adjusted for patient characteristics, clinical conditions, or medications known or suggested to be associated with colorectal cancer and thus able to confound the association between type 2 diabetes and colorectal cancer. Potential confounders determined at cohort entry were sex, alcohol consumption, and smoking status (27). Age (as determined by year of birth), the presence of medical conditions (as a medical diagnosis ever before), and current drug use (as a prescription in the past 180 days) were assessed in a time-dependent manner and updated at the start of each 90-day interval. As a significant risk factor for colorectal cancer, inflammatory bowel disease (27) was considered as a potential confounder. Comedication that was tested for confounding included opposed hormone replacement therapy, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, bisphosphonates, and supplementation with folate, calcium, magnesium, and vitamin B6.

### Statistical Analysis

Crude incidence rates were calculated as the number of events per 1,000 person-years of observation. The relative risks (RRs) and 95% CIs of colorectal cancer were estimated by hazard ratios (HRs) using time-dependent Cox proportional hazards models, with survival time in 90-day intervals as the time variable. The primary analyses compared the risk among patients with type 2 diabetes versus the comparison cohort. For the secondary analyses, the study population was restricted to the diabetic cohort. Here, the risk of colorectal cancer associated with the treatment stages and duration of obesity were estimated in two separate models. Both measures are intended to capture the patient's exposure to hyperinsulinemia and were therefore not combined in a single model.

RR estimates were adjusted for all potential confounders that generated a $>$5% change in the $\beta$-coefficient in an age-sex–adjusted model (28). For the primary analysis, BMI was not included in the model, as it was considered part of the exposure of interest. However, we did perform a sensitivity analysis of the primary model where duration of obesity was included. In a sensitivity analysis of the secondary outcomes, all patients on insulin monotherapy (stage 5) at cohort entry were excluded from the diabetic population. For a sensitivity analysis regarding the change in data quality caused by the implementation of QOF on the analysis concerning duration of obesity, the cohort was stratified to subjects with an index date before the introduction of QOF (here the end of follow-up was 31 March 2004) and those with an index date equal to or later than 1 April 2004. Data management and statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC).

## RESULTS

### Patient Characteristics

We followed 300,039 diabetic patients (median age 61 years, 53% male) for a median period of 4.5 years. The majority (80.1%) used a single NIAD at baseline (treatment stage 1), most often being metformin, followed by sulfonylureas. Compared with the matched nondiabetic reference population (median follow-up of 5 years), diabetic patients were more often obese (40.1 vs. 14.8%) and used more statins and NSAIDs (Table 1).

### Risk of Colorectal Cancer

During the study period, 2,759 colorectal cancer events (1,941 colon cancer

**Table 1—Baseline characteristics of type 2 diabetic patients and reference population**

| Characteristic | | Diabetic patients *n* = 300,039 | | Reference cohort *n* = 300,039 | |
|---|---|---|---|---|---|
| Follow-up (years) | Total | 1,668,354 | | 1,798,108 | |
| | Mean (SD) | 5.6 | (4.5) | 6.0 | (4.7) |
| | Median (IQR) | 4.5 | (1.9–8.4) | 5.0 | (2.2–8.9) |
| Sex | Male | 158,309 | (52.8) | 158,309 | (52.8) |
| Age | Median (IQR) | 61 | (50–71) | 61 | (50–71) |
| | 18–39 | 33,197 | (11.0) | 33,197 | (11.0) |
| | 40–59 | 104,977 | (35.0) | 104,977 | (35.0) |
| | 60–79 | 134,940 | (45.0) | 134,940 | (45.0) |
| | 80+ | 26,925 | (9.0) | 26,925 | (9.0) |
| BMI | Median (IQR) | 30.0 | (26.4–34.5) | 25.5 | (23.3–29.1) |
| | Unknown | 57,481 | (19.2) | 77,766 | (25.9) |
| | <20 | 3,866 | (1.3) | 12,577 | (4.2) |
| | 20–24.9 | 36,556 | (12.2) | 80,107 | (26.7) |
| | 25–29.9 | 81,865 | (27.3) | 85,165 | (28.4) |
| | ≥30 | 120,271 | (40.1) | 44,424 | (14.8) |
| Smoking | Never | 151,013 | (50.3) | 154,126 | (51.4) |
| | Current | 64,033 | (21.3) | 65,184 | (21.7) |
| | Ex | 72,802 | (24.3) | 60,551 | (20.2) |
| | Unknown | 12,191 | (4.1) | 20,178 | (6.7) |
| Alcohol use | No | 83,841 | (27.9) | 54,436 | (18.1) |
| | Yes | 184,827 | (61.6) | 200,134 | (66.7) |
| | Unknown | 31,371 | (10.5) | 45,469 | (15.2) |
| History of disease (ever before) | Inflammatory bowel disease | 1,075 | (0.4) | 1,173 | (0.4) |
| Use of hypoglycemic agents | Metformin | 193,531 | (64.5) | — | (0.0) |
| | Sulfonylureas | 95,923 | (32.0) | — | (0.0) |
| | Glinides | 883 | (0.3) | — | (0.0) |
| | Thiazolidinediones | 6,323 | (2.1) | — | (0.0) |
| | GLP-1 agonists | 389 | (0.1) | — | (0.0) |
| | DPP-4 inhibitors | 1,218 | (0.4) | — | (0.0) |
| | α-Glucosidase inhibitors | 1,991 | (0.7) | — | (0.0) |
| | Other NIADs | 98 | (0.0) | — | (0.0) |
| | Insulin | 33,194 | (11.1) | — | (0.0) |
| Treatment stage | Stage 1: NIAD monotherapy | 240,288 | (80.1) | — | (0.0) |
| | Stage 2: combined therapy 2 NIAD classes | 24,144 | (8.0) | — | (0.0) |
| | Stage 3: combined therapy >2 NIAD classes | 2,413 | (0.8) | — | (0.0) |
| | Stage 4: combined therapy NIAD/insulin | 3,940 | (1.3) | — | (0.0) |
| | Stage 5: insulin monotherapy | 29,254 | (9.8) | — | (0.0) |
| Medication use in the past 180 days | Hormone replacement therapy | 37,292 | (12.4) | 31,122 | (10.4) |
| | Vitamin B | 2,909 | (1.0) | 1,391 | (0.5) |
| | NSAIDs | 75,609 | (25.2) | 30,983 | (10.3) |
| | Magnesium | 29 | (0.0) | 13 | (0.0) |
| | Folate | 0 | (0.0) | 0 | (0.0) |
| | Calcium | 4,063 | (1.4) | 2,645 | (0.9) |
| | Bisphosphonates | 4,894 | (1.6) | 5,364 | (1.8) |
| | Aspirin | 1,996 | (0.7) | 3,359 | (1.1) |
| | Statins | 108,015 | (36.0) | 33,918 | (11.3) |

Data are number (%) of patients unless stated otherwise.

events and 819 rectal cancer events; one patient was diagnosed with both cancer types) were observed in the diabetic cohort (crude incidence rate 1.7/1,000 person-years), as compared with 2,359 (1,625 colon cancer events and 737 rectal cancer events; three patients were diagnosed with both cancer types) in the reference population (crude incidence rate 1.3/1,000 person-years). A moderate increased risk of colorectal cancer was found to be associated with type 2 diabetes (adjusted HR 1.26 [95% CI 1.18–1.33]). No relevant differences in risk estimates were observed between the anatomical regions (Table 2). Adjustment for duration of obesity led to a marginal reduction in the risk estimate (1.22 [1.15–1.30]).

Among patients with type 2 diabetes, no clear trend of increasing risk of colorectal cancer was observed with progressing treatment stages. Although the final two stages (combined NIAD/insulin therapy or insulin monotherapy) tended to be associated with a marginal increased risk of colorectal cancer as compared with stage 1 (NIAD monotherapy), none of the risk estimates reached statistical significance (adjusted HR 1.08 [95% CI 0.94–1.26] and 1.07 [0.95–1.20] for stages 4 and 5, respectively) (Table 3).

**Table 2—RR of colorectal cancer associated with type 2 diabetes ($n$ = 300,039) as compared with a reference cohort of patients without type 2 diabetes ($n$ = 300,039), matched by age, sex, and practice**

| | Diabetes, events (IR) | No diabetes, events (IR) | Age-sex–adjusted HR | Fully adjusted HR* |
|---|---|---|---|---|
| Colorectal cancer | 2,759 (1.7/1,000 py) | 2,359 (1.3/1,000 py) | 1.32 (1.25–1.40) | 1.26 (1.18–1.33) |
| Colon cancer† | 1,941 (1.2/1,000 py) | 1,625 (0.9/1,000 py) | 1.36 (1.27–1.45) | 1.26 (1.17–1.35) |
| Proximal | 319 (0.2/1,000 py) | 258 (0.1/1,000 py) | 1.42 (1.21–1.68) | 1.29 (1.08–1.54) |
| Distal | 255 (0.2/1,000 py) | 203 (0.1/1,000 py) | 1.42 (1.18–1.70) | 1.31 (1.07–1.60) |
| Unknown | 1,370 (0.8/1,000 py) | 1,164 (0.6/1,000 py) | 1.34 (1.23–1.44) | 1.25 (1.15–1.36) |
| Rectal cancer‡ | 819 (0.5/1,000 py) | 737 (0.4/1,000 py) | 1.25 (1.13–1.38) | 1.24 (1.12–1.38) |

IR, incidence rate in events/1,000 person-years (py). *Model adjusted for age, sex, statin use in the previous 6 months, smoking, and alcohol consumption. †There were three diabetic patients diagnosed with both distal and proximal colon cancer. ‡There was one diabetic patient and three reference patients diagnosed with both rectal cancer and colon cancer.

With regard to the risk of colorectal cancer associated with the duration of obesity, we observed a more pronounced trend, where the highest exposure categories conveyed the highest risk. An increased risk was observed for diabetic patients being obese for a cumulative duration of 4–8 years (adjusted HR 1.19 [95% CI 1.06–1.34]) and 8 years or more (1.28 [1.11–1.49]), as compared with nonobese diabetic patients (Table 3). The sensitivity analyses, where all patients receiving insulin monotherapy at baseline were excluded, regardless of age, showed similar results for all secondary analyses. In addition, the results from the stratified analyses of the follow-up period before and after the introduction of the QOF were comparable (see Supplementary Data).

## CONCLUSIONS

In this population-based cohort study, type 2 diabetes was associated with a 1.3-fold increased risk of colorectal cancer. This finding concurs with that of a recent meta-analysis, which reported a similar moderately increased risk (RR 1.27 [95% CI 1.21–1.36]) (29), indicating our diabetic cohort is representative of type 2 diabetic patients. Within the diabetic cohort, stratification to treatment stages did not reveal any noticeable trends in colorectal cancer risk. In contrast, cumulative duration of obesity did appear to be associated with increased colorectal cancer incidence. More specifically, an increased risk was observed among diabetic patients that were obese for long periods of time (>4 years) as compared with nonobese patients.

In our primary analyses, we did not adjust for obesity, since we considered it a key causal factor for both type 2 diabetes and colorectal cancer. In this perspective, type 2 diabetes and colorectal cancer coincide but are not causally related to each other. However, type 2 diabetic patients are characterized by increased insulin resistance and are therefore exposed to hyperinsulinemia, which in turn is regarded a key causal factor (12). Obesity is considered a major cause of insulin resistance and is highly associated with a hyperinsulinemic state (11,30). Adjusting for obesity would therefore annul a key characteristic that links type 2 diabetes to increased colorectal cancer risk. In our study, obesity (BMI ≥30 kg/m$^2$) was indeed far more common among diabetic patients than among comparison subjects at baseline (40.1 vs. 14.8%).

With our adaptation of treatment stages (21), we made an effort to develop a tool that, in contrast to simple diabetes duration, accounted for variations in insulin needs but also allowed patients to regress in insulin resistance status (through weight loss [24] or lifestyle intervention [26], for example).

**Table 3—RR of colorectal cancer among patients with type 2 diabetes according to treatment stage (model 1) and duration of obesity (model 2)**

| | Events | Person-years | Crude IR | Age-sex–adjusted HR (95% CI) | Fully adjusted* (95% CI) |
|---|---|---|---|---|---|
| Treatment stages (model 1)†,‡ | | | | | |
| Stage 1: NIAD monotherapy | 1,423 | 850,518 | (1.7/1,000 py) | 1 (reference) | 1 (reference) |
| Stage 2: combined therapy 2 NIAD classes | 645 | 397,811 | (1.6/1,000 py) | 0.95 (0.86–1.04) | 0.94 (0.86–1.03) |
| Stage 3: combined therapy >2 NIAD classes | 136 | 85,192 | (1.6/1,000 py) | 1.03 (0.86–1.23) | 1.01 (0.85–1.21) |
| Stage 4: combined therapy NIAD and insulin | 209 | 122,455 | (1.7/1,000 py) | 1.10 (0.95–1.28) | 1.08 (0.94–1.26) |
| Stage 5: insulin monotherapy | 346 | 212,379 | (1.6/1,000 py) | 1.07 (0.95–1.20) | 1.07 (0.95–1.20) |
| Duration of obesity (model 2)§,‖ | | | | | |
| Nonobese¶ | 1,395 | 772,184 | (1.8/1,000 py) | 1 (reference) | 1 (reference) |
| <1 year | 276 | 197,187 | (1.4/1,000 py) | 1.10 (0.96–1.25) | 1.09 (0.96–1.24) |
| 1–2 years | 192 | 146,809 | (1.3/1,000 py) | 1.05 (0.90–1.23) | 1.03 (0.88–1.20)# |
| 2–4 years | 298 | 212,123 | (1.4/1,000 py) | 1.09 (0.96–1.24) | 1.07 (0.94–1.22)# |
| 4–8 years | 383 | 230,495 | (1.7/1,000 py) | 1.21 (1.08–1.36) | 1.19 (1.06–1.34) |
| ≥8 years | 215 | 109,556 | (2.0/1,000 py) | 1.29 (1.11–1.50) | 1.28 (1.11–1.49) |

IR, incidence rate in events per 1,000 person-years (py). *Model adjusted for age, sex, smoking, alcohol consumption, and statin use in the previous 6 months. †See RESEARCH DESIGN AND METHODS for detailed description. ‡$P$-trend = 0.14, based on the slope of stage as a continuous variable in a fully adjusted model (HR 1.02 [95% CI 0.99–1.05]). §Cumulative duration of exposure to a BMI ≥30 kg/m$^2$. ‖$P$-trend = 0.0008, based on the slope of continuous cumulative duration of obesity in years in a fully adjusted model (HR 1.02 [95% CI 1.01–1.03]). ¶Included patient time with missing data on BMI. #Statistically significant difference ($P < 0.05$) with ≥8 years cumulative duration of obesity.

However, within the diabetic cohort, the risk of colorectal cancer did not appear to be associated with a specific treatment stage. The lack of association with colorectal cancer risk may, in part, be explained by the unknown level of endogenous insulin production. As β-cell functionality decreases over time (31), an intensified treatment does not necessarily entail exposure to a higher overall insulin level, as it can also indicate further deterioration of endogenous insulin production. In addition, if indicative of insulin resistance, present treatment intensity refers to the current insulin resistance status and may not accurately reflect historical exposure to hyperinsulinemia.

In a distinct attempt to stratify by total insulin requirement, we took BMI as a measure of insulin resistance resulting in hyperinsulinemia (11,30). Although previous studies have shown a link between the risk of colorectal cancer and body weight (6), the potential link between duration of obesity and colorectal cancer risk is seldom studied. As ultimately the degree of insulin resistance determines the required overall insulin level, duration of obesity was thought to reflect both level and duration of exposure to hyperinsulinemia. Stratification by cumulative duration of obesity showed that patients who suffered from obesity for an extended period of time (>4 years) had an increased risk of colorectal cancer as compared with patients without a history of obesity. These findings are in line with the observation of a growth-promoting effect of dietary hyperinsulinemia provided by preclinical studies (15). Although insulin resistance is affected by other factors, e.g., by genetic predisposition, age, exercise, physical fitness, and diet (32), and can be significantly reduced without weight loss (26), these factors are likely interrelated in daily practice. Therefore, the trend between duration of obesity and colorectal cancer risk observed here provides an indication that long-term exposure to hyperinsulinemia increases the risk of colorectal cancer in type 2 diabetic patients.

We consider the use of multiple records for BMI during follow-up in a time-dependent manner a major strength of our study. Moreover, the testing of duration of obesity (time dependently), instead of current BMI (or BMI at baseline), is a novel approach that, at least in theory, more accurately describes the total duration of exposure to high insulin dosages. The association found between duration of obesity and colorectal cancer risk is, in our opinion, therefore a valuable contribution to the research conducted in this field. In the diabetic cohort, on average 1.5 measurements per annum (interquartile range [IQR] 1.0–2.2) were recorded in CPRD during follow-up. For only 15.2% of the patients, no BMI measurement was recorded during follow-up. The introduction of the QOF led to an increase in the availability of BMI recordings (from 75.6 to 86.7%), but the average number of measurements per year did not increase drastically; median of 1.4 (IQR 0.8–2.3) to 1.6 (1.1–2.3). Moreover, the introduction of QOF did not have a notable impact on the observed risk estimates associated with duration of obesity. Other strengths include the large cohort, high data quality (20), and the availability of comprehensive patient characteristics.

Several limitations of our study should also be noted. First of all, the rationale for this study relies on the assumption that obesity-driven compensatory hyperinsulinemia, rather than the use of specific hypoglycemic agents, is the key causal factor that links type 2 diabetes to colorectal cancer. However, it should be noted that metformin and (to an extent) thiazolidinediones may, due to their pharmacological effect of increasing insulin sensitivity (25) and hence lowering compensatory hyperinsulinemia, in theory, have a favorable effect on colorectal cancer risk. Observational studies also reported a decreased colorectal cancer risk associated with metformin use (33). Nevertheless, studying these effects in observational studies has some inherent methodological challenges, as associations are bound to be influenced by confounding by indication as a result of the staggered treatment scheme applied in practice. In this study, beforehand we did not distinguish between treatments that increased insulin sensitivity and those that increased overall insulin levels in our definition of treatment stages. However, we performed a post hoc stratified analysis of subjects based on a first prescription for metformin. This analysis yielded an increased risk for both cohorts, as compared with the matched reference cohort, with a slightly lower risk increase for the metformin cohort: HR 1.21 (95% CI 1.12–1.32) and HR 1.30 (95% CI 1.19–1.41), respectively, for the metformin and nonmetformin cohort.

Second, biological mechanisms other than hyperinsulinemia are considered relevant in the link between obesity and cancer (34). Third, we did not validate our study outcome (e.g., through linkage with other databases). However, CPRD morbidity records can be regarded as a valid measure to capture colorectal cancer occurrence (35). Fourth, left truncation of our data hindered our ability to determine past duration of obesity at baseline, as well as time since the initiation of antidiabetic treatment. Given the existence of peripheral insulin resistance in prediabetic patients, this led to a skewed distribution with regard to past exposure to endogenous hyperinsulinemia at baseline. In addition, we were unable to estimate the potential effect of reversed causation (e.g., protopathic bias). Fifth, we included patient time with unknown BMI in the reference category for the analysis concerning duration of obesity. If anything, this may have biased our results toward the null. Sixth, using a single prescription for a hypoglycemic agent as the inclusion criteria for the diabetic cohort may have led to misclassification of patients. For our primary analysis, such misclassification would have biased our results toward the null, whereas in the secondary analyses, the effect would be in the opposite direction. Residual confounding by unmeasured risk factors (e.g., physical activity, red meat and coffee consumption, and high caloric diet) may also have influenced our results, particularly in the primary analysis. Last, detection bias may have affected our results, leading to an overestimation in our primary analysis.

In summary, we observed a moderate, yet (1.3-fold) significantly increased, risk of colorectal cancer in patients treated for type 2 diabetes. Among diabetic patients, an additional 1.2- to 1.3-fold increased risk was observed for patients who suffered from

obesity for a total duration of 4 years or more. This trend between cumulative duration of obesity and the risk of colorectal cancer provides an indication that long-term exposure to high levels of insulin increases the risk of colorectal cancer. Moreover, these findings signal that the risk of colorectal cancer increases the longer a patient with type 2 diabetes remains obese. Future studies could determine whether the increased risk observed here is reversible through weight loss.

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**Author Contributions.** P.J.H.L.P. contributed to the formulation of the study design, researched the data, and wrote the manuscript. M.T.B. and M.L.D.B. contributed to the formulation of the study design, contributed to the interpretation of the results, and reviewed and edited the manuscript. H.G.M.L. and F.d.V. reviewed the manuscript and contributed to the discussion. P.J.H.L.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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