Original Article

Metformin for Primary Colorectal Cancer Prevention in Patients With Diabetes: A Case-Control Study in a US Population

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BACKGROUND: Emerging evidence from observational studies has suggested that metformin may be beneficial in the primary prevention of colorectal cancer (CRC). However, to the authors' knowledge, none of these studies was conducted in a US population. Because environmental factors such as Western diet and obesity are implicated in the causation of CRC, a large case-control study was performed to assess the effects of metformin on the incidence of CRC in a US population. **METHODS:** MarketScan databases were used to identify diabetic patients with CRC. A case was defined as having an incident diagnosis of CRC. Up to 2 controls matched for age, sex, and geographical region were selected for each case. Metformin exposure was assessed by prescription tracking within the 12-month period before the index date. Conditional logistic regression was used to adjust for multiple potential confounders and to calculate adjusted odds ratios (AORs). **RESULTS:** The mean age of the study participants was 55 years and 57 years, respectively, in the control and case groups ($P = 1.0$). Approximately 60% of the study participants were male and 40% were female in each group. In the multivariable model, any metformin use was associated with a 15% reduction in the odds of CRC (AOR, 0.85; 95% confidence interval, 0.76-0.95 [$P = .007$]). After adjusting for health care use, the beneficial effect of metformin was reduced to 12% (AOR, 0.88; 95% confidence interval, 0.77-1.00 [$P = .05$]). The dose-response analyses demonstrated no significant association with metformin dose, duration, or total exposure. **CONCLUSIONS:** Metformin use appears to be associated with a reduced risk of developing CRC among diabetic patients in the United States. ***Cancer* 2014;000:000-000.** © *2014 American Cancer Society.*

KEYWORDS: metformin, colorectal cancer, chemoprevention, diabetes, MarketScan database.

INTRODUCTION

Cancer and diabetes are extremely prevalent diseases worldwide and are associated with substantial adverse health effects. Colorectal cancer (CRC) is the second most commonly diagnosed cancer in females and the third most commonly diagnosed cancer in males. Over 1.2 million incident cases and 608,700 deaths were recorded globally in 2008.[1] At least 6 case-control studies and 9 cohort studies to date have suggested that the relative risk of CRC is higher in patients with diabetes (predominantly type 2).[2] A recent consensus statement by the American Diabetes Association and the American Cancer Society concluded that there is a higher risk of CRC among patients with type 2 diabetes.[3] Diabetes is believed to promote the development of carcinogenesis through complex processes. These include hyperinsulinemia, hyperglycemia, and chronic inflammation.[3] Metformin is the most commonly prescribed drug for the treatment of type 2 diabetes mellitus. An important clue to the actions of metformin was the discovery that metformin upregulates AMP-activated protein kinase (AMPK),[4] which is a central regulator of cellular energy metabolism. Subsequent epidemiological studies linked metformin use to an anticancer effect,[5] which has led to great interest in repurposing metformin for cancer treatment and prevention.

Metformin is a generic, inexpensive, easily available drug that belongs to the biguanide class of agents. Its excellent safety profile makes it an attractive anticancer drug. Metformin is mainly used for the treatment of type 2 diabetes mellitus but is also used in patients with polycystic ovary disease (PCOD) and morbid obesity. Metformin causes its antihyperglycemic action by suppressing hepatic glucose output (inhibition of gluconeogenesis and glycogenolysis), thereby increasing peripheral tissue (skeletal muscle and adipocytes) insulin sensitivity and decreasing intestinal absorption of glucose.[6]

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Metformin is usually well tolerated with infrequent gastrointestinal adverse effects such as diarrhea, flatulence, and abdominal discomfort reported to be the major side effects.[7] Hypoglycemia is rare,[8] and lactic acidosis is extremely rare (0.03 cases per 1000 patient-years).[6]

There have been several observational studies from Europe and Asia suggesting a reduced incidence of CRC as well as other cancers including breast, lung, prostate, ovarian, and pancreatic cancer in patients with diabetes who are being treated with metformin.[9-13] Supporting these observations in humans, metformin has been shown to inhibit growth and induce apoptosis in cell lines and animal models for various cancers, including CRC.[14,15] A recent prospective, randomized, clinical trial demonstrated a decrease in the mean number of aberrant cryptic foci (a putative precursor lesion for CRC) in nondiabetic patients after 30 days of treatment with metformin compared with placebo.[16] There is a growing body of evidence indicating that metformin's anticancer activity is mediated by both its cellular and systemic effects.[17] The systemic effects of metformin are mainly reductions in hyperglycemia that can potentially counteract the Warburg effect (dependence of cancer cells on glucose as predominant source of energy). The cellular or direct effects are believed to involve activation of the AMPK pathway,[18-20] which can potentially counteract the effects of hyperinsulinemia by systemic inhibition of growth factors including glucose, insulin, insulin-like growth factor 1 (IGF-1), IGF-1 receptor, IGF-binding protein, and leptin (but an increase in adiponectin), eventually leading to the inhibition of protein synthesis and reductions in cell growth and proliferation.

Despite these observational studies and rationale, we know of no large, retrospective, nationwide studies performed in the US population that examined metformin's potential effectiveness in reducing the incidence of CRC. Furthermore, because environmental factors, especially Western diet and obesity, are believed to play important causal roles in the genesis of sporadic colon cancer, such a study in a US population is warranted to address the potential efficacy of metformin in this country.[21] Therefore, we conducted a case-control study using the MarketScan databases to address this question in a US population.

MATERIALS AND METHODS

Patients and Eligibility Criteria

The study was conducted using the MarketScan Commercial Claims and Encounters Database (Truven Health Analytics, Ann Arbor, Mich). MarketScan is a longitudinal database that contains individual-level, deidentified health insurance claims data from nearly 150 million individuals from all geographic areas of the United States. All patients aged >18 years with diabetes mellitus who were diagnosed with CRC from 2005 through 2010 were identified in the MarketScan database using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9-CM) codes (diabetes mellitus: ICD-9 codes 250.0-250.9 and CRC: ICD-9 codes 153.0-153.9, 154.0, 154.1, and 154.8). To reduce the false-positive rate of CRC cases, only patients with at least ≥2 claims of ICD-9 codes indicating CRC on different dates within a period of 3 months were included. In addition, only patients with continuous enrollment in the 12-month period before the earliest CRC diagnosis date were included in the current study to ensure completeness of the claims data. The primary objective of the study was to assess the odds of developing CRC among metformin users and nonusers. The study was approved by the Institutional Review Board of the University of Chicago.

Cases and Controls

A case was defined as a patient with diabetes who had an incident diagnosis of CRC. For the purpose of the current study, a CRC case was considered to be incident if there were no claims indicative of CRC in the previous year so as to ensure metformin use before the development of CRC. A control was defined as a patient with diabetes without a diagnosis of CRC. The controls were identified by first matching patients by age, sex, and geographical region (ie, Northeast, North Central, South, West, and unknown region) to a case, then by ascertaining those that were enrolled within the same month as the month of diagnosis of the matching case, and finally by retaining only those patients with 12-month continuous enrollment as controls. Therefore, up to 2 controls individually matched for age, sex, and geographical region were selected per case.

Exposure Ascertainment

The exposure to metformin was estimated by tracking the prescriptions within the 12 months before the index date. The index date for cases was defined as the earliest date of CRC diagnosis. Similarly, the index date for controls was defined as the date of diagnosis of the case that was used to find the matched controls. We gathered the dose and duration of metformin use for each study participant. The exposure assessment in the year before the CRC diagnosis ensured the inclusion of only incident cases of CRC to the best extent possible for the current study.

TABLE 1. Characteristics of the Study Population in the Case and Control Groups

Characteristic		Cases N = 2682 (33.33%)	Controls N = 5364 (66.67%)	*P* (Chi-Square Test)[a]
Mean age (SD) [range], y		57.37 (±5.51) [26-64]	55.23 (±5.69) [23-64]	1.0 (Student *t* test)
Sex, no. (%)				1.0
Male		1603 (59.77)	3203 (59.77)	
Female		1079 (40.23)	2158 (40.23)	
Region/zip code, no. (%)	Northeast	191 (7.12)	383 (7.14)	.92
	North Central	731 (27.26)	1477 (27.54)	
	South	1404 (52.35)	2790 (52.01)	
	West	345 (12.86)	684 (12.75)	
	Unknown	11 (0.41)	30 (0.56)	
Year of diagnosis, no. (%)	2005	310 (11.56)	620 (11.56)	1
	2006	282 (10.51)	564 (10.51)	
	2007	570 (21.25)	1140 (21.25)	
	2008	536 (19.99)	1072 (19.99)	
	2009	593 (22.11)	1186 (22.11)	
	2010	391 (14.58)	782 (14.58)	
Obesity, no. (%)		112 (4.18)	193 (3.6)	.20
Inflammatory bowel disease, no. (%)		29 (1.08)	29 (0.54)	.007
Coronary artery disease, no. (%)		389 (14.5)	641 (11.95)	.001
Polycystic ovary disease, no. (%)		1 (0.04)	6 (0.1)	.28
Statins, no. (%)		992 (36.99)	2091 (38.98)	.083
Metformin, no. (%)		983 (36.65)	2059 (38.39)	.13
NSAIDs, no. (%)		372 (13.87)	865 (16.13)	.008
Sulfonylurea, no. (%)		683 (25.47)	1359 (25.34)	.89
Insulin, no. (%)		502 (18.72)	913 (17.02)	.06
Thiazolidinedione, no. (%)		488 (18.22)	1069 (19.93)	.06
Charlson comorbidity index		1.10 ± 1.04	1.47 ± 0.87	<.001 (Student *t* test)
No. of admissions (mean ± SD)		0.58 ± 0.96	0.19 ± 0.62	<.001 (Student *t* test)
No. of outpatient visits (mean ± SD)		19.99 ± 19.42	15.91 ± 16.81	<.001 (Student *t* test)

Abbreviations: NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation.
[a] Univariate *P* value was calculated using the chi-square test unless otherwise specified.

Potential Confounders

We collected data regarding multiple potential confounders of patient-related variables and concurrent medications 12 months before the index date. The patient-related variables for this purpose included obesity (ICD-9 codes 278.00 and 278.01), PCOD (ICD-9 code 256.4), inflammatory bowel disease (IBD) (ICD-9 codes 556.0-556.9, 555.0-555.2, and 555.9), coronary artery disease (CAD) (ICD-9 codes 410.0-410.9, 414.0-414.4, 414.8, 414.9, and 429.2), age, sex, geographic region, and comorbidity scores. The comorbidity scores were calculated using the modified Charlson algorithm available from the Surveillance, Epidemiology, and End Results-Medicare Web site[22] and revised to fit the data structure in MarketScan. Medications being used concurrently within the last year (including the index date) for which statistical model adjustments were made included prescribed nonsteroidal antiinflammatory drugs (NSAIDs) (but excluded over-the-counter aspirin) (ibuprofen, naproxen, indomethacin, diclofenac, piroxicam, etodolac, fenoprofen, flurbiprofen, ketoprofen, meclofenamate, meloxicam, nabumetone, oxaprozin, sulindac, tolmetin, and celecoxib), statins, sulfonylureas (SUs), thiazolidinediones (TZD), and insulin. We also gathered data concerning health care use by counting the number of outpatient visits and the number of hospitalizations during the 12 months before the index date.

Statistical Analyses

The differences between the case and control groups with regard to covariates were determined using the chi-square or Student *t* test. In the primary analyses, the odds of developing CRC for patients with diabetes who were exposed to metformin and those not exposed to metformin was calculated. Conditional logistic regression was used to estimate the adjusted odds ratio (AOR) and 95% confidence interval (95% CI), adjusting for patient-related variables, concomitant medications, and health

TABLE 2. Results of Metformin Exposure and Odds of Developing Colorectal Cancer in a Multivariate Regression Model[a]

Variable	COR (95% CI)	*P*	AOR (95% CI)	*P*
Associated with increased odds				
Insulin use	1.12 (0.99-1.27)	.05	1.45 (1.27-1.65)	<.001
Coronary artery disease	1.25 (1.09-1.43)	.001	1.66 (1.43-1.93)	<.001
Inflammatory bowel disease	2 (1.19-3.34)	.008	1.95 (1.14-3.34)	.01
Sulfonylurea use	1.00 (0.90-1.12)	.89	1.15 (1.02-1.31)	.02
No. of hospital admissions	1.95 (1.81-2.10)	<.001	2.55 (2.32-2.81)	<.001
No. of outpatient visits	1.012 (1.010-1.015)	<.001	1.01 (1.011-1.019)	<.001
Associated with decreased odds				
Metformin	0.92 (0.84-1.02)	.12	0.85 (0.76-0.95)	.007
Prescribed NSAIDs	0.83 (0.72-0.95)	.007	0.84 (0.73-0.96)	.01
Charlson comorbidity index	0.58 (0.55-0.62)	<.001	0.54 (0.50-0.58)	<.001
No significant association noted				
Obesity	1.16 (0.92-1.47)	.20	1.19 (0.93-1.52)	.16
Polycystic ovary disease	0.33 (0.04-2.76)	.30	0.32 (0.03-2.75)	.30
Statins	0.91 (0.83-1.01)	.07	0.91 (0.82-1.01)	.10
Thiazolidinediones	0.89 (0.79-1.00)	.06	0.92 (0.81-1.06)	.28

Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio; COR, crude odds ratio; NSAIDs, nonsteroidal antiinflammatory drugs.
[a] Model was adjusted for obesity, polycystic ovary disease, inflammatory bowel disease, sulfonylurea use, coronary artery disease, prescribed NSAIDs, insulin use, metformin use, thiazolidinedione use, Charlson comorbidity index, number of hospital admissions, and number of outpatient visits.

TABLE 3. Results of Metformin Exposure and Odds of Developing Colorectal Cancer in a Multivariate Regression Model That Included Health Care Use[a]

Variable	AOR[a]	*P*[a]
Metformin	0.88 (0.77-1.00)	.05
No. of hospital admissions	2.55 (2.32-2.81)	<.001
No. of outpatient visits	1.01 (1.011-1.019)	<.001

Abbreviation: AOR, adjusted odds ratio.
[a] Model was adjusted for obesity; inflammatory bowel disease; polycystic ovary disease; coronary artery disease; Charlson comorbidity index; and use of nonsteroidal antiinflammatory drugs, sulfonylureas, thiazolidinediones, statins, and insulin.

care use. In the secondary analyses, we calculated the magnitude of effect of the dose, duration, and total exposure of metformin on CRC risk. To study dose-response relationships, we collected data regarding the dose and duration of metformin for the study participants with at least 1 prescription claim for metformin within the past year. We divided the duration of use into 4 quartiles (≤123 days, 124-240 days, 241-313 days, and ≥314 days) for statistical analyses. Similarly, the daily dose of metformin was divided into 4 quartiles (≤1000 mg, 1001-1500 mg, 1501-2000 mg, and ≥2001 mg) for statistical analyses. We also calculated the total metformin exposure by multiplying the metformin dose with duration of use. A *P* value was considered to be statistically significant if the 2-sided *P* value was ≤.05. The data management was performed using SAS statistical software (version 5.1; SAS Institute Inc, Cary, NC) and all statistical analyses were performed using STATA statistical software (version 12.0; StataCorp LP, College Station, Tex).

RESULTS

Study Participants

The total number of study participants was 8046, with 2682 patients in the case group and 5364 individuals in the control group. The mean age was 57 years and 55 years, respectively, in the case and control groups ($P = 1.0$). There were 60% males and 40% females in each group. Any metformin exposure was noted in 36.6% of patients in the case group and 38.4% of those in the control group, respectively. On univariate analysis, there were no significant differences observed in terms of age; sex; geographical region; year of diagnosis; obesity; presence of PCOD; and use of statins, metformin, SUs, TZD, and insulin. However, comorbidities, including IBD and CAD, and NSAIDs use were significantly different between the 2 groups, with higher percentages noted in the case group compared with the control group with the exception of NSAID use (Table 1). The Charlson comorbidity index was significantly higher in the control group but the number of hospital admissions and outpatient visits were significantly higher in the case group compared with controls (Table 1).

Metformin and Odds of Developing CRC

In a multivariate model, any metformin use was associated with a 15% reduced odds of CRC (AOR, 0.85; 95% CI, 0.76-0.95 [$P = .007$]) while controlling for all the patient-related variables, concomitant medications, and Charlson comorbidity index (Table 2). We found that PCOD, obesity, and use of statins and TZD demonstrated no

TABLE 4. arStratified Analysis by Metformin Dose, Duration, and Total Exposure (Dose × Duration)[a]

Variable Name	Quartiles	No. (%)	AOR (95% CI)	*P*	*P* for Trend
Metformin duration, days(days)	≤123	755 (25.07)	1.00	.33	
	124-240	754 (25.04)	1.12 (0.81-1.55)		.48
	241-313	760 (25.24)	1.04 (0.75-1.44)		.79
	≥314	742 (24.64)	0.89 (0.63-1.26)		.54
Metformin dose, mg	≤1000	1231 (40.88)	1.00	.97	
	1001-1500	326 (10.83)	1.09 (0.73-1.62)		.64
	1501-2000	1313 (43.61)	1.04 (0.79-1.36)		.77
	>2001	141 (4.68)	0.89 (0.51-1.55)		.69
Total metformin exposure (dose × duration)	≤150,000	785 (26.07)	1.00	.40	
	150,001-306,000	730 (24.24)	1.12 (0.81-1.55)		.48
	306,001-522,000	747 (24.81)	1.04 (0.75-1.44)		.79
	>522,001	749 (24.88)	0.89 (0.63-1.26)		.54

Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio.
[a] Model was adjusted for obesity; inflammatory bowel disease; polycystic ovary disease; coronary artery disease; Charlson comorbidity index; and use of nonsteroidal antiinflammatory drugs, sulfonylureas, thiazolidinediones, statins, and insulin.

significant association with the odds of developing CRC, whereas the Charlson comorbidity index and prescribed NSAIDs were associated with a significantly decreased odds of developing CRC. IBD, use of SUs, CAD, use of insulin, number of hospital admissions, and number of outpatient visits were associated with a significantly increased odds of developing CRC (Table 2). Adjustment for health care use in the multivariate model (besides all other covariates) resulted in 12% reduced odds of CRC with any metformin use (AOR, 0.88; 95% CI, 0.77-1.00 [P =.05]) compared with no metformin use (Table 3).

Dose-Response Analysis With Metformin

The mean and median duration of metformin intake was 218 days and 240 days, respectively. The mean and median metformin daily dose taken by study participants was 1500 mg, whereas the mean and median metformin total dose taken by study participants was 3,29,300 mg and 3,02,000 mg, respectively. However, no significant dose-response relationship was found between metformin dose, duration, or total exposure (dose × duration) and odds of developing CRC (Table 4).

DISCUSSION

There is growing interest in exploring the role of metformin as a chemopreventive agent given the experimental evidence in support of metformin as an anticancer drug.[15,23] In a large case-control study of patients with diabetes, we found a 12% to 15% statistically significantly reduced risk of developing CRC with any metformin use. However, the dose-response analyses did not demonstrate any significant relationship between dose, duration, or total exposure of metformin and CRC. Although a clear dose-response effect would have strengthened the findings of the current study, the lack of a dose-response effect might be due to a threshold effect achieved at the lowest dose. In this regard, Lee et al, in another epidemiological study, found a significantly reduced CRC risk at all dose levels of metformin (500 mg, 500-1000 mg, and 1000 mg) in female metformin users (but not in male users).[9] Similarly, Tseng reported that the beneficial effect of metformin becomes significant only after 3 years of use.[24]

We believe the current study is unique because to our knowledge there are no prior studies to date addressing the effectiveness of metformin in reducing the risk of CRC among patients with diabetes in a US population. This population, moreover, has relatively distinct environmental risk factors, especially Western diet and obesity. In addition, the patient population in the current study was relatively younger (median age of approximately 59 years; range, 18-64 years) compared with median age at the time of CRC diagnosis in the United States (approximately 68 years).[25] The population of the current study was also relatively younger compared with previously published studies (Table 5).[9-11,24]

There has been a consistent association reported between diabetes and many cancers, including colon cancer. As noted above, the key mechanisms linked to cancer in a diabetic patient population are hyperglycemia, hyperinsulinemia, and chronic inflammation.[3] In the current analyses, insulin use was found to be associated with a significantly increased risk of developing CRC (AOR, 1.45; 95% CI, 1.27-1.65 [P<.001]), which supports the hypothesis that insulin may be increasing CRC risk by promoting signaling through IGF receptors, resulting in increased cell growth, proliferation, survival, and migration. Similarly, SUs, which act by promoting insulin secretion, were also found to

TABLE 5. Studies Evaluating the Role of Metformin in Reducing the Incidence of Colorectal Cancer

Study	Design	Sample Size	Mean Age, Years	Data Source/Collection Period	Outcome	HR/OR ($P < .05$ for All Studies)
Positive observational studies						
Currie 2009[11]	Retrospective cohort	62,809	64	UK Health Information Network database, 2000-2005	Incidence	HR, 0.56 (95% CI, 0.40-0.76) (metformin vs sulfonylurea)
Libby 2009[10]	Retrospective cohort	8170	66	Health Informatics Centre (Scotland), 1994-2003	Incidence	HR, 0.6 (95% CI, 0.38-0.94)
Lee 2011[9]	Retrospective cohort	480,984	NR (aged ≥20)	Taiwanese National Health Insurance database, 2000-2007	Incidence	HR, 0.36 (95% CI, 0.13-0.98)
Tseng 2012[24]	Retrospective cohort	114,562	NR (all ages)	Taiwanese National Health Insurance database, 1996-2005	Incidence	HR, 0.73 (95% CI, 0.58-0.92)
Negative observational studies						
Bodmer 2012[31]	Case-control	6440	70	UK General Practice Research Database, 1995-2009	Incidence	OR, 1.43 (95% CI, 1.08-1.90)
Yang 2004[29]	Nested case-control	24,918	75	UK General Practice Research Database, 1987-2002	Incidence	OR, 1.0 (95% CI, 0.6-1.7)

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; NR, not reported; OR, odds ratio.

be associated with an increased risk of CRC (AOR, 1.15; 95% CI, 1.02-1.31 [$P = .02$]).

In addition to diabetes, other chronic diseases found to be associated with a higher incidence of CRC were IBD (AOR, 1.95; 95% CI, 1.14-3.34 [$P = .01$]) and CAD (AOR, 1.66; 95% CI, 1.43-1.93 [$P < .001$]). This finding might be related to common risk factors as well as common pathological changes observed in these diseases (eg, chronic inflammation in the colon in patients with IBD and systemic inflammation among patients with CAD). Although we expected to find a higher incidence of CRC in individuals with obesity and PCOD, we did not find any significant association, which might be due to the unexpected underreporting of obesity (with a prevalence of approximately 4%) and PCOD (prevalence of <1%) in the current study data set. The influence of these comorbidities should be considered in future studies using data sets with adequate representation of individuals affected with obesity and PCOD. Last, an enormous body of evidence has suggested that the use of aspirin/NSAIDs is associated with a reduced risk of developing CRC.[26-28] We evaluated the effect of prescribed NSAIDs and found a 16% decreased odds of developing CRC (AOR, 0.84; 95% CI, 0.73-0.96 [$P = .01$]). To the best of our knowledge, only 2 other studies in the current metformin literature controlled for aspirin/NSAID use but found no statistically significant association.[24,29] Similarly, statins are believed to decrease the incidence of CRC due to several of their pleiotropic effects (most importantly antiinflammatory properties).[30] Although not statistically significant, we found that the use of statins was associated with a 9% lower odds of developing CRC (AOR, 0.91; 95% CI, 0.82-1.01 [$P = .10$]).

The results of the current study are similar to the results of several other observational studies that were conducted using either the Health Information Network database of the United Kingdom or the Taiwanese National Health Insurance database. In these studies, metformin was associated with a statistically significant reduction of 27% to 44% in the incidence of CRC (except for one study that reported a 64% reduction) (Table 5).[9-11,24,29,31] Despite these positive studies, 2 nested case-control studies using the UK General Practice Research Database found no effect of metformin on CRC risk (Table 5).[9-11,24,29,31] However, 3 large meta-analyses, including case-control and cohort studies, have demonstrated a statistically significant reduction in the risk (approximately 32%-37%) of developing CRC in individuals receiving metformin compared with those not receiving metformin with mild to moderate heterogeneity (I^2 index, 24%-44%).[32-34] Collectively, these numerous positive observational studies and meta-analyses suggest

that metformin use is associated with a reduction in the incidence of CRC. However, the magnitude of beneficial effect noted in the current study is much smaller than that of the meta-analyses. There are at least 2 possible factors that might have contributed to this finding. First, the current study had a relatively younger population, which may have resulted in missing some CRC cases because the cancer incidence increases with age. Second, the current study was comprised of a relatively healthier population as evidenced by the lower Charlson comorbidity index (mean of 1.1 in cases and 1.47 in controls), which also could have resulted in the underdiagnosis of CRC.

We emphasize that the current study has many strengths. First, the large sample size provided sufficient power to address the impact of metformin use on the risk of developing CRC. Second, a computerized prescription database was used for assessing exposure to the drugs of interest, thereby minimizing recall bias. Third, several steps were taken to avoid misclassification bias, such as using a stringent case definition (as described earlier) and studying only those patients with at least 12 months of continuous enrollment before the date of diagnosis. Fourth, we controlled for many potential confounders including diseases and concomitant medications during the 12 months before the date of diagnosis. Fifth, we adjusted for health care use by estimating the number of outpatient visits and hospital admissions. Disparities in health care use can induce a potential bias in a case-control study. For example, if patients in the case group are using more health care resources compared with the control group, this can erroneously result in better outcomes being reported in the case group. This was true in the current study because the case group used more health care resources. Thus, the beneficial effect of metformin was reduced when we adjusted for health care use (Table 3).

The major limitation of the current study is its retrospective study design, which limits the ability to control for unknown potential confounders and sometimes known confounders when the data are not available (data such as race and body mass index are not available in the MarketScan databases). It is possible that such confounders have affected the current study results. First, we were unable to control for aspirin use because this is mainly available as an over-the-counter drug in the United States and therefore this information was not available in the MarketScan databases. It is theoretically possible that the beneficial effect of metformin observed in the current study is partially driven by the higher use of over-the-counter aspirin in the case group. Individuals with CAD are more likely to take aspirin. The univariate analysis of the data from the current study does demonstrate a higher rate of CAD in the case group, which could suggest that a higher percentage of individuals in the case group might be taking aspirin. However, because we adjusted for CAD in our multivariate model, it is unlikely that the results of the current study merely reflect potential confounding by aspirin. Second, it is possible that a higher health-conscious behavior such as screening colonoscopy is associated with increased metformin use. Therefore, it is possible that the reduced incidence of CRC noted in the case group is due to a greater likelihood of adhering to cancer screening guidelines among metformin users. However, we could not adjust for screening colonoscopy in the current study because the guideline-recommended screening interval for colonoscopy is every 5 to 10 years, and given our study duration of only 1 year, we would have missed many screening colonoscopies outside of our observation period. However, we did adjust for overall health care use, which indicated a higher rate of use of health care resources in the case group compared with the control group, which reduced the beneficial effect of metformin (AOR, 0.88; 95% CI, 0.77-1.00 [$P = .05$]). Therefore, it is possible that the current study results of a beneficial effect of metformin are in part due to greater health-conscious behavior in the case group compared with the control group. Third, we could not adjust for lifestyle (diet and exercise) and socioeconomic factors in the current analysis. However, we do not expect that these variables would be significantly different enough between the 2 groups to explain the findings of the current study. In addition, we matched for age, sex, geographical region, and year of diagnosis that would have balanced these factors between the case and control groups. Fourth, we could not adjust for smoking and alcohol consumption because this information is not available in the MarketScan databases. Last, the data from the current study were not linked to cancer registries and therefore there could be ascertainment bias in the incident cohort as identified from claims using ICD-9 codes.

The results of the current study suggest that metformin may have a beneficial effect in reducing the risk of CRC among patients with diabetes in the US population. The magnitude of the effect we measured is smaller than that presented in prior studies from Asia and Europe. This may reflect the relatively younger population in the current study and differences in adjustments for potential confounders among different studies. Furthermore, due to the inherent nature of the design of the current study, a causal relationship cannot be established. Furthermore,

prospective controlled studies are needed to rigorously test the efficacy of metformin as a colon cancer chemopreventive agent.

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CONFLICT OF INTEREST DISCLOSURES

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