Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Cohort Study of Metformin and Colorectal Cancer Risk among Patients with Diabetes Mellitus

Marie C. Bradley[1], Assiamira Ferrara[2], Ninah Achacoso[2], Samantha F. Ehrlich[2], Charles P. Quesenberry Jr[2], and Laurel A. Habel[2]

Abstract

Background: Several epidemiologic studies have reported strong inverse associations between metformin use and risk of colorectal cancer, although time-related biases, such as immortal time bias, may in part explain these findings. We reexamined this association using methods to minimize these biases.

Methods: A cohort study was conducted among 47,351 members of Kaiser Permanente Northern California with diabetes and no history of cancer or metformin use. Follow-up for incident colorectal cancer occurred from January 1, 1997, until June 30, 2012. Cox regression was used to calculate HRs and 95% confidence intervals (CIs) for colorectal cancer risk associated with metformin use (ever use, total duration, recency of use, and cumulative dose).

Results: No association was observed between ever use of metformin and colorectal cancer risk (HR, 0.90; 95% CI, 0.76–1.07) and there was no consistent pattern of decreasing risk with increasing total duration, dose, or recency of use. However, long-term use (≥5.0 years) appeared to be associated with reduced risk of colorectal cancer in the full population (HR, 0.78; 95% CI, 0.60–1.02), among current users (HR, 0.78; 95% CI, 0.59–1.04), and in men (HR, 0.65; 95% CI, 0.45–0.94) but not in women. Higher cumulative doses of metformin were associated with reduced risk. In initial users of sulfonylureas, switching to or adding metformin was also associated with decreased colorectal cancer risk.

Conclusions: Our findings showed an inverse association between long-term use of metformin and colorectal cancer risk. Findings, especially the risk reduction among men, need to be confirmed in large, well-conducted studies.

Impact: If our findings are confirmed, metformin may have a role in the chemoprevention of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 27(5); 525–30. ©2018 AACR.*

See related commentary by Jackson and García-Albéniz, p. 520

Introduction

Metformin is the most common first-line treatment for type II diabetes mellitus (T2DM) and may be used in combination with other antidiabetic drugs. It improves blood glucose control and increases insulin sensitivity by reducing hepatic glucose production and intestinal glucose absorption as well as stimulating peripheral glucose uptake (1, 2).

Several *in vitro* and animal studies have demonstrated that metformin slows the growth and proliferation of colorectal cancer cells, via activation of AMP-activated protein kinase (AMPK; ref. 3). However, findings from several epidemiologic studies, using either case–control or cohort designs, investigating the association between metformin use and colorectal cancer risk have been inconsistent; with some reporting a decreased risk (4–10), some no association (11–15), and some an increased risk of colorectal cancer (16, 17).

Time-related biases have been proposed to account for some of the inverse associations observed between metformin use and cancer risk reported in epidemiologic studies (18, 19). These include immortal time bias when unexposed time is misclassified as exposed in cohort studies, time-window bias when the time window for capturing exposure differs between cases and controls in case/control studies, or time-lag bias when treatment differs across stages of the disease being treated and disease stage is also associated with risk of the outcome.

Our objective was to examine the association of colorectal cancer risk with several measures of metformin exposure, including duration and recency. To reduce methodologic biases encountered in previous studies, we evaluated the incidence of colorectal cancer in new users of metformin, accounting for time varying exposure to metformin and other diabetes medications and adjusting for diabetes duration, history of lower endoscopy, and other potential confounding factors.

Materials and Methods

Setting

A retrospective cohort study was conducted in Kaiser Permanente Northern California (KPNC). KPNC is a large nonprofit integrated health care delivery system, with an enrolled membership that is generally representative of the insured population in Northern California, except for extremes of the socioeconomic spectrum (20). KPNC owns and operates its hospitals and clinics, employs its own physicians, manages its own pharmacies, and archives data generated from clinical encounters in the form of electronic health records.

Study cohort

The cohort included 60,520 members of the KPNC Diabetes Registry who completed a health survey between 1994 and 1996

[1]Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland. [2]Division of Research, Kaiser Permanente Northern California, Oakland, California.

Corresponding Author: Laurel A. Habel, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3715; Fax: 510-891-3898; E-mail: laurel.habel@kp.org

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and were 40 years of age or older at baseline (July 1, 1997) and had no prior history of cancer. The KPNC Diabetes Registry was established in 1993 to capture information on all health plan members with diabetes from automated clinical databases on an annual basis, who meet at least one of the following criteria: A primary hospital discharge diagnosis of diabetes; at least two outpatient visit diagnoses of diabetes; at least one prescription of a diabetes-related medication; and any laboratory record of an abnormal hemoglobin A1c (HbA1c) test. Those without continuous KPNC enrollment for at least two years before baseline (3,355), those less than 40 years old (3,416), and previous metformin users (6,398), were excluded. Continuous enrollment of two years or more allowed adequate assessment of medical history (prescriptions and comorbidities), identification of new users of metformin, and incident cancers. Institutional review board approval was obtained for the study. Written informed consent was waived.

Exposure of interest

Prescriptions for diabetes medications (metformin, sulfonylureas, thiazolidinediones, insulin, and other oral antidiabetic agents) filled from January 1995 to June 2012 were identified by record linkage to the KPNC pharmacy database. Metformin became available on the KPNC formulary in May 1995. Ever users of diabetes medications were defined as those who filled two or more prescriptions for that medication within a 6-month period. Total duration of metformin use was calculated from the number of days supply on each metformin prescription. Recency of metformin use was defined into mutually exclusive categories of former use (stopped 1+ years ago), recent use (stopped <1 year ago), or current use for <5 or $\geq$5 years. Duration of current use was based on the period(s) of days supplied. Recent use included the one-year period after end of current use, whereas former use encompassed the period more than one year after end of current use. Cumulative dose was calculated as the total prescribed dose, defined as the sum of number of pills on each prescription multiplied by the dose per pill, for all metformin prescriptions dispensed during follow-up. Prescriptions not finished at the end of follow-up had total duration and cumulative dose adjusted to include only doses before then.

Follow-up and outcomes

Patients were followed from January 1, 1997, until diagnosis of first primary colorectal cancer, a diagnosis of another invasive cancer, a gap of four months in membership or prescription benefits, death, or study close (June 30, 2012), whichever occurred first. First primary colorectal cancers were identified from the KPNC Cancer Registry that reports to the California Cancer Registry and the National Cancer Institute's Surveillance, Epidemiology and End Results program of registries (SEER). The registry dates back to the late 1940s and has covered all KPNC medical facilities since 1988. The data quality is comparable with SEER and recorded information includes cancer site, diagnosis date, tumor characteristics, and treatment.

Potential confounding variables

Data on the following potential confounders were collected by survey and were recorded on or before the start of follow-up: birth year, gender race/ethnicity, smoking status, alcohol use, income, education level, diabetes duration, and body mass index (BMI). Data on use of lower endoscopy (colonoscopy and sigmoidoscopy) before the index date and during follow-up was obtained from procedure records. Baseline HbA1c and creatinine levels (metformin is contraindicated in those with elevated creatinine levels) were also obtained. Charlson comorbidity index scores were calculated using data from clinical records (both outpatient and inpatient) on comorbid conditions documented in the 2 years before baseline.

Statistical analysis

Multivariable Cox regression modeling was used to calculate point estimates and 95% confidence intervals (95% CIs) of the relative hazards for colorectal cancer associated with metformin use, including ever use (two prescriptions within a 6-month period), total duration (<2 years, 2–4.9 years and 5.0+ years), recency of use (stopped 1+ years ago, stopped < 1 years ago, current user), and cumulative dose (in quartiles). The reference group for all comparisons was never users of metformin. In addition to those with no metformin fills, never users included those with fewer than two metformin prescription fills in a 6-month period and those who used diabetes medications other than metformin.

To avoid immortal time bias (i.e., misclassification of unexposed time as exposed), metformin use and use of other classes of antidiabetic medications (i.e., sulfonylureas, thiazolidinediones, insulin, all others) were modeled as time-varying. Person-time from the start of follow-up until first use of a given medication was classified as never use for that medication. For ever use, cumulative duration or cumulative dose of metformin, once a patient met the exposure definition, he or she was considered exposed from that point forward, even if they later discontinued metformin. In the recency analyses, patients who discontinued metformin became former users (i.e., stopped 1+ years ago, stopped <1 years ago). In addition, two separate covariates, indicating never use of any antidiabetic medication and never having two prescriptions of the same medication filled within 6 months, were modeled as time-dependent covariates.

Regression models included potential confounding variables selected a priori, including birth year, gender, race/ethnicity, smoking status, alcohol use, income, education level, diabetes duration, BMI, Charlson comorbidity index, history of lower endoscopy (fixed at baseline) and, first lower endoscopy after baseline (time-varying), baseline HbA1c, creatinine levels and use of other types of diabetes medications (time-varying). In addition, to minimize possible time lag bias, we adjusted for diabetes duration.

Sulfonylurea use, another first line T2DM medication, has been associated with increased cancer risk in some studies (21), as have other medications used to treat T2DM, such as insulin (22, 23) and pioglitazone (21), complicating the interpretation of results of studies of metformin. To simplify, we conducted sub analyses to examine whether switching from use of sulfonylurea only to metformin would influence risk of colorectal cancer. These analyses excluded individuals who had used any other T2DM medications before or at baseline and follow-up was censored when switching to or adding any T2DM medication other than metformin. This allowed direct comparisons of metformin users who switched from using sulfonylureas to patients who used sulfonylureas only. Additional subgroup analyses explored if any associations differed by gender (24).

Results

The final cohort included 47,351 patients with diabetes of whom 21,524 received metformin during follow-up (Table 1). During 428,451.93 person-years of follow-up [mean (SD) 9.0 (5.3) years], 812 (1.7%) patients were diagnosed with colorectal cancer (23% were rectal cancers). Among those who never used metformin, the median duration of follow-up was 5.5 years (interquartile range, 2.7–10.5 years). In metformin users, the median duration of metformin therapy was 3.1 years (interquartile range, 1.5–5.2 years) during a median follow-up of 13.9 years (interquartile range, 8.1–15.5 years). Metformin users were more frequently younger, never smokers, had a higher median household income and were more likely to have had at least some college education compared with never users. Only minimal racial or ethnic differences were observed between the two groups. Metformin users had higher baseline HbA1c levels compared with never users, indicating more poorly controlled diabetes, as well as a higher median BMI. They also tended to have a shorter duration of diabetes [median time since diagnosis 6 years (range 3–11) vs. 11 years (range, 5–19) in never users] and almost 40% of metformin users had used the drug for more than 4 years.

Table 1. Baseline characteristics of 47,351 patients with diabetes

	Ever user, *n* = 21,524 (45.5%) *n* (%)	**Never user, *n* = 25,827 (54.5%) *n* (%)**
Age, y		
40–49	4,228 (19.6)	3,023 (11.7)
50–59	6,800 (31.6)	4,969 (19.2)
60–69	6,830 (31.7)	7,756 (30.0)
70+	3,666 (17.0)	10,079 (39.0)
Sex		
Male	11,254 (52.3)	14,294 (55.3)
Female	10,270 (47.7)	11,533 (44.7)
Race/ethnicity		
Non-Hispanic white	10,748 (49.9)	14,291 (55.3)
Black	2,420 (11.2)	3,335 (12.9)
Asian or Pacific Islander	3,173 (14.7)	2,358 (9.1)
Hispanic	2,921 (13.6)	2,543 (9.8)
Other	580 (2.7)	745 (2.9)
Missing	1,682 (7.8)	2,555 (9.9)
Median household income		
Low	10,091 (46.9)	13,011 (50.4)
High	11,133 (51.7)	11,976 (46.4)
Missing	300 (1.4)	840 (3.2)
Education level		
Less than high school	2,553 (11.9)	3,990 (15.5)
High school graduate	4,953 (23.0)	6,021 (23.3)
Some college	5,775 (26.8)	6,201 (24.0)
College graduate	2,293 (10.7)	2,221 (8.6)
Post-graduate	2,466 (11.5)	2,684 (10.4)
Missing	3,484 (16.2)	4,710 (18.2)
Smoking history		
Never	9,013 (41.9)	9,470 (36.7)
Former	6,947 (32.3)	8,997 (34.8)
Current	2,031 (9.4)	2,438 (9.4)
Missing	3,533 (16.4)	4,922 (19.1)
Alcohol history		
Never	3,638 (16.9)	4,255 (16.5)
Former	4,437 (20.6)	5,960 (23.1)
Current	9,557 (44.4)	10,179 (39.4)
Missing	3,892 (18.1)	5,433 (21.0)
HbA1c (%)		
<7	4,467 (20.8)	7,502 (29.0)
7–7.9	4,352 (20.2)	5,201 (20.1)
8–8.9	3,202 (14.9)	3,279 (12.7)
9–9.9	2,267 (10.5)	2,075 (8.0)
10+	3,975 (18.5)	2,978 (11.5)
Missing	3,261 (15.1)	4,792 (18.6)
Body mass index, kg/m^2[a]	29.8 (26.3–34.2)	27.9 (24.8–31.9)
Creatinine[a]	0.8 (0.7–1.0)	1.0 (0.8–1.3)
Time since diabetes diagnosis (y)[a]	6.0 (3.0–11.0)	11.0 (5.0–19.0)
Prior endoscopy use		
Yes	2,930 (13.6)	3,059 (11.8)
No	18,594 (86.4)	22,768 (88.2)
Time since initiation of metformin, years		
<1	3,560 (16.5)	
1–2	3,485 (16.2)	
2–3	3,385 (15.7)	
3–4	3,088 (14.4)	
4+	8,006 (37.2)	

[a]Median (interquartile range).

Overall, in the fully adjusted model, there was no association between ever use of metformin and colorectal cancer risk (HR, 0.90; 95% CI, 0.76–1.07; Table 2). Similarly, no clear pattern of decreasing risk was seen with increasing cumulative duration (P_{trend}, 0.17) or recency (P_{trend}, 0.23). However, there was a decreased risk in long-term users overall (≥5.0 years; HR, 0.78; 95% CI, 0.60–1.02), and among current long-term users (HR, 0.78; 95% CI, 0.59–1.04; Table 2). Higher doses of metformin were also associated with a reduced risk (HR, 0.67; 95% CI 0.45–0.98). When the study population was stratified by sex, there was a decreased risk of colorectal cancer with increasing duration of metformin use among men ($P_{trend} = 0.05$; HR = 0.65; 95% CI, 0.45–0.94 for ≥5.0 years of metformin use) but not among women (P_{trend} 0.98; HR, 0.95; 95% CI, 0.65–1.38 ≥5.0 years of metformin use; Table 3). Among users of sulfonylureas only at baseline, risk of colorectal cancer was decreased among those who subsequently initiated metformin compared with those who remained on sulfonylureas. The association was strongest among those who used metformin for ≥5.0 years (HR, 0.62; 95% CI, 0.38–1.01; Table 4).

Discussion

In this large retrospective cohort study, no association was found between ever use of metformin and colorectal cancer risk in patients with diabetes. There was also no consistent pattern of decreasing risk with total duration, dose or recency of metformin use. However, there was a suggestion of a reduced colorectal cancer risk among those using metformin for ≥5.0 years—although this reduction appeared to be restricted to men. There also appeared to be a reduced risk in those who switched to metformin from sulfonylureas, especially for long-term metformin users (≥5.0 years).

Although examining ever use of metformin is less informative in terms of effects on cancer risk than dose or duration of use, previous studies, that have also accounted for methods that minimize time-related biases, have used it and similarly found no association between ever use of metformin and colorectal cancer risk (19). Two large cohort studies conducted in the UK Clinical Practice Research Datalink (CPRD; refs. 14, 25), one using a nested case–control analysis and the other an intention to treat analysis, similarly observed no association. However, a third study conducted in CPRD reported an increased risk of colorectal cancer among metformin users, (16) although, that study did not match on or adjust for duration of diabetes. In a cohort study focusing on pioglitazone use and cancer risk within Kaiser

Table 2. Estimates of colorectal cancer risk associated with metformin use

Metformin use	No. of events	Person-years	Adjusted[a] HR (95% CI)
Never	487	257,530.93	1.00 (reference)
Ever	325	170,921.00	0.90 (0.76–1.07)
Total duration (y)			
<2.0	104	61,029.82	0.88 (0.70–1.10)
2.0–4.9	122	56,393.23	1.02 (0.81–1.27)
≥5.0	99	53,497.95	0.78 (0.60–1.02)
			P_{trend} =0.17
Recency of use			
Former	74	33,469.11	0.90 (0.68–1.19)
Recent	34	21,468.90	0.75 (0.52–1.07)
Current			
<5.0 years	143	75,344.55	0.98 (0.80–1.21)
≥5.0 years	74	40,638.44	0.78 (0.59–1.04)
			P_{trend} = 0.23
Cumulative dose (mg), quartiles			
≤750,000	94	55,340.38	0.85 (0.68–1.10)
750,001–2,300,000	109	52,092.48	0.99 (0.78–1.24)
2,300,001–4,930,000	87	41,074.69	0.95 (0.73–1.24)
>4,930,000	35	22,413.44	0.67 (0.45–0.98)
			P_{trend} =0.18

[a]Adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, smoking status, Charlson comorbidity index, education, income level, creatinine, HbA1c, history of lower endoscopy (all fixed at baseline); first lower endoscopy after baseline (time-varying) and use of other types of diabetes medications (time-varying).

Permanente Northern California, there was no association between use (ever vs. never) of other antidiabetic drugs, including metformin, and colorectal cancer risk among patients with diabetes (11). However, these analyses did not include duration, dose or recency of metformin use.

Two large randomized controlled trials (RCTs)—The ADOPT (A Diabetes Outcome Progression Trial) and The RECORD trial (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes; ref. 26)—as well as two meta-analyses of RCTs also found no overall protective effect of metformin on risk of any cancer (27, 28). In contrast, a recent RCT investigating the potential of metformin for prevention of colorectal adenoma or polyps (premalignant colorectal growths) in postpolypectomy patients, without diabetes, found that use of low dose metformin for one year reduced the prevalence and number of adenomas or polyps (29). In type II diabetes hyperinsulinemia, due to insulin resistance, and its influence on insulin-like growth factor receptors promotes an environment that may favor carcinogenesis (30). Indeed the presence of diabetes itself has been associated with an approximately 30% increased risk of colorectal cancer (31). Therefore, metformin may protect against colorectal cancer by reducing insulin resistance and lowering insulin levels. Considering this, poorly controlled diabetes may be a potentially strong time-varying confounder and the intermediate effect of insulin levels should be investigated in future studies using marginal structural models.

We observed a reduced risk of colorectal cancer among long-term users (≥5.0 years) of metformin particularly among men and among current users; a reduced colorectal cancer risk was also observed among those receiving the highest cumulative doses of metformin. A similar trend was noted in the study by Smiechowski and colleagues (14), where, despite also reporting no association with ever use of metformin, there was a modest reduced risk of colorectal cancer among longer-term users (845–1,447 days), although statistical significance was not achieved. A Danish case–control study reported a similar protective effect with long-term metformin use (defined as a cumulative dose of 1000 DDD within 5 years before the index date) but in contrast with our findings, this was limited to women (4). The reason for these differences in subgroup findings is unclear and could of course be attributed to small numbers and chance findings. However, these findings along with those of the recent colorectal adenoma/polyp trial (29) may suggest that metformin exhibits some chemopreventive properties that may reduce the risk of colorectal cancer. A few recent studies have also reported improved survival among colorectal cancer patients who used metformin compared with other antidiabetic drugs (32–34).

Table 3. Estimates of colorectal cancer risk associated with metformin use, by gender

	Male			Female		
Metformin use	No. of events	Person-years	Adjusted[a] HR (95% CI)	No. of events	Person-years	Adjusted[a] HR (95% CI)
Never	288	138,490.83	1.00 (reference)	199	119,040.10	1.00 (reference)
Ever	166	87,405.38	0.81 (0.65–1.03)	159	83,515.62	1.01 (0.78–1.31)
Total duration, years						
<2.0	54	30,979.85	0.80 (0.59–1.08)	50	30,049.97	0.98 (0.71–1.37)
2.0–4.9	67	29,269.83	0.95 (0.71–1.28)	55	27,123.40	1.10 (0.79–1.55)
≥5.0	45	27,155.70	0.65 (0.45–0.94)	54	26,342.25	0.95 (0.65–1.38)
			P_{trend} = 0.05			P_{trend} = 0.98

[a]Adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, smoking status, Charlson comorbidity index, education, income level, creatinine, HbA1c, history of lower endoscopy (all fixed at baseline); first lower endoscopy after baseline (time-varying) and use of other types of diabetes medications (time-varying).

Table 4. Estimates of colorectal cancer risk associated with metformin use after sulfonylurea use

Antidiabetic drug use	Person years	No. of events	Adjusted[a] HR (95% CI)
Sulfonlyurea only	80,847.12	167	1.00 (reference)
Sulfonylurea+metformin	58,725.95	122	0.85 (0.65–1.12)
Duration metformin			
Never	80,847.12	167	1.00 (reference)
<2.0 years	25,050.73	50	0.93 (0.67–1.29)
2.0–4.9 years	20,701.60	44	0.88 (0.60–1.27)
≥5.0 years	12,973.62	28	0.62 (0.38–1.01)
			$P_{trend} = 0.08$

Diabetes is a condition seldom managed with a single agent and, among diabetes patients there is frequent switching between drugs. Adherence to metformin or sulfonylurea monotherapy after five years was around 20% in one study (25) and as low as 1% for more than 1 year in another (35). As a result, some previous studies have restricted study populations to those using single-agent monotherapy and excluded drug switchers due to the concerns that a cancer caused by an initial drug may be attributed to the new agent after switching (12). This can make it difficult to achieve required power and may not reflect real life practice. To address concerns about the lack of a single comparator drug for metformin and the possible link between sulfonylurea use and increased cancer risk, sensitivity analyses were conducted comparing sulfonylurea only users with those who used sulfonylureas before initiating metformin. These showed a consistent pattern of reduced colorectal cancer risk with increasing duration of metformin use, although statistical significance was not achieved. These findings along with the apparent decreased risk among long-term users, particularly men, in our main analysis suggest that metformin may reduce the risk of colorectal cancer. However, the observed sex difference in the association between long-term use of metformin and reduced colorectal cancer risk remains unexplained and may merit further investigation.

Strengths

This study has several strengths, including the availability of a large cohort of patients with diabetes with long-term follow-up in the KPNC diabetes registry. The comprehensive health care and lifestyle data available from the electronic health records and the health survey allowed for evaluation of multiple potential confounders, such as race/ethnicity, income, BMI and duration of diabetes. The use of time-dependent exposure modelling and adjustment for diabetes duration minimized the effects of time-related biases such as immortal time and time lag bias which were present in some previous studies. Extensive information on drug prescribing and dispensing from KPNC pharmacy database allowed comprehensive exposure ascertainment.

Limitations

Detection bias relating to colorectal cancer screening by lower endoscopy remains a concern in this study. It is known that many colorectal cancers are found incidentally on screening in the absence of major symptoms and those who manage their diabetes with pharmacotherapy may be more likely to undergo screening. Indeed, compared to sulfonylurea only users, metformin users and those on sulfonylurea/ metformin combinations have been reported to more frequently receive a lower endoscopy procedure (36), which may be related to metformin's gastrointestinal side effect profile. We observed more frequent lower endoscopy use among metformin users in this study. Thus, we adjusted for history of lower endoscopy at cohort entry and as a time varying covariate during follow-up.

Despite having comprehensive data on medication prescribing and dispensing, we could not determine whether patients actually complied with their diabetes drug regimens. We attempted to minimize any potential exposure misclassification by requiring two or more prescriptions to have been filled within a 6-month period to be eligible for the study. It was not possible to differentiate patients with type 2 versus type 1 diabetes and so eligibility was restricted to patients age ≥40 years, a group that comprises a larger number of those with type 2 diabetes. Although data were available on a range of potential confounding variables, most were assessed only once (i.e., before baseline) and were not updated during the study. As in all observational studies, there is the potential for residual confounding from unmeasured factors such as diabetes control despite adjustment for baseline HbA1C. KPNC has a drug formulary and patterns of diabetes drug prescribing may differ from other health care settings in the United States. As the participants of this study were from an existing diabetes registry, metformin was frequently not the first-line diabetes drug given (metformin was only added to the KPNC formulary in 1995). To account for this, we adjusted all analyses for use of other diabetes drug using time dependent exposure modeling.

In summary, our study found an inverse association between metformin use and colorectal cancer risk. The decreased risk observed for long-term metformin use, particularly in men, and with a high cumulative dose of metformin needs to be confirmed in larger, well-characterized cohorts of persons with diabetes over an extended period of follow-up, accounting for time-related and other potential biases. Further prospective studies to evaluate the effect of metformin on colorectal cancer recurrence and adenoma formation are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Ferrara, L.A. Habel
Development of methodology: M.C. Bradley, L.A. Habel
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Ferrara, N. Achacoso, S.F. Ehrlich, L.A. Habel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.C. Bradley, N. Achacoso, S.F. Ehrlich, C.P. Quesenberry Jr, L.A. Habel
Writing, review, and/or revision of the manuscript: M.C. Bradley, A. Ferrara, N. Achacoso, S.F. Ehrlich, C.P. Quesenberry Jr, L.A. Habel

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Achacoso, L.A. Habel
Study supervision: L.A. Habel

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