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Research Article

Use of Metformin Is Not Associated with a Decreased Risk of Colorectal Cancer: A Case–Control Analysis

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Abstract

Background: To explore the association between use of metformin or other antidiabetic drugs and the risk of colorectal cancer.

Methods: Using the United Kingdom–based General Practice Research Database (GPRD), we conducted a nested case–control analysis in patients with diabetes mellitus. Cases had an incident diagnosis of colorectal cancer, and up to 6 controls per case were matched on age, sex, calendar time, general practice, and number of years of active history in the GPRD prior to the index date. Results were adjusted for multiple potential confounders.

Results: We identified 920 diabetic patients with colorectal cancer. Mean age ± SD was 70.2 ± 8.6 years and 63.3% were male. Extensive use (≥50 prescriptions) of metformin was associated with a slightly increased risk of colorectal cancer (adjusted OR = 1.43, 95% CI: 1.08–1.90) as compared with non use, with an adjustment of OR = 1.81 (95% CI: 1.25–2.62) in men and of 1.00 (95% CI: 0.63–1.58) in women. Neither extensive use of sulfonylureas (adjusted OR = 0.79, 95% CI: 0.60–1.03) nor insulin (adjusted OR = 0.90, 95% CI: 0.63–1.28) were associated with an increased risk of colorectal cancer. A long-term history of diabetes (>10 years) was not associated with a materially increased risk of colorectal cancer compared with short-term diabetes duration (<2 years; adjusted OR = 1.14, 95% CI: 0.90–1.46).

Conclusion: Use of metformin was linked to an increased risk of colorectal cancer in men. Use of sulfonylureas or insulin was not associated with an altered risk of colorectal cancer.

Impact: Metformin does not prevent colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 21(2); 280–6. ©2011 AACR.*

Introduction

Colorectal cancer is a leading cause of cancer-related morbidity and mortality in the Western world. Obesity, sedentary lifestyle, and Western diet have been associated with an increased risk of colorectal cancer (1, 2) and are also important risk factors for development of type 2 diabetes mellitus, a condition primarily characterized by hyperinsulinemia. Substantial evidence is available linking diabetes mellitus with an increased risk of colorectal cancer. In a large meta-analysis encompassing some 2.5 million people, diabetes mellitus was associated with a relative risk of developing colorectal cancer of 1.30 (95% CI: 1.20–1.40), independent of gender, anatomic site, or study design. However, results stratified by duration of diabetes mellitus and by exposure to various hypoglycemic drugs were not reported in that study (3). In a retrospective cohort study, chronic insulin therapy was associated with an increased risk of colorectal cancer among patients with type 2 diabetes mellitus (4). A history of cholecystectomy has been linked to a marginally increased risk of colon, but not rectal cancer (5), but results from a subsequent large meta-analysis were conflicting (6). Regular use of aspirin and non-steroidal anti-inflammatory drugs (NSAID) has been linked to a decreased risk of colon cancer (7, 8) and rectal cancer (7). In addition, evidence from clinical trials and observational studies support a modest protective effect of statins and estrogen replacement therapy on the risk of colorectal cancer (9, 10).

Metformin, a widely used oral antidiabetic agent, has been shown to exert potentially important anticancer effects (11). The antitumor activity of metformin is thought to be based on mainly 2 different mechanisms. First, metformin decreases insulin resistance and lowers circulating insulin levels by activating AMP-activated protein kinase (AMPK), leading to decreased hepatic gluconeogenesis (12) and increased uptake of glucose in muscle. Second, metformin has been shown to act as a

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tumor growth inhibitor, at least in part, by upregulation of AMPK activity and by downstream suppression of signaling through the mTOR (11).

Metformin use has been linked to a decreased risk of cancer overall (13, 14), of breast cancer (15), and of pancreatic cancer (16), whereas evidence for an altered risk of colorectal cancer remains conflicting; Libby (14) and Currie (13) found a decreased risk of colorectal cancer among users of metformin, whereas Yang (4) did not observe such a risk reduction. Evidence from basic science study and from a small clinical series suggests that metformin inhibits AMPK-dependent development of aberrant colorectal crypt foci (17, 18), inhibits colon carcinoma growth induced by high-fat diet (19), and inhibits colon cancer cell growth *in vitro* (20), as well as intestinal polyp growth in mice (21).

To explore whether use of metformin is associated with an altered risk of colorectal cancer in diabetic patients, we conducted a large case–control analysis using the United Kingdom–based General Practice Research Database (GPRD). We additionally intended to examine the risk of colorectal cancer in relation to duration of diabetes mellitus.

Methods

Data source

Data were derived from the United Kingdom–based GPRD, which was established around 1987 and encompasses data on more than 5 million individuals (22). Patients enrolled in participating practices are representative of the United Kingdom with regard to age, sex, geographic distribution, and annual turnover rate. General practitioners (GP) have been trained to record medical information including demographic data, medical diagnoses, hospitalizations, deaths, and drug prescriptions using standard software and standard coding systems. The GPs generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record. It contains the name of the preparation, instructions for use, route of administration, dose, and number of tablets for each prescription. In addition, the GPRD holds information about lifestyle variables, such as body mass index (BMI), smoking, and alcohol consumption. The recorded information on drug exposure and diagnoses has been repeatedly validated and proven to be of high quality (23, 24). The GPRD has been the source of many observational studies, including research on diabetes and on antidiabetic drugs (25, 26) as well as on cancer (15, 27). The study was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Study population

Using medical READ codes, we first identified all subjects in the GPRD who had an incident diagnosis of colorectal cancer below the age of 90 years between 1995 and 2009. The date of this first recorded diagnosis will be referred to as the "index date." Within this group of patients, we identified those who had a history of diabetes prior to the index date. Patients with less than 3 years of active history in the database prior to the index date, as well as those with a history of any other cancer (except non–melanoma skin cancer), alcoholism, or a human immunodeficiency virus infection prior to the index date were excluded.

From the base population of diabetic subjects, up to 6 controls without any evidence for colorectal cancer were identified at random for each case with colorectal cancer, matched on calendar time (same index date), age (same year of birth), sex, general practice, and number of years of active history in the GPRD prior to the index date. The same exclusion criteria were applied to controls as to cases.

Diabetes duration and exposure to metformin or other hypoglycemic agents. We assessed from the computer records the duration of diabetes prior to the index date. In the main analysis, the index date was shifted by 3 years backwards in time, both for cases and controls, for 2 reasons. First, we intended to minimize detection bias, and second, we intended to minimize potential influence of subclinical cancer on glycemic control and subsequent initiation, intensification, or change of hypoglycemic drug therapy. To study the association between a history of diabetes and the risk of developing colorectal cancer, we carried out 2 analyses with or without index dates shifted by 3 years backwards in time. We thereby intended to stratify cancer risk by diabetes duration and to quantify the short-term effects of diabetes mellitus on diagnosis of colorectal cancer.

We further assessed use of insulin and of the oral hypoglycemic drugs metformin, sulfonylureas, thiazolidinediones, glinides, and glucosidase inhibitors prior to the index date for cases and controls. We defined several exposure levels based on the recorded number of prescriptions for oral antidiabetics prior to the index date as short term (1–9 prescriptions), medium term (10–24 prescriptions), long term (30–49), and extensive ($\geq$50 prescriptions) use. Thiazolidinediones, glucosidase inhibitors, and prandial glucose regulators were not included in the final multivariate model, as exposure to these drugs was low.

Covariates and sensitivity analyses. We explored the association between various potential confounders such as hemoglobin A1C, congestive heart failure, ischemic heart disease, ischemic or hemorrhagic stroke, transient ischemic attack, arterial hypertension, dyslipidemia, and use of estrogens in relation to colorectal cancer in univariate analyses. Because these variables did not alter the relative risk estimates for the association of colorectal cancer and use of metformin by more than 10%, they were not included in the final multivariate analyses. We did adjust for diabetes duration, use of statins, NSAIDs, and aspirin prior to the index date in the final model, as well as smoking (non-smoker, current, past, or unknown)

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and BMI (<25, 25–29.9, >30 kg/m^2, or unknown). We finally adjusted our analyses for mixed drug use, which means that results linking use of a particular antidiabetic drug to an altered risk of colorectal cancer were adjusted for concomitant use of other antidiabetic drugs.

In one sensitivity analysis, we only included cases with colorectal cancer with recorded radio/chemotherapy, colon surgery, or specific oncology codes to assess potential misclassification of cancer cases. In another sensitivity analysis, we explored whether missing values for BMI or smoking status had a material impact on the relative risk estimates. Finally, we stratified the analyses by gender to explore whether effect modification was present.

Statistical analysis

We conducted conditional logistic regression analyses using the SAS statistical software version 9.2 (SAS Institute Inc.) to calculate relative risk estimates as ORs with 95% CIs. We considered a 2-sided P value of <0.05 as statistically significant.

Results

We identified a total of 920 cases with incident colorectal cancer and 5,519 matched controls. Their characteristics are displayed in Table 1. The mean (± SD) age of cases and controls was 70.2 ± 8.6 years at the index date.

Compared with the reference group of diabetic patients who did not take metformin, the adjusted ORs for metformin use of 1–9, 10–29, 30–49, or ≥50 prescriptions prior to the index date were 1.05 (95% CI: 0.83–1.33, 1.05 (95% CI: 0.84–1.33), 1.17 (95% CI: 0.88–1.55), and 1.43 (95% CI: 1.08–1.90), respectively (Table 2). These findings did not materially change when we restricted the analysis to cases who had recorded colorectal surgery, radio-/chemotherapy, or another oncology code (adjusted OR = 1.46, 95% CI: 1.03–2.06) for ≥50 prescriptions. Overall, use of sulfonylureas or insulin was not associated with an altered risk of colorectal cancer (Table 2). As with metformin, the findings were closely similar in the subgroup of cases with colorectal surgery, radio-/chemotherapy, or another oncology code. To assess whether our results were influenced by unknown BMI or unknown smoking status, we ran sensitivity analyses restricted to diabetic subjects with known BMI and known smoking status yielding closely similar findings (results not shown).

We finally analyzed the risk of colorectal cancer in association with use of various hypoglycemic agents in men and women separately (Table 3). This analysis yielded some evidence that extensive use of metformin was associated with an increased risk of colorectal cancer only in men (adjusted OR = 1.81, 95% CI: 1.25–2.62) but not in women (adjusted OR = 1.00, 95% CI: 0.63–1.58).

Colorectal cancer was neither meaningfully associated with cardiovascular disease nor comorbid conditions to diabetes mellitus (Table 1). If we stratified our analyses by diabetes duration, colorectal cancer risk was highest in patients with short-term (<2 years) compared with longer term diabetes mellitus (adjusted OR = 0.82, 95% CI: 0.67–1.01 for >10 years) in the analysis with the original index date. In the analysis with the shifted index date, colorectal cancer risk was closely similar in patients with short compared with longer term diabetes duration (Table 4). Use of NSAIDs (adjusted OR = 0.70, 95% CI: 0.57–0.88 for ≥10 prescriptions) as well as of aspirin (adjusted OR = 0.69, 95% CI: 0.55–0.85 for ≥15 prescriptions) were associated with decreased risks for colorectal cancer. Neither use of estrogens nor statins was associated with an altered risk of colorectal cancer in our study (Table 1).

Discussion

Our results provide evidence that use of metformin is not associated with a decreased risk of colorectal cancer. In our study, there was even a tendency toward an increased risk with prolonged use of metformin. These findings did not materially differ across the predefined sensitivity analyses. Of interest, our results suggest, although based on a limited number of cases and controls, that gender may play a role in the association of colorectal cancer and metformin use, as prolonged use of this drug was associated with an increased risk of colorectal cancer in men, but not in women.

Overall, use of sulfonylureas and insulin were not associated with a materially altered relative risk estimate of colorectal cancer. However, there was a trend toward a decreased risk of colorectal cancer among men, but not women, with ≥50 prescriptions of sulfonylureas. Again, this gender-specific result has to be interpreted with caution because it is based on a small number of cases and controls.

In our study, neither short-term nor long-term duration of diabetes mellitus was associated with an altered risk of colorectal cancer when the index date was shifted by 3 years backwards in time. However, when the index date was not shifted, short-term duration of diabetes mellitus was associated with an increased risk of colorectal cancer compared with longer term diabetes duration. This observation is in line with the results of a recent meta-analysis. In this study, the authors reported a relative risk of 1.30 (95% CI: 1.20–1.40) for colorectal cancer, in association with a diagnosis of diabetes mellitus (3). Of importance, in this study, stratification by antidiabetic drug regimen or by diabetes duration was not reported. Because it is biologically implausible that short-term, but not long-term, duration of diabetes mellitus should be causally associated with an altered risk of colorectal cancer, we intended to minimize potential confounding by detection bias and/or influence of worsening glycemic control due to preclinical cancer by shifting the index date 3 years backwards in time. As expected, by shifting the index date 3 years backwards in time, influence of short-term drug effects on the risk of colorectal cancer was largely eliminated. Our findings are closely similar to the results reported by Yang and colleagues (4) who found an increased risk of colorectal cancer in patients with

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Table 1. Characteristics of diabetic patients with colorectal cancer and their controls

	Cases (%; $n = 920$)	Controls (%; $n = 5{,}520$)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Age (y)				
<40	1 (0.1)	5 (0.1)	—	—
40–49	18 (2.0)	114 (2.1)	—	—
50–59	79 (8.6)	492 (8.9)	—	—
60–69	296 (32.2)	1,742 (31.6)	—	—
70–79	390 (42.4)	2,365 (42.8)	—	—
≥80	136 (14.8)	802 (14.5)	—	—
Sex				
Male	582 (63.3)	3,492 (63.3)	—	—
Female	338 (36.7)	2,028 (36.7)	—	—
Smoking				
Nonsmoker	458 (49.8)	2,621 (47.5)	1.00 (referent)	1.00 (referent)
Current	89 (9.7)	759 (13.8)	0.66 (0.52–0.85)	0.68 (0.53–0.87)
Past	283 (30.8)	1,590 (28.8)	1.02 (0.86–1.21)	1.03 (0.87–1.22)
Unknown	90 (9.8)	550 (10.0)	0.93 (0.72–1.20)	0.90 (0.65–1.23)
BMI				
<25	147 (16.0)	1,071 (19.4)	1.00 (referent)	1.00 (referent)
25–29.9	338 (36.7)	1,936 (35.1)	1.28 (1.04–1.57)	1.27 (1.03–1.57)
≥30	316 (34.4)	1,773 (32.1)	1.32 (1.06–1.63)	1.34 (1.08–1.68)
Unknown	119 (12.9)	740 (13.9)	1.16 (0.89–1.52)	1.15 (0.84–1.58)
Comorbidities				
CHF	74 (8.0)	519 (9.4)	0.84 (0.65–1.09)	0.89 (0.69–1.17)
IHD	239 (26.0)	1,533 (27.8)	0.91 (0.77–1.07)	1.05 (0.88–1.27)
Stroke/TIA	91 (9.9)	650 (11.8)	0.82 (0.65–1.04)	0.91 (0.72–1.16)
Hypertension	545 (59.2)	3,161 (57.3)	1.09 (0.94–1.27)	1.08 (0.93–1.26)
Dyslipidemia	208 (22.6)	1,248 (22.6)	1.00 (0.84–1.20)	1.03 (0.85–1.26)
Acetylsalicylic acid use				
No use	557 (60.5)	3,056 (55.4)	1.00 (referent)	1.00 (referent)
1–14 prescriptions	171 (18.6)	1,021 (18.5)	0.90 (0.74–1.09)	0.89 (0.72–1.09)
≥15 prescriptions	192 (20.9)	1,443 (26.1)	0.69 (0.57–0.84)	0.69 (0.55–0.85)
NSAID use				
No use	407 (44.2)	2,281 (41.3)	1.00 (referent)	1.00 (referent)
1–9 prescriptions	373 (40.5)	2,170 (39.3)	0.95 (0.81–1.11)	0.95 (0.80–1.16)
≥10 prescriptions	140 (15.2)	1,069 (19.4)	0.72 (0.58–0.89)	0.70 (0.57–0.88)
Estrogen use (women only)				
No use	294 (87.0)	1,731 (85.4)	1.00 (referent)	1.00 (referent)
1–14 prescriptions	24 (7.1)	144 (7.1)	0.96 (0.60–1.54)	0.98 (0.61–1.57)
≥15 prescriptions	20 (5.9)	153 (7.5)	0.74 (0.45–1.24)	0.78 (0.47–1.31)
Statin use				
No use	580 (63.0)	3,438 (62.3)	1.00 (referent)	1.00 (referent)
1–9 prescriptions	156 (17.0)	891 (16.1)	1.02 (0.82–1.26)	1.02 (0.81–1.28)
≥10 prescriptions	184 (20.0)	1191 (21.6)	0.89 (0.72–1.10)	0.96 (0.75–1.22)

[a]Adjusted for all other variable in the table (estrogens women only).

CHF = congestive heart failure; IHD = ischemic heart disease; TIA = transient ischemic attack.

short-term and intermediate-term, but not long-term, diabetes mellitus, which does not support a causal role for diabetes mellitus in development of early stage colorectal cancer.

In a large prospective cohort study, Currie and colleagues reported an increased risk of colorectal cancer in patients using sulfonylurea or insulin-based drug regimens compared with metformin monotherapy (13). However, neither results stratified by duration of use nor gender-specific findings were reported. In accordance with Currie and colleagues (13), Libby and colleagues reported a decreased risk of colorectal cancer in users of

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Table 2. Risk of colorectal cancer and antidiabetic drug use in diabetic cases and controls

Drugs and no. prescriptions	Cases (%; $n = 920$)	Controls (%; $n = 5,519$)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Metformin				
No prior use	504 (54.8)	3,165 (57.3)	1.00 (referent)	1.00 (referent)
1–9	111 (12.1)	665 (12.1)	1.06 (0.84–1.32)	1.05 (0.83–1.33)
10–29	126 (13.6)	763 (13.8)	1.05 (0.85–1.30)	1.05 (0.84–1.33)
30–49	79 (8.6)	430 (7.8)	1.17 (0.90–1.52)	1.17 (0.88–1.55)
≥50	100 (10.9)	496 (9.0)	1.29 (1.01–1.65)	1.43 (1.08–1.90)
Sulfonylureas				
No prior use	462 (50.2)	2,783 (50.4)	1.00 (referent)	1.00 (referent)
1–9	94 (10.2)	540 (9.8)	1.05 (0.83–1.34)	1.01 (0.79–1.30)
10–29	143 (15.6)	884 (16.0)	0.98 (0.79–1.20)	0.92 (0.74–1.14)
30–49	104 (11.3)	559 (10.1)	1.12 (0.89–1.42)	1.05 (0.81–1.35)
≥50	117 (12.7)	753 (13.7)	0.93 (0.74–1.17)	0.79 (0.60–1.03)
Insulin				
No prior use	776 (84.3)	4,583 (83.1)	1.00 (referent)	1.00 (referent)
1–9	32 (3.5)	173 (3.1)	1.09 (0.74–1.60)	1.11 (0.75–1.64)
10–29	31 (3.4)	277 (5.0)	0.66 (0.45–0.96)	0.64 (0.44–0.95)
30–49	36 (3.9)	198 (3.6)	1.07 (0.74–1.54)	1.07 (0.73–1.57)
≥50	45 (4.9)	288 (5.2)	0.92 (0.66–1.28)	0.90 (0.63–1.28)

[a]Adjusted for each other, BMI, smoking, diabetes duration, prior use of aspirin, NSAID, and statins.

metformin as compared with individuals not using this drug (14). Of importance, their findings were based on only 40 metformin users and on 76 users of comparator drugs. Again, neither stratification by duration of drug use nor gender effects were reported. Furthermore, analyses were not adjusted for potential confounders such as

Table 3. Risk of colorectal cancer in users of antidiabetic drugs, stratified by gender

	Men		Women	
Drugs and no. prescriptions	Cases/ Controls	Adjusted OR[a] (95% CI)	Cases/ Controls	Adjusted OR[a] (95% CI)
Metformin				
No prior use	312/2,039	1.00 (ref)	192/1,126	1.00 (ref)
1–9	73/420	1.18 (0.88–1.58)	38/245	0.85 (0.57–1.27)
10–29	84/479	1.23 (0.93–1.64)	42/284	0.82 (0.55–1.21)
30–49	51/277	1.29 (0.90–1.84)	28/153	0.98 (0.61–1.57)
≥50	62/277	1.81 (1.25–2.62)	38/220	1.00 (0.63–1.58)
Sulfonylureas				
No prior use	291/1,746	1.00 (ref)	171/1,037	1.00 (ref)
1–9	61/335	1.04 (0.76–1.41)	33/205	1.01 (0.67–1.53)
10–29	95/582	0.89 (0.67–1.16)	48/302	0.98 (0.67–1.42)
30–49	65/351	0.97 (0.70–1.35)	39/208	1.19 (0.78–1.81)
≥50	70/478	0.65 (0.46–0.92)	47/276	1.05 (0.68–1.61)
Insulin				
No prior use	498/2,927	1.00 (ref)	278/1657	1.00 (ref)
1–9	19/100	1.15 (0.69–1.91)	13/73	1.08 (0.58–2.00)
10–29	21/170	0.71 (0.44–1.14)	10/107	0.55 (0.28–1.08)
30–49	21/117	1.10 (0.67–1.81)	15/81	1.11 (0.61–2.02)
≥50	23/178	0.72 (0.44–1.17)	22/110	1.17 (0.69–2.00)

[a]Adjusted for each other, diabetes duration, BMI, smoking, prior use of aspirin, NSAID, and statins (women: additionally adjusted for estrogen use).

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Table 4. Duration of diabetes mellitus and risk of colorectal cancer

	Main analysis (shifted index date 3 years backwards in time)		Analysis with original index date (no shift)	
Diabetes duration (y)	Cases/ Controls	Adjusted OR[a] (95% CI)	Cases/ Controls	Adjusted OR[a] (95% CI)
<2	178/1,118	1.00 (ref)	267/1,502	1.00 (ref.)
2–5	209/1,288	1.04 (0.83–1.30)	323/1,967	0.90 (0.75–1.08)
5–10	235/1,354	1.11 (0.88–1.40)	354/2,161	0.85 (0.70–1.02)
>10	298/1,760	1.14 (0.90–1.46)	450/2,729	0.82 (0.67–1.01)

[a]Adjusted for BMI, smoking, prior use of metformin, sulfonylureas, insulin, aspirin, NSAID, and statins.

use of aspirin, NSAIDs, or statins. In addition, various risk estimates for users of metformin and their comparators were already noted within the first months of observation and were attenuated with prolonged observation periods. These findings strongly argue against a causal role of metformin for prevention of a chronic disease which takes years to develop. In contrast to the findings of Currie (13) and Libby (14) and colleagues, and in line with our results, Yang and colleagues did not find a decreased risk of colorectal cancer in association with use of metformin (4).

Use of NSAIDs and aspirin were associated with a decreased risk of colorectal cancer, an observation which is consistent with a recent large prospective cohort study (7) and a meta-analysis (6). In our study, statin use was not associated with a reduced risk of colorectal cancer, a finding which is also in line with a recent study (28). However, results from individual trials remain conflicting, and a recent meta-analysis suggested a modest protective effect for statins (10).

Several limitations of this study should be addressed. We may have missed some colorectal cancer cases due to underdiagnosing. However, the GPRD has been used numerous times for studies on various cancers (4, 15, 27), and previous validation studies provided convincing evidence that diagnoses are recorded with high validity (23, 29). Because pathology data are not routinely available in the GPRD, misclassification of colorectal cancer cases might have occurred. However, when we ran a sensitivity analysis restricted to cancer cases with recorded surgery, radiotherapy, chemotherapy, or other evidence for oncologic interventions in specialized oncology clinics, the results were closely similar to the main finding.

It is possible that preclinical colorectal cancer might have influenced glycemic control and thereby affected use of hypoglycemic agents in the cases. To reduce the risk of such a bias, we shifted the index date by 3 years backwards in time for cases and controls. We were not in a position to adjust for various risk factors for colorectal cancer which are not routinely recorded in the GPRD, such as diet, physical activity, genetic predisposition, or a positive familial history. Except for diet, however, these risk factors are unlikely to confound the association between metformin and colorectal cancer, as they are most likely not associated with metformin use. For a certain number of cases and controls, information on smoking status and BMI was lacking. However, sensitivity analyses restricted to diabetic subjects with known BMI and known smoking status yielded closely similar results. We did adjust our analyses for diabetes duration and for concomitant antidiabetic drug use, and we assessed the role of hemoglobin A1C and comorbidities associated with diabetes, but we cannot completely rule out some residual confounding by diabetes mellitus severity and/or glycemic control. Finally, we could not assess the risk of colorectal cancer in association with use of hypoglycemic agents across different ethnicities, as this information was not routinely available in the GPRD. However, our results are most likely representative of Caucasians as 92% of individuals living in the United Kingdom are white (27).

Our population-based study has several strengths. First, we were in a position to study a large number of colorectal cancer cases in a longitudinal, well-established, and validated primary care database. Due to the recording of individual prescriptions by the GPs, we were able to stratify use of antidiabetic drugs by duration of use. Because information on diseases and drug exposure was routinely entered in the GPRD in the absence of any study hypothesis, recall bias is not an issue of concern. We further controlled for a range of potential confounders such as BMI, smoking status, comorbidities, and drug therapies, most importantly use of NSAIDs, aspirin, and statins. By shifting the index date 3 years backwards in time, we minimized the influence of cancer-associated metabolic changes and subsequent modifications of the antidiabetic therapy. Lastly, by excluding all patients with less than 3 years of recorded history in the database prior to the index date, we reduced the risk of including prevalent rather than incident cancer cases.

In conclusion, this large observational study provides evidence that use of metformin is not associated with a decreased risk of colorectal cancer; there was even a tendency toward an increased risk of colorectal cancer in men, but not in women. Use of insulin or sulfonylureas was not associated with a materially altered risk of colorectal cancer.

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Disclosure of Potential Conflicts of Interest

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