Research Article

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The Use of Metformin and Colorectal Cancer Incidence in Patients with Type II Diabetes Mellitus

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Abstract

Background: Experimental studies have suggested that metformin may decrease the incidence of colorectal cancer in patients with type II diabetes. However, previous observational studies have reported contradictory results, which are likely due to important methodologic limitations. Thus, the objective of this study was to assess whether the use of metformin is associated with the incidence of colorectal cancer in patients with type II diabetes.

Methods: A cohort study of patients newly treated with non-insulin antidiabetic agents was assembled using the United Kingdom Clinical Practice Research Datalink. A nested case–control analysis was conducted, where all incident cases of colorectal cancer occurring during follow-up were identified and randomly matched with up to 10 controls. Conditional logistic regression was used to estimate adjusted rate ratios (RR) of colorectal cancer associated with ever use, and cumulative duration of use of metformin. All models accounted for latency and were adjusted for relevant potential confounding factors.

Results: Overall, ever use of metformin was not associated with the incidence of colorectal cancer [RR: 0.93; 95% confidence interval (CI), 0.73–1.18]. Similarly, no dose–response relationship was observed in terms of cumulative duration of use.

Conclusions: The use of metformin was not associated with the incidence of colorectal cancer in patients with type II diabetes.

Impact: The results of this study do not support the launch of metformin randomized controlled trials for the chemoprevention of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 22(10); 1877–83. ©2013 AACR.*

Introduction

Metformin is an insulin sensitizer that has been shown to decrease plasma insulin, reduce insulin resistance, and lower levels of circulating glucose in patients with type II diabetes (1–3). In addition, this first-line treatment has been shown to slow the growth and proliferation of colorectal cancer cells in several *in vitro* and animal studies (4). However, observational studies investigating the association between metformin and colorectal cancer incidence or survival have reported conflicting findings, with some reporting decreased risks (5–8), others null results (9–11), and one study reporting a dose-dependent increased risk (12). Despite these discrepant results, randomized controlled trials are now being conducted in patients with colorectal cancer (13–16).

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The aforementioned observational studies (5–12) had a number of important methodologic limitations. These include time-related biases such as immortal time bias, selection bias, and confounding. Thus, additional carefully designed population-based studies are needed to evaluate the association between the use of metformin and colorectal cancer incidence. Using a robust pharmacoepidemiologic approach, this population-based study is specifically designed to avoid the methodologic shortcomings of the previous observational studies. Thus, the objective of this study was to determine whether the use of metformin is associated with the incidence of colorectal cancer in patients with type II diabetes.

Materials and Methods

Data source

This study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database. The CPRD is the world's largest computerized database of longitudinal records from primary care, and is the representative of the UK general population, with comparable age and sex distributions as those reported by the UK National Population Census (17). The CPRD contains the primary longitudinal records

of more than 12 million patients across the UK, and all data collected in the CPRD have been subjected to validation studies and found to be consistent and of high quality (18).

This study was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

Study cohort

We assembled a cohort of all patients, at least 40 years of age, who had received at least one antidiabetic prescription between January 1, 1988 and December 31, 2009. Cohort entry was defined by the date of a first-ever prescription for a non-insulin antidiabetic agent [biguanides, sulfonylureas, thiazolidinediones, megalitinides, glucosidases, dipeptidyl peptidase-4 (DPP-4) inhibitors, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) analogs, and guar gum] during the study period, with a minimum of at least one year of medical history in the CPRD before that first prescription. Restricting the cohort to patients with treated type II diabetes was to minimize confounding by indication because this condition has been independently associated with an increased risk of colorectal cancer (19). We excluded patient for whom insulin was their first antidiabetic treatment, to ensure that patients with type I diabetes or with advanced type II diabetes were not included in the cohort. However, patients who eventually required insulin after cohort entry were retained in the cohort. Finally, patients diagnosed with colorectal cancer at any time before cohort entry were excluded. Patients included in the cohort were from 'up-to-standard' general practices and met CPRD research quality standards. All patients were followed until a first-ever diagnosis of colorectal cancer, death from any cause, end of registration with a general practice, or end of the study period (December 31, 2009), whichever came first.

Selection of cases and controls

A nested case–control analysis was conducted within the cohort defined above. We used Read diagnostic codes to identify all incident cases of colorectal cancer occurring during follow-up. The date of each case's colorectal cancer diagnosis was defined as their index date. For all analyses, only patients with at least one year of follow-up were retained to consider a minimum latency period. Up to 10 controls were randomly selected from the risk set and matched to each case on age (year of birth), sex, calendar year of cohort entry, and duration of follow-up (i.e., time since the first prescription of non-insulin antidiabetic agent). Controls were assigned the same index date as the cases, ensuring that both cases and matched controls had equal duration of treated diabetes before index date. To avoid excluding cases, the matching criteria was relaxed for two colorectal cancer cases to year of cohort entry ± 1 year.

Exposure to metformin

We obtained information on all antidiabetic agents prescribed between cohort entry and index date for cases and matched controls. Exposures initiated in the year immediately before index date were excluded to account for a latency time window and minimize reverse causality. The primary exposure definition consisted of ever use of metformin, defined as receiving at least one prescription between cohort entry and the year before index date.

Among patients deemed to be ever users of metformin, we also considered whether there was a duration–response relationship between the use of metformin and colorectal cancer incidence. For this analysis, cumulative duration of use was calculated by summing the prescribed duration associated with each metformin prescription received between cohort entry and index date. This secondary exposure variable was categorized into quartiles based on the distribution of use on the controls. We also considered other dose–response variables, such as the number of metformin prescriptions received and cumulative dose. The analysis of these variables yielded nearly identical results as those with cumulative duration of use due to the high correlation between these variables and the latter variable (84% and 92%, respectively; data not shown).

Potential confounders

All risk estimates were adjusted for potential confounders known to be associated with colorectal cancer and that may have influenced the choice of an antidiabetic therapy. These potential confounders were measured at any time from at least one year before cohort entry up to one year before index date (to account for latency, as with the exposure variable). The potential confounders consisted of obesity [body mass index (BMI) $\geq$ 30 kg/m^2, most recent value before the year prior to index date], excessive alcohol use, smoking status (ever, never, or unknown), cholecystectomy, inflammatory bowel disease (Crohn disease and ulcerative colitis), history of polyps, previous cancer (other than nonmelanoma skin cancer), and ever use of statins, aspirin, other nonsteroidal anti-inflammatory drugs. The models were also adjusted for the ever use of other antidiabetic agents, included individually in the models [sulfonylureas, thiazolidinediones, insulins, and others (megalitinides, glucosidases, DPP-4 inhibitors, α-glucosidase inhibitors, GLP-1 analogs, or guar gum)]. In an effort to control for the potential differential surveillance bias between the different antidiabetic exposures, the models were further adjusted for referrals to colonoscopy and sigmoidoscopy. Finally, to control for diabetes severity, we adjusted the models for diabetes duration before cohort entry [defined as the time between either the first elevated glycated hemoglobin (HbA_{1c}) level (>7.0%) or a diagnosis of type II diabetes, and cohort entry], and HbA_{1c} (most recent value before the year prior to index date).

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cases and matched controls. The overall colorectal cancer incidence rate and corresponding 95% confidence intervals (CI) based on the Poisson distribution were calculated by dividing the total number of incident cases by the total number of person-years of follow-up. Conditional logistic regression was used to estimate ORs along with corresponding 95% CIs of colorectal cancer associated with the use of metformin, which in the context of the risk set sampling used in this nested case–control analysis are unbiased estimators of rate ratios (RR).

We also conducted a secondary analysis to determine whether there was a duration–response relationship between the use of metformin and colorectal cancer in terms of cumulative duration of use. Linear trend was evaluated by entering this dose–response variable as continuous variables in the models. For all of the analyses above, the models were conditioned on four matching factors (age, sex, calendar year of cohort entry, and duration of follow-up) and were adjusted for the potential confounders listed above.

Sensitivity analyses

We conducted three sensitivity analyses to assess the robustness of our findings. Initially, we had restricted all of our analyses to cases and matched controls with at least one year of follow-up, and excluded antidiabetic medications initiated during the year before the index date to consider a latency time window. Thus, the first sensitivity analysis consisted of repeating the analyses by varying the latency time windows to 6 months and 2 years. In the second sensitivity analysis, we assessed the impact of adjusting for variables potentially on the casual pathway between metformin use and diagnosis of colorectal cancer. Thus, in this sensitivity analysis, we adjusted for all potential confounders measured at cohort entry (i.e., before initiation of any of non-insulin antidiabetic agent). Finally, in the third sensitivity analysis, we repeated the primary analysis by restricting to the cases and controls that had received at least two prescriptions of any antidiabetic agent in the first 3 months of follow-up, thus maximizing the inclusion of patients with a true diagnosis of type II diabetes. All analyses were conducted with conducted with SAS version 9.2 (SAS Institute).

Results

A total of 115,578 patients newly treated with non-insulin antidiabetic agents met the study inclusion criteria (Fig. 1). Of those, 67.4% received metformin in monotherapy, 29.7% received sulfonylureas in monotherapy, whereas the remaining 2.9% received other antidiabetic agents or combinations.

There were 760 incident cases of colorectal cancer during a mean (SD) duration of follow-up of 4.5 (3.6) years, generating an overall incident rate of 140 cases per 100,000 persons per year (95% CI, 130–160). The analyses were restricted to the 607 cases and 5,837 matched controls with at least one year of follow-up necessary for latency considerations. The characteristics of these cases and matched controls are presented in Table 1. As expected, compared with controls, cases were more likely to have had a history of polyps and cholecystectomy, but were less likely to have used statins (Table 1).

Table 2 presents the results of the primary and secondary analyses. In the primary analysis, after adjusting for the potential confounders, ever use of metformin was not associated with a decreased risk of colorectal cancer (RR: 0.93; 95% CI, 0.73–1.18). In the secondary analysis, no duration–response relationship was observed in terms of cumulative duration of use ($P_{\text{trend}} = 0.69$).

Sensitivity analyses

In the first sensitivity analysis, varying the latency time window to 6 months and 2 years yielded results consistent with those of the primary analysis (RR: 1.08; 95% CI, 0.85–1.36 and RR: 1.02; 95% CI, 0.80–1.29, respectively). In the second sensitivity analysis, adjustment for potential confounders at baseline did not materially change the point estimates (RR: 0.94; 95% CI, 0.74–1.20). Finally, restricting to the 563 cases and 5,283 controls that had received at least two prescriptions within the first 3 months of follow-up yielded consistent results (RR: 0.92; 95% CI, 0.72–1.19).

Discussion

In this large population-based study, the use of metformin was not associated with the incidence of colorectal cancer in patients with type II diabetes. Furthermore, no dose–response relationship was observed in terms of cumulative duration of use. These results remained consistent after conducting several sensitivity analyses, which included varying the length of latency time window and adjustment for potential confounders at cohort entry.

The results of this study contrast with those of some of the previous observational studies (5–8, 12). In a recent meta-analysis that included several of these studies, the use of metformin was associated with an overall 37% decreased risk of colorectal cancer (RR: 0.63; 95% CI, 0.47–0.84; 20). However, many of these studies had important time-related biases, such as immortal time bias, which have been described in detail elsewhere (21). Briefly, immortal time bias was introduced by using time-fixed analyses that misclassified the time between cohort entry and the date of a first metformin prescription during follow-up as exposed person-time (22). Furthermore, that misclassified person-time is immortal because patients had to survive from cohort entry to the first metformin prescription to be considered exposed. Thus, all patients who experienced the outcome before the first metformin prescription during follow-up were necessarily included in the unexposed group. This bias is likely to have greatly exaggerated the potential benefits of metformin on colorectal cancer incidence (6–8, 10). Perhaps our results contrast the most with those of another CPRD study that has investigated the same question (12). On the basis of a

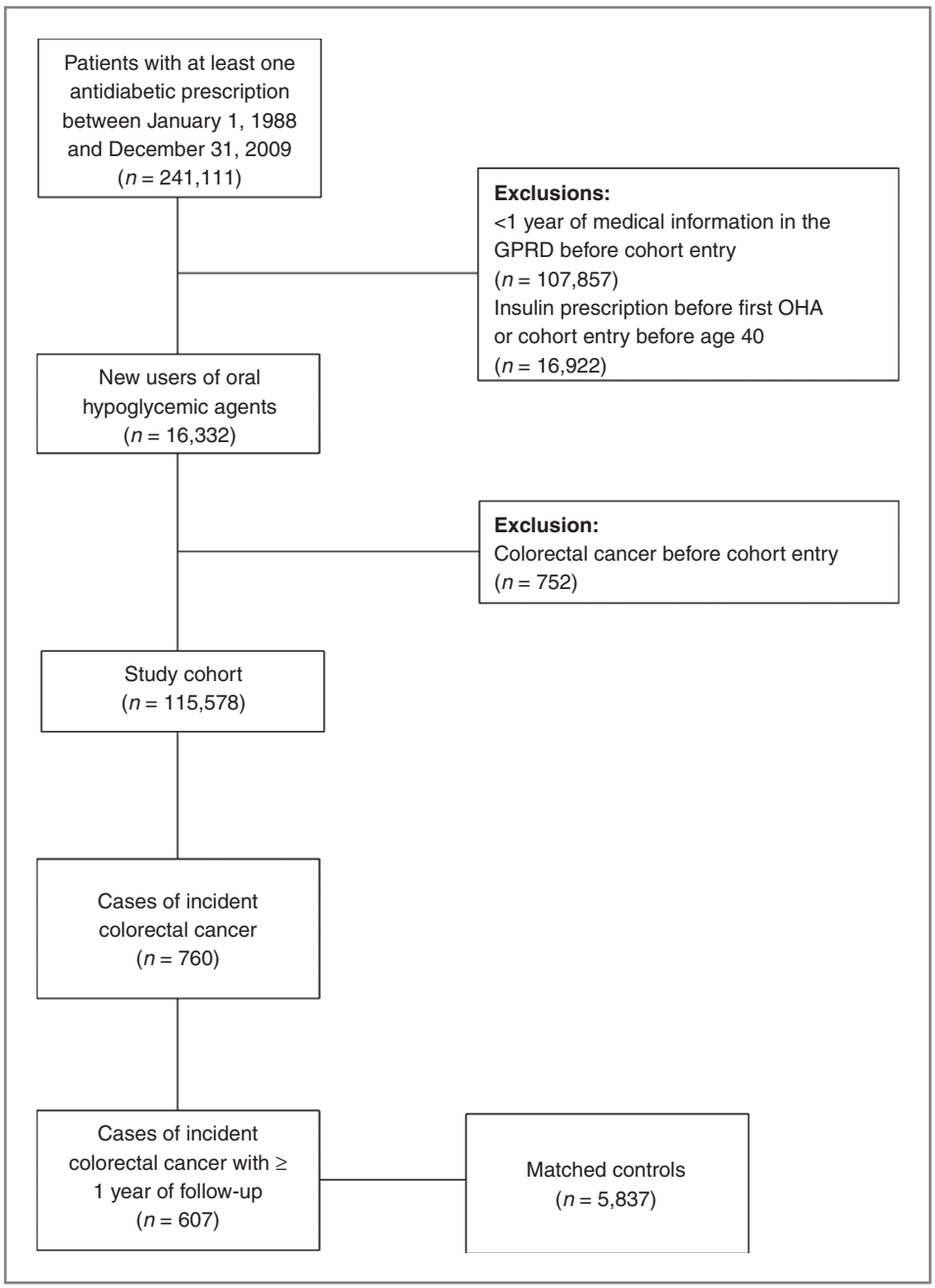

Figure 1. Flowchart of study subjects.

nested case–control analysis of 920 cases and 5,519 controls, the authors found that receiving more than 50 metformin prescriptions was associated with a 43% increased risk (OR: 1.43; 95% CI, 1.08–1.90) of colorectal cancer (12). Although immortal time bias was not a methodologic issue in that study, cases and controls were not matched on duration of treated diabetes, which may have introduced time-window bias (21), a situation where the exposure opportunity is differential between cases and controls. In this case, it is possible that cases had a longer exposure time window than the randomly selected controls, and thus a greater opportunity to receive additional metformin. Such imbalance in exposure opportunity can generate spurious findings, and in this case, an increased risk of colorectal cancer with longer use of metformin. Other studies had other biases, such as time-lag bias introduced by comparing second- and third-line treatments, such as sulfonylureas and insulin, to a first-line treatment, such as metformin (5), and flawed cohort definitions (9).

Overall, this study does not support the biologic hypothesis that metformin may reduce the risk of colorectal cancer. Although experimental research has suggested that metformin may have antineoplastic activity

Table 1. Characteristics of the colorectal cancer cases and matched controls

	Cases	Controls
Number of subjects	607	5,837
Males (%)	384 (63.3)	3,712 (63.6)
Age at index date (y), mean (SD)[a]	72.8 (8.7)	72.5 (8.5)
Duration of follow-up (y), mean (SD)[a]	4.8 (3.1)	4.8 (2.9)
Diabetes duration (y), mean (SD)[b]	2.0 (3.4)	2.1 (3.9)
HbA1c (%), median, *n* (%)	7.3	7.1
<6.5	99 (16.3)	1,067 (18.3)
6.5–7.4	185 (30.5)	1,860 (31.9)
7.5–8.9	144 (23.7)	1,224 (21.0)
≥9	64 (10.5)	545 (9.3)
Unknown	115 (19.0)	1,141 (19.6)
BMI (kg/m^2), *n* (%)		
<18.5	2 (0.3)	30 (0.5)
18.5–25	121 (19.9)	1,082 (18.5)
25–30	235 (38.7)	2,339 (40.1)
≥30	232 (38.2)	2,278 (39.0)
Unknown	17 (2.8)	108 (1.9)
Smoking status, *n* (%)		
Never	235 (38.7)	2,243 (38.4)
Ever	356 (58.7)	3,447 (59.0)
Unknown	16 (2.6)	147 (2.5)
Excessive alcohol use, *n* (%)	74 (12.2)	623 (10.7)
Referrals to colonoscopy, *n* (%)	24 (4.0)	204 (3.5)
Referrals to sigmoidoscopy, *n* (%)	7 (1.2)	75 (1.3)
History of polyps, *n* (%)	18 (3.0)	105 (1.8)
Inflammatory bowel disease, *n* (%)	8 (1.3)	90 (1.5)
Cholecystectomy, *n* (%)	39 (6.4)	317 (5.4)
Ever use of nonsteroidal anti-inflammatory drugs, *n* (%)	358 (58.8)	3,424 (58.7)
Ever use of aspirin, *n* (%)	347 (57.2)	3,412 (58.5)
Ever use of statins, *n* (%)	357 (58.8)	3,643 (62.4)

[a]Controls matched to cases on these variables along with year of cohort entry.
[b]Diabetes duration before cohort entry.

making it a safe and promising chemopreventive agent for colorectal cancer (2, 23), it is unclear whether such results can be extrapolated at the populational level. Specifically, experimental research may have used less complicated cancer models, along with higher exposure levels than the conventional doses used in the treatment of diabetes. Furthermore, many of the complex mechanisms and comorbidities that exist in patients with type II diabetes, such as circulating insulin and glucose levels, changes in disease severity, use of different drugs, obesity, and lifestyle choices are not captured in simple, experimental cell or animal models, therefore producing results that are not necessarily generalizable or relevant to human patients.

This study has a number of strengths and some limitations. First, we assembled a large cohort of patients newly treated with non-insulin antidiabetic agents, thus avoiding biases related to prevalent user designs (24). Second, the CPRD collects information on a number of variables known to be associated with colorectal cancer, including history of polyps, cholecystectomies, smoking, drug exposures, and excess alcohol use. However, the CPRD lacks information on certain potential confounders, such as race, level of physical activity, family history, diet, and information on past biopsies, scans, and other hospital procedures. Although these missing variables can introduce residual confounding, it is unclear how they would influence physicians to prescribe one antidiabetic over another. Therefore, it is reasonable to assume that these variables would be nondifferentially distributed between the exposure groups. Third, there was no recall bias because data are prospectively collected in the CPRD, although prescriptions represent those written by general practitioners and thus it is unknown whether patients complied with the treatment. In the present study, we observed no association in patients who received high numbers of metformin prescriptions, indicating that misclassification of exposure by noncompliance is unlikely to explain the null results.

Table 2. Crude and adjusted rate ratios of colorectal cancer associated with the use of metformin

Exposure to metformin	Cases ($n = 607$)	Controls ($n = 5,837$)	Crude RR	Adjusted RR (95% CI)[a]
Never use, *n* (%)	163 (26.9)	1,431 (24.5)	1.00	1.00 (reference)
Ever use, *n* (%)	444 (73.2)	4,406 (75.5)	0.90	0.94 (0.74–1.19)
Cumulative duration of use (d), n (%)[b]				
<449	132 (21.8)	1,100 (18.9)	1.12	1.13 (0.85–1.49)
449–845	98 (16.1)	1,099 (18.8)	0.79	0.82 (0.60–1.12)
845–1447	98 (16.1)	1,105 (18.9)	0.77	0.80 (0.58–1.10)
				$P_{trend} = 0.69$

[a]Adjusted for: obesity, smoking, statins, nonsteroidal anti-inflammatory drugs, aspirin, excessive alcohol use, HbA1c, diabetes duration, cholecystectomy, inflammatory bowel diseases, referrals to colonoscopy, referrals to sigmoidoscopy, history of polyps, previous cancer (other than nonmelanoma skin cancer), and use of sulfonylureas, thiazolidinediones, insulins, and other antidiabetic agents.

[b]Quartiles based on the distribution of use in the controls.

In summary, this study provides no evidence that the use of metformin is associated with a decreased risk of colorectal cancer in patients with type II diabetes. The results remained consistent after conducting several dose–response and sensitivity analyses. These null results come at time when randomized controlled trials are being planned and conducted in patients with colorectal cancer (13–16). This raises important questions as to whether such efforts are truly substantiated by the available pharmacoepidemiologic evidence. As such, additional observational studies using different designs and populations specifically avoiding time-related biases are needed to confirm our findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B. Smiechowski, L. Azoulay, M.N. Pollak, S. Suissa

Development of methodology: B. Smiechowski, L. Azoulay, S. Suissa

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Suissa

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B. Smiechowski, L. Azoulay, M.N. Pollak, S. Suissa

Writing, review, and/or revision of the manuscript: B. Smiechowski, L. Azoulay, M.N. Pollak, S. Suissa

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Smiechowski, H. Yin

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