Research Article

Cancer Epidemiology, Biomarkers & Prevention

Metformin, Diabetes, and Survival among U.S. Veterans with Colorectal Cancer

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Abstract

Background: Metformin has been associated with improved colorectal cancer survival, but investigations are limited by small numbers of patients and confounding by diabetic severity. We examined the association between metformin use and overall survival (OS) in patients with diabetes and colorectal cancer in a large population of U.S. veterans, while adjusting for measures of diabetic severity.

Methods: Patients diagnosed with colorectal cancer from January 2001 to December 2008 were identified from the Veterans Affairs Central Cancer Registry. Multivariable models were used to examine the adjusted association of OS with diabetes and use of antidiabetic medications.

Results: There were 21,352 patients diagnosed with colorectal cancer identified ($n = 16{,}355$ nondiabetic patients, $n = 2{,}038$ diabetic patients on metformin, $n = 2{,}136$ diabetic patients on medications other than metformin, $n = 823$ diabetic patients not on antidiabetic medication). Diabetic patients had a significantly worse OS than nondiabetic patients, but metformin users had only a 10% increase in death (HR_{adj} 1.10; 95% CI, 1.03–1.17, $P = 0.004$), as compared with 22% for users of other antidiabetic medications (HR_{adj} 1.22; 95% CI, 1.15–1.29, $P < 0.0001$). Among colorectal cancer patients with diabetes, metformin users had a 13% improved OS versus patients taking other antidiabetic medications (HR_{adj} 0.87; 95% CI, 0.79–0.95, $P = 0.003$), while diabetic patients not on any antidiabetic medications did not differ with respect to OS (HR_{adj} 1.02; 95% CI, 0.90–1.15, $P = 0.76$).

Conclusions: Among diabetics with colorectal cancer, metformin use is associated with improved survival, despite adjustments for diabetes severity and other risk factors.

Impact: These data lend further support to the conduct of randomized studies of possible anticancer effects of metformin among patients with colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 25(10); 1418–25. ©2016 AACR.*

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in men and women worldwide, and the fourth most common cause of cancer death (1, 2). Diabetes has also become a major global health challenge (3), and there are epidemiological and biological data linking these two diseases. In several large population studies, an increased risk of cancer—including colorectal cancer—has been observed in patients with diabetes or abnormal glucose metabolism (4–9). A metabolic component of colorectal cancer prognosis is supported by observations that low dietary glycemic load, physical activity, and HgA1c < 7.5% are associated with improved colorectal cancer survival (10–13).

In light of these data, the possible role of diabetic therapies in cancer initiation and progression has garnered significant attention. Evidence from *in vitro* and *in vivo* studies suggests that the diabetic therapy metformin may also have anticancer activity via effects on blood insulin and glucose, cancer cell proliferation and apoptosis, and cancer stem cell growth by activating the adenosine monophosphate-activated protein kinase (AMPK)/liver kinase B-1 (LKB1) pathway, inhibiting the mammalian target of rapamycin (mTOR), and lowering insulin-like growth factor-1 (IGF-1) levels (14–17).

In epidemiologic investigations, use of metformin has been associated with lower cancer incidence in diabetic populations (18–20). In a meta-analysis including nearly 850,000 individuals with diabetes, metformin use as compared with non-use was associated with an 11% reduced risk of colorectal cancer (21). A number of epidemiologic investigations have found that metformin use is also associated with improved colorectal cancer outcomes (22–25). A meta-analysis of six epidemiologic studies, including roughly 2,400 diabetic patients with colorectal cancer reported a reduction in risk of overall and colorectal cancer–specific mortality of 44% and 34%, respectively, among ever-users of metformin (26). However, significant heterogeneity between studies was observed and not fully explored. Moreover, existing individual studies are limited by small numbers of patients with both diabetes and colorectal cancer, and lack information on diabetes severity, which is critical to account for potential confounding by indication, given known associations between diabetes and survival.

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Presentation: An earlier version of these data was presented as a Poster Highlights Session at the 2014 ASCO Annual Meeting in Chicago, IL.

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To address the challenges of sample size and potential confounding by indication, we examined the associations between diabetes, metformin use, and overall survival in the Veterans Affairs Central Cancer Registry (VACCR), which features information on diabetic severity and other predictors of colorectal cancer mortality, and includes nearly 5,000 patients with both colorectal cancer and diabetes.

Materials and Methods

Study population and data sources

This population-based retrospective study included patients diagnosed with colorectal cancer between January 1, 2001, and December 31, 2008. Data for this study were obtained from the national VACCR and the Veterans Affairs (VA) Corporate Data Warehouse (CDW). The VACCR contains all patients diagnosed with or treated for cancer in the VA (27) and was used to identify the cohort of patients diagnosed with colorectal cancer between 2001 and 2008 and provide data regarding patient demographics and characteristics, tumor characteristics, and primary treatment. Registry data were linked using scrambled social security numbers to several databases in the CDW, which was used to obtain pharmacy, diagnostic, laboratory, and vital status data. This study was approved by the Durham VA Institutional Review Board.

Assessment of type II diabetes mellitus

The primary exposures were diagnosis of type II diabetes mellitus and, among those with diabetes, administration of antidiabetes medication. Patients were defined as having type II diabetes mellitus based on having an appropriate ICD-9 code (250.x0 or 250.x2) between 6 and 15 months prior to the colorectal cancer diagnosis. This interval was chosen to identify patients likely to have a preexisting diabetes diagnosis. If patients had no diabetes care for more than a year (i.e., >15 months), then the relevance of the diagnosis may be questioned; if it was simultaneous (i.e., <6 months) with the diagnosis of colorectal cancer, then we would question the preexisting nature. Pharmacy data from the Decision Support System databases were used to identify patients receiving antidiabetic medication, including the drug name and date of dispensation. Antidiabetic medication use was defined as at least two fills within the 6 months before and after colorectal cancer diagnosis. We used a four-level categorical variable that classified patients as nondiabetic, diabetic with metformin use, diabetic with non-metformin use, and diabetic with no treatment.

Overall survival

The primary outcome was overall survival, based on death from any cause. Mortality was determined by the date of death in the VA Vital status file, which incorporates information from the VA, Medicare, and the Social Security Administration (28). Patient information was assessed from the diagnosis date until death or through December 31, 2014 (censor date).

Assessment of potential confounders

Clinical and demographic covariates assessed included patients' age at diagnosis, race (white, black, other, unknown), American Joint Committee on Cancer stage (29) at diagnosis (I, II, III, IV), body mass index (underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese ($\geq$30 kg/m^2), missing), smoking status (never, current, former, missing), comorbidity, colorectal cancer treatment, primary site (colon—including colon, cecum, and rectosigmoid junction vs. rectum) and hemoglobin A1c (HgA1c) and creatinine levels, providing surrogate information on diabetes severity. Comorbidity information was evaluated according to the Charlson comorbidity index (30), and we assessed diagnosis of each condition documented within 15 months prior to the colorectal cancer diagnosis date. To examine comorbidity burden, patients were further classified based on whether their comorbidity index was 0, 1–3, or greater than or equal to 4. Cardiovascular disease was specifically defined as diagnoses of coronary heart disease, stroke/cerebrovascular disease, hypertension, or heart failure. The VA laboratory database was used to obtain HgA1c and creatinine values closest to the colorectal cancer diagnosis date, up to 6 months after diagnosis. Primary cancer treatment was obtained from the VACCR and defined as treatment (none, surgery only, surgery + radiotherapy (RT), surgery + chemotherapy (CT), surgery + RT + CT, RT only, CT only, and CT + RT) within 4 months before to 6 months after colorectal cancer diagnosis.

Statistical analysis

Demographic and treatment characteristics of colorectal cancer cases were summarized using medians (with interquartile ranges), frequencies, and proportions, by diabetes and diabetes treatment status. Cox proportional hazards modeling was used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals for the associations between diabetes status, diabetes treatment, and overall survival. Multivariable models were developed based on *a priori* selection of possible confounders using clinical expertise and literature review to identify factors associated with colorectal cancer survival and likelihood of diabetic treatment regimen. Age, race, stage, smoking status, BMI, Charlson comorbidity index, and colorectal cancer treatment were included in all models, and HgA1c and creatinine were included in models of patients with diabetes. Stratified analyses were designated *a priori* based on plausible modifiers of the association between diabetes therapy and survival, and included stratification by BMI (normal weight, overweight/obese), primary cancer site (colon vs. rectum) and AJCC cancer stage (I, II, III, IV). The statistical significance of effect modification was tested by creating a cross product term between the stratification variable and diabetes therapy. Survival curves were obtained using the Kaplan–Meier method. All significance tests were two-sided and P values less than 0.05 were considered statistically significant. Analyses were conducted using SAS 9.2 (SAS Institute).

Results

Cohort clinical and demographic characteristics

The predominantly male (98%) study population included 16,309 nondiabetic and 4,983 diabetic colorectal cancer cases identified from the VACCR who were diagnosed with colorectal cancer between 2001 and 2008. Among the diabetic patients, there were 2,033 metformin users, 2,132 users of other diabetic medications, and 818 diabetic patients with no diabetic treatment within the 6 months before and after the date of colorectal cancer diagnosis. The median age at colorectal cancer diagnosis was 68.6, 67.9, 73.3, and 72.6 years for nondiabetic cases, metformin users, users of other diabetic medications, and those with no diabetic treatment, respectively (Table 1). Metformin users were more likely to be of white race and to have fewer comorbidities than the other two cohorts of diabetic patients. The median HgA1c

Table 1. Demographic and treatment characteristics of colorectal cancer cases by diabetes and diabetes treatment status

		Diabetic cases		
	Nondiabetic cases (*N* = 16,309)	**Metformin (*N* = 2,033)**	**Non-metformin treatment (*N* = 2,132)**	**No diabetic treatment (*N* = 818)**
Age at diagnosis (years)				
Median	68.6	67.9	73.3	72.6
IQR	17.1	14.0	14.3	14.5
Age category, *n* (%)				
<65	6,731 (41.3)	821 (40.4)	519 (24.3)	209 (25.5)
≥65	9,578 (58.7)	1,212 (59.6)	1,613 (75.7)	609 (74.4)
Sex, *n* (%)				
Female	341 (2.1)	33 (1.6)	27 (1.3)	15 (1.8)
Male	15,968 (97.9)	2,000 (98.4)	2,105 (98.7)	803 (98.2)
Race, *n* (%)				
Black	2,777 (17.0)	285 (14.0)	438 (20.5)	160 (19.6)
White	13,113 (80.4)	1,689 (83.1)	1,633 (76.6)	644 (78.6)
Other	161 (1.0)	21 (1.0)	33 (1.5)	9 (1.1)
Unknown	258 (1.6)	38 (1.9)	28 (1.3)	5 (0.7)
BMI (kg/m^2)				
Median	26.6	30.4	29.0	28.3
IQR	6.8	7.8	7.3	7.1
Category, %				
Underweight (<18.5)	492 (3.0)	11 (0.5)	26 (1.2)	11 (1.3)
Normal (18.5–24.9)	4,942 (30.3)	284 (14.0)	387 (18.1)	186 (22.7)
Overweight (25.0–29.9)	5,555 (34.1)	659 (32.4)	774 (36.3)	291 (35.6)
Obese (≥30)	4,019 (24.6)	1,066 (52.4)	924 (43.3)	304 (37.3)
Missing	1,301 (8.0)	13 (0.6)	21 (1.0)	26 (3.2)
Smoking status, *n* (%)				
Never smoked	3,494 (21.4)	533 (26.2)	539 (25.3)	232 (28.4)
Current smoker	4,713 (28.9)	408 (20.1)	387 (18.1)	156 (19.1)
Former smoker	5,866 (36.0)	833 (41.0)	883 (41.4)	299 (36.5)
Missing	2,236 (13.7)	259 (12.7)	323 (15.1)	131 (16.0)
AJCC cancer stage, *n* (%)				
I	4,289 (26.3)	635 (31.2)	605 (28.4)	246 (30.1)
II	4,394 (26.9)	559 (27.5)	611 (28.7)	203 (24.8)
III	4,017 (24.6)	509 (25.0)	540 (25.3)	186 (22.7)
IV	3,609 (22.1)	330 (16.2)	376 (17.6)	183 (22.4)
Comorbidities, *n* (%)[a]				
0	7,764 (47.6)	905 (44.5)	618 (29.0)	262 (32.0)
1–3	7,229 (44.3)	942 (46.3)	1,114 (52.2)	441 (54.1)
≥4	1,316 (8.1)	186 (9.2)	400 (18.7)	115 (14.0)
Cardiovascular disease[b], *n* (%)	10,123 (62.1)	1,812 (89.1)	1,943 (91.1)	720 (88.0)
Creatinine (mg/dL)				
Median		1.0	1.2	1.1
IQR		0.3	0.5	0.4
Category, %				
<1.1		1,074 (52.8)	681 (31.9)	373 (45.6)
≥1.1		887 (43.6)	1,373 (64.4)	406 (49.6)
Missing (%)		72 (3.5)	78 (3.7)	39 (4.8)
HgA1c (%)				
Median		6.9	6.8	6.2
IQR		1.5	1.5	1.2
Category, %				
<6.8		734 (36.1)	875 (41.0)	440 (53.7)
≥6.8		1,041 (51.2)	960 (45.0)	182 (22.2)
Missing		258 (12.7)	297 (14.0)	196 (24.0)
Cancer treatment, *n* (%)				
None	1,800 (11.0)	158 (7.7)	232 (11.0)	137 (16.8)
Surgery only	7,868 (48.2)	1,088 (53.5)	1,219 (57.2)	448 (54.6)
Surgery + RT	347 (2.1)	31 (1.5)	25 (1.2)	19 (2.3)
Surgery + CT	3,224 (19.8)	426 (20.9)	378 (17.7)	121 (14.9)
Surgery + RT + CT	1,200 (7.3)	142 (7.0)	101 (4.7)	28 (3.4)
RT	275 (1.7)	25 (1.2)	22 (1.0)	15 (1.8)
CT	835 (5.1)	90 (4.5)	79 (3.7)	32 (4.0)
CT + RT	760 (4.6)	73 (3.6)	76 (3.6)	18 (2.2)
Primary site				
Colon[c]	12,380 (75.9)	1,654 (81.4)	1,742 (81.7)	676 (82.6)
Rectum	3,929 (24.1)	379 (18.6)	390 (18.3)	142 (17.4)
Median survival time (mos), (IQR)	62.6 (86.0)	75.4 (73.3)	45.1 (81.1)	49.9 (88.1)
5-year overall survival, *N* (%)	7,974 (48.9)	1,107 (54.4)	837 (39.3)	344 (42.0)

[a]Based on the Charlson comorbidity index.

[b]Based on ICD-9 codes for coronary heart disease, stroke, cardiovascular disease, hypertension, and heart failure.

[c]Includes colon, cecum, and rectosigmoid junction.

Table 2. Diabetes treatment and overall survival in Cox proportional hazards models in patients with colorectal cancer

All patients ($N = 21,292$)						Diabetic patients ($N = 4,983$)				
Diabetes therapy	***N* deaths/total *N***	**Unadj HR (95% CI)**	***P***	**AHR[a] (95% CI)**	***P*[a]**	**Diabetes therapy**	**Unadj HR (95% CI)**	***P***	**AHR[b] (95% CI)**	***P*[b]**
No diabetes	10,647/16,309	1.00	Ref	1.00	Ref	Non-Metformin	1.00	Ref	1.00	Ref
Metformin	1,282/2,033	0.92 (0.87–0.97)	0.004	1.10 (1.03–1.17)	0.004	Metformin	0.70 (0.65–0.76)	<0.0001	0.87 (0.79–0.95)	0.003
Non-metformin	1,591/2,132	1.30 (1.23–1.37)	<0.0001	1.22 (1.15–1.29)	<0.0001	None	0.94 (0.85–1.03)	0.17	1.02 (0.90–1.15)	0.76
None	607/818	1.22 (1.13–1.33)	<0.0001	1.16 (1.06–1.27)	0.002					

[a]Adjusted for age (years), race (black, white, other, unknown), AJCC stage (I, II, III, IV), BMI (kg/m^2), comorbidity index (number), colorectal cancer treatment (none, surgery only, surgery + RT, surgery + CT, surgery + RT + CT RT, CT, CT + RT), and smoking status (current, former, never, missing).
[b]Adjusted for age (years), race (black, white, other, unknown), AJCC stage (I, II, III, IV), BMI (kg/m^2), comorbidity index (number), colorectal cancer treatment (none, surgery only, surgery + RT, surgery + CT, surgery + RT + CT RT, CT, CT + RT, smoking status (current, former, never, missing), HgA1c (%), and creatinine (mg/dL).

level for metformin users was 6.9%, compared with 6.8% for users of other diabetic medications and 6.2% for those with no diabetic medication use.

Diabetes status, diabetes treatments, and overall survival among colorectal cancer patients

In crude analysis, diabetic patients using treatments other than metformin or no diabetic treatment had a statistically significantly worse overall survival compared with nondiabetic patients ($P < 0.0001$ for both comparisons). However, patients using metformin did not have a significantly different survival rate than nondiabetics ($P = 0.09$; Kaplan–Meier curves presented in Supplementary Fig. S1, global log rank $P < 0.0001$). After adjustment for age, race, smoking status, AJCC cancer stage, BMI, comorbidity index, and colorectal cancer treatment, diabetics using metformin ($HR_{adj} = 1.10$; 95% CI, 1.03–1.17, $P = 0.004$) and diabetics using other medications (HR_{adj}=1.22; 95% CI, 1.15–1.29, $P < 0.0001$) had a statistically significantly worse overall survival compared with nondiabetics (Table 2). Among the 4,983 colorectal cancer patients with diabetes, metformin users had a significant 13% reduction in mortality compared with users of other diabetic medications (HR_{adj}= 0.87; 95% CI, 0.79–0.95, $P = 0.003$), after adjustment for HgA1c and creatinine, as well as age, race, smoking status, AJCC cancer stage, BMI, comorbidity index, and colorectal cancer treatment. Diabetics not using diabetic medications did not have a significantly different survival than diabetic users of other diabetic medications ($P = 0.76$).

Diabetes, diabetes treatments, and OS: subgroup analysis by AJCC stage

The association of diabetes status and diabetic treatments with overall survival among all colorectal cancer patients was significantly different depending on AJCC stage (Table 3, P for interaction <0.0001). Diabetic patients using metformin or other therapies had a significantly higher risk of death compared with nondiabetic patients in patients with stage I–III colorectal cancer, but not among patients with stage IV disease. In the subset of patients with diabetes, there was not a significant interaction between stage and diabetes treatment ($P = 0.99$).

Diabetes treatments and OS: subgroup analysis by BMI and primary site

The protective association between use of metformin and overall survival among diabetics was not modified by BMI (P for interaction = 0.98). Use of metformin was associated with improved survival in both normal weight ($HR_{adj} = 0.77$, 95% CI, 0.62–0.96, $P = 0.02$) and overweight or obese subjects ($HR_{adj} = 0.89$, 95% CI, 0.80–0.99, $P = 0.03$; see Supplementary Table S1). There was no significant interaction between diabetes therapy and primary site (colon vs. rectum; $P = 0.43$; see Supplementary Table S2).

Discussion

In an analysis of nearly 5,000 patients with colorectal cancer and diabetes, we found that the use of metformin is associated with improved survival relative to patients treated with other therapies for their diabetes, even after adjustment for possible confounding by indication. This analysis presents the largest epidemiologic study of the association between metformin use and survival among patients with diabetes and colorectal cancer and includes more patients than a recent meta-analysis aggregating data from individual studies (26). While it has been observed that diabetics with cancer have inferior outcomes compared with nondiabetics, the use of metformin is associated with a reduction in this survival disadvantage in the cohort of patients evaluated in this study. Diabetic patients taking metformin had only a 10% increase in mortality rate relative to nondiabetic patients with colorectal cancer, as compared with a 22% increase for those diabetics treated with diabetic therapies other than metformin.

One potential biological mechanism linking diabetes and colorectal cancer includes the state of insulin resistance/hyperinsulinemia, which stimulates the IGFR pathway and, in turn, may promote tumor cell proliferation and angiogenesis (31). Hyperglycemia itself and resulting oxidative stress, accumulation of advanced glycation end products, and chronic inflammation may enhance malignant transformation, cancer cell proliferation, metastasis, perineural invasion, and chemotherapy resistance, and inhibit apoptosis (32–35). Cancer has increased insulin–IGF-1 receptors, which may be associated with mitogenic signaling, and can be activated by insulin or insulin analogues (36, 37). The use of insulin, compared with non-insulin antidiabetic drugs, has been associated with increased risk of colorectal cancer in a meta-analysis of epidemiologic studies (38). There is less information on the role of the sulfonylurea family—drugs that block ATP-sensitive potassium channels in pancreatic beta cells to increase insulin release—on cancer cell growth, although there is some evidence that sulfonylurea receptors are associated with antitumor activity (39). Metformin acts through adenosine monophosphate-activated protein kinase (AMPK)/liver kinase B-1 (LKB1) pathway activation, but also inhibits the mammalian target of rapamycin (mTOR) and lowers IGF-1 levels, directly suppressing cell proliferation and indirectly reducing glucose and insulin levels (14, 15). These effects are particularly intriguing for colorectal cancer because Peutz–Jeghers

Table 3. Diabetes treatment and overall survival in Cox proportional hazards models in patients with colorectal cancer, by stage

All patients, stage I ($N = 5,775$)[a]						Diabetic patients, stage I ($N = 1,486$)[b]				
Diabetes therapy	N deaths/total N	Unadj HR (95% CI)	P	AHR[c] (95% CI)	P[c]	Diabetes therapy	Unadj HR (95% CI)	P	AHR[d] (95% CI)	P[d]
No diabetes	2,167/4,289	1.00	Ref	1.00	Ref	Non-metformin	1.00	Ref	1.00	Ref
Metformin	324/635	1.05 (0.94–1.18)	0.39	1.28 (1.13–1.46)	0.0002	Metformin	0.64 (0.56–0.75)	<0.0001	0.91 (0.76–1.10)	0.35
Non-metformin	401/605	1.63 (1.47–1.81)	<0.0001	1.33 (1.17–1.50)	<0.0001	None	0.85 (0.70–1.02)	0.0806	0.93 (0.72–1.19)	0.55
None	154/246	1.39 (1.18–1.64)	<0.0001	1.13 (0.94–1.36)	0.20					

All patients, stage II ($N = 5,767$)						Diabetic patients, stage II ($N = 1,373$)				
Diabetes therapy	N deaths/total N	Unadj HR (95% CI)	P	AHR[c] (95% CI)	P[c]	Diabetes therapy	Unadj HR (95% CI)	P	AHR[d] (95% CI)	P[d]
No diabetes	2,638/4,394	1.00	Ref	1.00	Ref	Non-metformin	1.00	Ref	1.00	Ref
Metformin	337/559	0.98 (0.88–1.10)	0.76	1.16 (1.02–1.31)	0.0235	Metformin	0.67 (0.58–0.78)	<0.0001	0.87 (0.73–1.04)	0.13
Non-metformin	443/611	1.45 (1.31–1.61)	<0.0001	1.36 (1.21–1.52)	<0.0001	None	0.87 (0.72–1.05)	0.15	1.03 (0.80–1.32)	0.84
None	147/203	1.27 (1.10–1.50)	0.0044	1.14 (0.94–1.38)	0.18					

All patients, stage III ($N = 5,252$)						Diabetic patients, stage III ($N = 1,235$)				
Diabetes therapy	N deaths/total N	Unadj HR (95% CI)	P	AHR[c] (95% CI)	P[c]	Diabetes therapy	Unadj HR (95% CI)	P	AHR[d] (95% CI)	P[d]
No diabetes	2,509/4,017	1.00	Ref	1.00	Ref	Non-metformin	1.00	Ref	1.00	Ref
Metformin	319/509	1.00 (0.89–1.12)	0.98	1.17 (1.03–1.33)	0.0171	Metformin	0.71 (0.61–0.83)	<0.0001	0.84 (0.70–1.00)	0.05
Non-metformin	398/540	1.40 (1.26–1.56)	<0.0001	1.33 (1.18–1.50)	<0.0001	None	0.87 (0.72–1.06)	0.18	0.97 (0.76–1.25)	0.82
None	136/186	1.22 (1.03–1.45)	0.024	1.14 (0.94–1.38)	0.17					

All patients, stage IV ($N = 4,498$)						Diabetic patients, stage IV ($N = 889$)				
Diabetes therapy	N deaths/total N	Unadj HR (95% CI)	P	AHR[c] (95% CI)	P[c]	Diabetes therapy	Unadj HR (95% CI)	P	AHR[d] (95% CI)	P[d]
No diabetes	3,333/3,609	1.00	Ref	1.00	Ref	Non-Metformin	1.00	Ref	1.00	Ref
Metformin	302/330	0.91 (0.81–1.02)	0.12	0.96 (0.84–1.10)	0.56	Metformin	0.79 (0.68–0.92)	0.0026	0.89 (0.73–1.08)	0.23
Non-metformin	349/379	1.17 (1.04–1.30)	0.007	1.05 (0.93–1.19)	0.42	None	1.09 (0.91–1.31)	0.34	1.10 (0.87–1.42)	0.40
None	170/183	1.28 (1.10–1.49)	0.002	1.20 (1.01–1.43)	0.04					

[a]Wald *P* value for metformin status*stage interaction term (adjusted for age, race, BMI, comorbidity, and colorectal cancer treatment) among all patients: <0.0001.
[b]Wald *P* value for metformin status*stage interaction term (adjusted for age, race, BMI, comorbidity, colorectal cancer treatment, HgA1c, and creatinine) among diabetic patients: 0.99.
[c]Adjusted for age, race, BMI, comorbidity index, colorectal cancer treatment, and smoking status.
[d]Adjusted for age, race, BMI, comorbidity index, colorectal cancer treatment, smoking status, HgA1c, and creatinine.

polyposis involves loss of *LKB1*, a tumor suppressor that also regulates *AMPK*. Metformin also appears to inhibit polyp formation and aberrant crypt foci (40–42).

Our results are concordant with several other epidemiologic investigations of the association between metformin use and survival among diabetic patients with colorectal cancer. Metformin use was significantly associated with lower overall and colorectal cancer–specific mortality in a cohort of patients with type II diabetes (43). In an analysis of women enrolled in the Women's Health Initiative randomized trial, metformin use was associated with a 22% reduction in colorectal cancer–specific mortality after propensity score adjustment, although this finding was not statistically significant (22). However, a recent cohort study including 382 colorectal cancer deaths and adjusting for time-related biases failed to find any relation between metformin use and colorectal cancer survival (44). Evidence synthesis techniques have been used to address the challenge of low numbers of cases of colorectal cancer among diabetic patients by combining published epidemiologic studies on the metformin–survival association (26, 45, 46). Although these investigations also support a beneficial effect of metformin use on survival among colorectal cancer patients, inference from these studies is limited by significant between-study heterogeneity that remains unexplained, as well as typical challenges of meta-analysis of aggregated data, including non-standardized exposure and outcome definitions and heterogeneous approaches for confounding control. The present study overcomes many of these limitations due to the large database and comprehensive clinical detail available.

Although disease-specific survival would be the ideal outcome measure to understand the anticancer potential of metformin in this population, this information is not readily available in the VA database. Overall survival was the only endpoint available at the time of this analysis, so observed treatment differences could represent residual and unmeasured confounding by diabetes treatment indications and contraindications, or the beneficial effect of improved glycemic control on diabetes-related complications and non-cancer death in users of metformin, rather than cancer-specific effects. However, our analyses are adjusted for a surrogate of glycemic control, HgA1c, as well as other variables related to diabetes status, including serum creatinine, body mass index, and other comorbidities. This allowed us to control for several possible mechanisms of confounding by indication and contraindication. Notably, the metformin-treated group was similar to the non–metformin-treated group with respect to HgA1c status and AJCC stage, while patients not receiving diabetic therapy may represent a relatively healthier user group, with a lower median HgA1c. Additionally, it is interesting that the strongest adjusted hazard ratio is observed in the population diagnosed with AJCC stage III colorectal cancer. This is a population that has greater potential survival benefit from a cancer-focused intervention compared with AJCC stage I or II disease, as the majority of patients with stage I and II disease are cured of their cancer with surgery. Survival of patients with AJCC stage IV

colorectal cancer, on the other hand, appears less influenced by diabetes in general, regardless of treatment. This may speak to the biologic timeframe by which diabetes, as well as potential intervention with metformin, may impact cancer, or reflect underlying differences in metformin responsiveness between colorectal cancer presenting as stage III compared with stage IV.

This study is limited by a lack of detailed information on intensity of metformin treatment in terms of dosage and duration of use, and we did not evaluate diabetic therapy as a time-dependent exposure or have direct measures of compliance with dispensed drug. Nonetheless, the possible misspecification and misclassification of exposure is not expected to differ depending on survival outcomes, given the prospective capture of information in VA data systems and the relative homogeneity of health care access and quality among U.S. veterans seeking cancer care within the VA system, so we expect misclassification to induce a bias toward the null that would underestimate the potential survival advantage associated with metformin use. The risk of time-related biases in pharmacoepidemiologic studies of metformin has received significant attention (47). While our approach to defining metformin exposure required documentation of two prescriptions, our investigation is less likely to be affected by this bias because our baseline was defined as cancer diagnosis (rather than prescription date), and exposure definitions were applied in the same way to both the metformin and the non–metformin-treated group, the primary comparison group of interest.

This study advances our understanding of the association between metformin and improved survival in diabetic colorectal cancer patients and adds to a foundation of evidence supporting the anticancer effects of metformin. Unlike insulin and sulfonoureas, metformin does not cause hypoglycemia in either patients with diabetes or normal subjects (48). Indeed, it has been used safely in polycystic ovary syndrome (49), non-alcoholic fatty liver disease (50), HIV lipodystrophy (51), and premature puberty (52). Several trials have been performed with metformin in nondiabetic patients with malignancies other than colorectal cancer with tolerable safety profile (53–59), while a combination of metformin with temsirolimus was not well tolerated (60). Metformin has been safely administered in a neoadjuvant colorectal cancer setting (61) and in combination with cytotoxic chemotherapy, including agents commonly used in colorectal cancer adjuvant settings (62), with a number of additional colorectal cancer studies under way. More definitive evidence of the potential clinical benefit of metformin in colorectal cancer will require evaluation using randomized controlled designs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.D. Williams, R.E. Martell

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