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Metformin use and survival after colorectal cancer: A population-based cohort study

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Preclinical evidence suggests that metformin could delay cancer progression. Previous epidemiological studies however have been limited by small sample sizes and certain time-related biases. This study aimed to investigate whether colorectal cancer patients with type 2 diabetes who were exposed to metformin had reduced cancer-specific mortality. We conducted a retrospective cohort study of 1,197 colorectal cancer patients newly diagnosed from 1998 to 2009 (identified from English cancer registries) with type 2 diabetes (based upon Clinical Practice Research Datalink, CPRD, prescription and diagnosis records). In this cohort 382 colorectal cancer-specific deaths occurred up to 2012 from the Office of National Statistics (ONS) mortality data. Metformin use was identified from CPRD prescription records. Using time-dependent Cox regression models, unadjusted and adjusted hazard ratios (HR) and 95% CIs were calculated for the association between post-diagnostic exposure to metformin and colorectal cancer-specific mortality. Overall, there was no evidence of an association between metformin use and cancer-specific death before or after adjustment for potential confounders (adjusted HR 1.06, 95% CI 0.80, 1.40). In addition, after adjustment for confounders, there was also no evidence of associations between other diabetic medications and cancer-specific mortality including sulfonylureas (HR 1.14, 95% CI 0.86, 1.51), insulin use (HR 1.35, 95% CI 0.95, 1.93) or other anti-diabetic medications including thiazolidinediones (HR 0.73, 95% CI 0.46, 1.14). Similar associations were observed by duration of use and for all-cause mortality. This population-based study, the largest to date, does not support a protective association between metformin and survival in colorectal cancer patients.

Despite advances in surgical techniques and adjuvant therapies, colorectal cancer remains the third leading cause of cancer death.[1] Preclinical evidence suggests a beneficial role for metformin, a first-line oral anti-diabetic agent, in colorectal cancer progression.[2–4] Although not fully elucidated, the potential anti-tumour effects of metformin are thought to be due to inhibition of the mammalian target of rapamycin (mTOR) signalling pathway, resulting in suppression of cellular proliferation[5] tumour cell migration and invasion[6] as well as an increase in apoptosis.[7]

Despite mounting preclinical evidence supporting a possible therapeutic role for metformin in colorectal cancer, only two epidemiological studies have evaluated the impact of post-diagnostic metformin exposure on cancer outcomes in colorectal cancer patients with type 2 diabetes. A Korean study of 595 colorectal cancer patients with type 2 diabetes reported substantial reductions in risk of colorectal cancer-specific and all-cause mortality among metformin users after diagnosis.[8] However, individuals in this study were improperly classified as exposed to metformin in the period from cohort entry to first metformin prescription and therefore these findings have been attributed to immortal time bias.[9] A Singaporean study among 344 colorectal cancer patients with diabetes detected marked improvements in recurrence-free survival (HR 0.63, 95% CI 0.41, 0.96) and overall survival (HR 0.23, 95% CI 0.15-0.35) in those exposed to metformin at diagnosis.[10] These epidemiological studies were subject to a number of limitations including small sample sizes (*e.g.*, 99 colorectal cancer relapses[10] and 159 colorectal cancer deaths[8]), medication use determined at one time-point[8] and no report of dose-response associations.[8,10] Other

Key words: metformin, colorectal cancer survival, type 2 diabetes, pharmacoepidemiology

Abbreviations: BMI: body mass index; CIs: confidence intervals; CPRD: clinical practice research datalink; DDD: daily defined dose; GP: general practitioner; HR: hazard ratio; ICD: international classification of diseases; NCDR: national cancer data repository; ONS: office of national statistics; OR: odds ratio; UK: United Kingdom

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What's new?

Preclinical evidence suggests that metformin, a first-line oral anti-diabetic agent, can delay colorectal cancer progression. Previous epidemiological studies however have been limited by small sample sizes and certain time-related biases. Here, the authors set to determine whether colorectal cancer patients with type 2 diabetes who were exposed to metformin after cancer diagnosis had reduced cancer-specific mortality. In the largest cohort study to date, the authors did not observe a protective association between metformin use and colorectal cancer mortality. These findings will help inform the decision whether to conduct randomised controlled trials of metformin as an adjunct treatment in colorectal cancer.

epidemiological studies[11,12] have investigated metformin and all-cause mortality only, however, this could reflect non-cancer related mortality. Additional epidemiological studies[12] have compared cancer outcomes in metformin users with non-metformin users without restricting to type 2 diabetes patients but this will introduce confounding as colorectal cancer patients with Type 2 diabetes are known to have different cancer-specific and all-cause mortality to patients without diabetes.[13] A number of clinical trials of metformin in colorectal cancer patients are ongoing[14–17] however they primarily focus on metformin in combination with chemotherapeutic regimens in patients with advanced disease and are early phase so will not report upon efficacy. Therefore, there is a need for well-designed observational studies to inform the decision to conduct large scale clinical trials of the effect of metformin on cancer progression in colorectal cancer patients.

We carried out a large population-based study to determine whether colorectal cancer patients with type 2 diabetes who were exposed to metformin after cancer diagnosis had reduced cancer-specific mortality. The associations for other anti-diabetic medications were also investigated.

Material and Methods

Data sources

A cohort study was conducted utilising recent linkages between the National Cancer Data Repository (NCDR), the UK Clinical Practice Research Datalink (CPRD) and the Office of National Statistics (ONS) death registrations. NCDR data was available containing all cancer patients diagnosed in England, including the date and site of primary cancer diagnoses, tumour characteristics (stage and grade) and cancer treatments received. The CPRD is the world's largest computerised dataset of anonymised longitudinal primary care records covering approximately 7% of the United Kingdom population. It contains high quality, individual patient-level information on demographics, clinical diagnoses and prescriptions issued.[18,19] ONS death registrations provide details on date and cause of death up to January 2012. Ethical approval for all observational studies conducted using CPRD data has been obtained from a multicenter research ethics committee.

Study design

Patients with newly diagnosed colorectal cancer (including ICD codes C18 for colon and C19/C20 for rectum) who had a prior diagnosis of type 2 diabetes were identified for inclusion. Individuals were classified as having diabetes if they had a general practitioner (GP) recorded diagnosis of diabetes or had at least one anti-diabetic medication prescription prior to colorectal cancer diagnosis. Patients with type 1 diabetes were excluded from the cohort and were defined as those with a GP-recorded diagnosis for type 1 diabetes in addition to at least one prescription for insulin before their cancer diagnosis. With the exception of *in situ* neoplasms and non-melanoma skin cancers, patients with a previous NCDR cancer diagnosis were removed. Patients were also omitted if their diagnosis date preceded CPRD research quality records or if death registration records were unavailable. Colorectal cancer-specific deaths based on the underlying cause of death were identified using the ICD-10 cause of death codes C18, C19, C20, C21, or C26. Short-term post-diagnostic medication usage is unlikely to exert an influence on cancer death; hence, patients who died within the first 6 months after cancer diagnosis were excluded. Patients were followed up from 6 months after colorectal cancer diagnosis until death, end of registration with the general practice, last date of data collection from general practice, or end of ONS follow-up.

Exposure data

Data on post-diagnostic anti-diabetic medication usage was determined from GP prescribing records contained within the CPRD according to the British National Formulary (BNF)[20] including metformin (section 6.1.2.2), sulfonylureas (section 6.1.2.1), insulin (section 6.1.1) or other anti-diabetic medications (including thiazolidinediones) (section 6.1.2.3). Anti-diabetic medications were classified according to the number of prescriptions received in addition to defined daily doses (DDD), as defined by the WHO.[21] Medications were treated as time-varying covariates, to avoid immortal time bias.[22] Medication usage was lagged by 6 months, to remove prescriptions in the last 6 months prior to death as these may reflect changes due to end-of-life treatment. Consequently, patients were considered to be unexposed from 6 months after diagnosis until 6 months after their first prescription and then considered exposed thereafter. To investigate dose-response associations, analyses were carried out in

which patients were considered as non-users prior to 6 months after their first prescription, short term after 6 months after their first prescription and longer term users from 6 months after their 12th prescription (or 365th DDD).

Covariates

Clinical information on colorectal cancer stage and grade were taken from NCDR, in addition to data on cancer treatments received within the 6 months after cancer diagnosis including surgery, chemotherapy and radiotherapy. Smoking, alcohol and BMI status was also available and derived from the closest GP records within 10 years prior to colorectal cancer diagnosis. Comorbidities prior to colorectal cancer diagnosis were extracted from GP-recorded clinical diagnoses and were based on the comorbidity codes included in a recent adaptation of the Charlson Comorbidity index for GPRD.[23] A measure of socioeconomic status was obtained from deprivation measures within CPRD records which were based on residential postcodes (using the 2004 index of multiple deprivations for England).[24] Other medications (including low-dose aspirin and statins) were extracted from GP prescription records. Haemoglobin A_{1c} (HbA1c) levels in the year prior to diagnosis were obtained from GP records.

Data analysis

Cox regression models were used to produce hazard ratios (HRs) and 95% confidence intervals (CI) for post-diagnostic drug use and colorectal cancer mortality. As previously described, drug use was treated as a time-varying covariate with metformin users not considered to be exposed until 6 months after their first prescription. Similar analysis was carried out for sulfonylureas, insulin and other anti-diabetic medications (including thiazolidinediones). Analyses were conducted for metformin and sulfonylureas by number of prescriptions and number of DDDs and repeated for all-cause mortality for all anti-diabetic medications. All models were adjusted for potential confounders which were available for the whole cohort including year of cancer diagnosis (in 2-year bands), age (continuous), sex (male or female), site (colon or rectal), deprivation (in fifths) surgery (yes or no), radiotherapy (yes or no), chemotherapy (yes or no), comorbidities (yes or no) and other post-diagnosis medication usage (yes or no), including low-dose aspirin and statins which were treated as time-varying covariates. Separate analyses were carried out which additionally controlled for colorectal cancer stage at diagnosis among individuals with available data. Subgroup analyses were performed by site (colon or rectal), sex (male or female), stage (I–III, IV), pre-diagnosis drug use (yes or no), BMI ($\leq$25 kg m^{-2} or $>$25 kg m^{-2}), HbA1c level in the year prior to diagnosis ($\leq$6.5% or $>$6.5%) and length of minimum follow-up ($\geq$5 years or $<$5 years). Tests for interactions were performed for each sub-group analysis using interaction terms within the Cox regression. We also conducted a number of sensitivity analyses. The lag was increased from 6 months to 1 and 2 years, a longer duration of drug exposure was investigated and analyses additionally adjusting for BMI, pre-diagnostic drug use, grade and smoking and diabetes duration were carried out. An analysis was conducted excluding patients who died within 3 months of their diagnosis (correspondingly the lag was reduced to 3 months to prevent immortal time bias[22]) and a simplified analysis was conducted assessing the impact of anti-diabetic drug use in the first year after colorectal cancer diagnosis compared to non-use among patients who survived at least 1 year after. Using this design, an analysis was conducted imputing stage. First, an ordinal logistic regression model was used to impute stage with explanatory variables including death status and cumulative hazard (as recommended[25]), along with all confounders mentioned above but with medication use restricted to the first year after diagnosis. Ten imputations were conducted and results were combined using Rubin's rules.[26] To verify the robustness of results, the entire cohort was converted to case-control data to carry out a nested case-control analysis (Supporting Information Table 2). Based upon the observed cohort size (1,200), the number of cancer-specific deaths (380) and 50% metformin usage, the study would have over 80% power to detect as statistically significant a HR of 0.75, using a method based upon the log rank test[27] implemented in STATA 11 (StataCorp, College Station, TX).

Results

Patient cohort

A total of 15,353 colorectal cancer patients were identified during the study period. Of these, 130 were excluded as they were type 1 diabetic and a further 3,628 were excluded as they died within 6 months after cancer diagnosis. In the final cohort, 1,197 colorectal cancer patients were identified as having a prior diagnosis of type 2 diabetes. Average follow-up from diagnosis in the study cohort was 4 years and ranged from 6 months to 14 years. Absolute 3- and 5-year survival for the whole cohort was 74 and 54%, respectively. Patient characteristics by metformin and sulfonylureas use are shown in Table 1. Users of metformin were more likely to have been diagnosed more recently, be younger at diagnosis and to have a higher BMI. Stage and grade were generally similar between metformin users and non-users however a slightly smaller proportion of users had stage 4 disease (3.7% versus 8.4% stage IV). Metformin users were also less likely to have certain comorbid conditions including congestive heart disease (6.8% versus 10.7%), myocardial infarction (6.7% versus 13.2%) and peripheral vascular disease (7% versus 10.3%). Use of other medications was more prevalent among metformin users such as low-dose aspirin and statins, sulfonylureas and other antidiabetic medications (including thiazolidinediones). Users of metformin were also more likely to have higher HbA1c levels in the year prior to diagnosis. A similar distribution of characteristics was observed between users and non-users of sulfonylureas. However, users were less likely to receive chemotherapy after diagnosis and

Table 1. Characteristics of colorectal patients with type 2 diabetes before cancer diagnosis by metformin and sulfonylurea use after diagnosis

Characteristics	Total	Metformin use after diagnosis		Sulfonylurea use after diagnosis	
		Ever n (%)	Never n (%)	Ever n (%)	Never n (%)
	(n = 1,197)	*(n = 675)*	*(n = 522)*	*(n = 617)*	*(n = 580)*
Year of diagnosis					
1998–2000	129 (10.8)	67 (9.9)	62 (11.9)	85 (13.8)	44 (7.6)
2001–2003	256 (21.2)	130 (19.3)	126 (24.1)	155 (25.1)	101 (17.4)
2004–2006	364 (30.4)	205 (30.4)	159 (30.5)	174 (28.2)	190 (32.8)
2007–2009	448 (37.4)	273 (40.4)	175 (33.5)	203 (32.9)	245 (42.2)
Age at diagnosis					
<50	11 (0.9)	5 (0.7)	6 (1.6)	4 (0.7)	7 (1.2)
50–59	90 (7.5)	66 (9.8)	24 (4.6)	50 (8.1)	40 (6.9)
60–69	307 (25.7)	203 (30.1)	104 (19.9)	164 (26.6)	143 (24.7)
70–79	528 (44.1)	293 (43.4)	235 (45.0)	276 (44.7)	252 (43.5)
80–89	244 (20.4)	104 (15.4)	140 (26.8)	118 (19.1)	126 (21.7)
≥ 90	17 (1.4)	4 (0.6)	13 (2.5)	5 (0.8)	12 (2.1)
Gender					
Males	759 (63.4)	437 (64.7)	322 (61.7)	400 (64.8)	359 (61.9)
Stage					
I	156 (13.0)	95 (14.1)	61 (11.7)	9 (14.6)	66 (11.4)
II	328 (27.4)	198 (29.3)	130 (24.9)	183 (29.7)	145 (25.0)
III	366 (30.6)	219 (32.4)	147 (28.2)	177 (28.7)	189 (32.6)
IV	69 (5.8)	25 (3.7)	44 (8.4)	26 (4.2)	43 (7.4)
Missing	278 (23.2)	138 (20.4)	140 (26.8)	141 (22.9)	137 (23.6)
Grade					
Well	56 (4.7)	42 (6.2)	14 (2.7)	34 (5.5)	22 (3.8)
Moderately	803 (67.1)	461 (68.3)	342 (65.5)	424 (68.7)	379 (65.3)
Poorly	148 (12.4)	87 (12.9)	61 (11.7)	69 (11.2)	79 (13.6)
Missing	190 (15.9)	85 (12.6)	105 (20.1)	90 (14.6)	100 (17.2)
Treatment within 6 months of cancer diagnosis					
Surgery	1,008 (84.2)	599 (88.7)	409 (78.4)	531 (86.1)	477 (82.2)
Chemotherapy	318 (26.6)	189 (28.0)	129 (24.7)	140 (22.7)	178 (30.7)
Radiotherapy	168 (14.0)	101 (15.0)	67 (12.8)	94 (15.2)	74 (12.8)
Smoking status prior to cancer diagnosis					
Non-smoker	520 (43.4)	288 (42.7)	232 (44.4)	271 (43.9)	249 (42.9)
Ex-smoker	494 (41.3)	294 (43.6)	200 (38.3)	245 (39.7)	249 (42.9)
Current smoker	107 (8.9)	54 (8.0)	53 (10.2)	57 (9.2)	50 (8.6)
Missing	76 (6.4)	39 (5.8)	37 (7.1)	44 (7.1)	32 (5.5)
Alcohol consumption prior to diagnosis					
Never	227 (19.0)	125 (18.5)	102 (19.5)	112 (18.2)	115 (19.8)
Ever	853 (71.3)	483 (71.6)	370 (70.9)	440 (71.3)	413 (71.2)
Missing	117 (9.8)	67 (9.9)	50 (9.6)	65 (10.5)	52 (9.0)
BMI (kg m^{-2}) prior to diagnosis					
Mean (SD)	29 (5.0)	29 (4.9)	28 (5.0)	29 (5.0)	28 (5.1)
Underweight (<18.5)	12 (1.0)	0 (0)	12 (2.3)	2 (0.3)	10 (1.7)

Table 1. Characteristics of colorectal patients with type 2 diabetes before cancer diagnosis by metformin and sulfonylurea use after diagnosis (Continued)

		Metformin use after diagnosis		Sulfonylurea use after diagnosis	
Characteristics	**Total**	**Ever n (%)**	**Never n (%)**	**Ever n (%)**	**Never n (%)**
Normal (18.5–25)	246 (20.6)	111 (16.4)	135 (25.9)	129 (20.9)	117 (20.2)
Overweight (25–30)	490 (40.9)	280 (41.5)	210 (40.2)	235 (38.1)	255 (44.0)
Obese (>30)	388 (32.4)	255 (37.8)	133 (25.5)	215 (34.9)	173 (29.8)
Missing	61 (5.1)	32 (6.1)	32 (6.1)	36 (5.8)	25 (4.3)
Deprivation fifth:					
1st (least deprived)	235 (19.6)	132 (19.6)	103 (19.7)	111 (18.0)	124 (21.4)
2nd	283 (23.6)	150 (22.2)	133 (25.5)	140 (22.7)	143 (24.7)
3rd	260 (21.7)	158 (23.4)	102 (19.5)	135 (21.9)	125 (21.6)
4th	246 (20.1)	136 (20.2)	110 (21.1)	126 (20.4)	120 (20.7)
5th (most deprived)	172 (14.4)	98 (14.5)	74 (14.2)	105 (17.0)	105 (17.0)
Missing	1 (0.1)	1 (0.2)	0 (0)	0 (0)	1 (0.2)
Comorbidity prior to cancer diagnosis					
Cerebrovascular disease	118 (9.9)	58 (8.6)	60 (11.5)	67 (10.9)	51 (8.8)
Chronic pulmonary disease	192 (16.0)	110 (16.3)	82 (15.7)	94 (15.2)	98 (16.9)
Congestive heart disease	102 (8.5)	46 (6.8)	56 (10.7)	54 (8.8)	48 (8.3)
Myocardial infarction	114 (9.5)	69 (6.7)	69 (13.2)	53 (8.6)	61 (10.5)
Peptic ulcer disease	75 (6.3)	43 (6.4)	32 (6.1)	42 (6.8)	33 (5.7)
Peripheral vascular disease	101 (8.4)	47 (7.0)	54 (10.3)	50 (8.1)	51 (8.8)
Renal disease	150 (12.5)	74 (14.2)	76 (11.3)	70 (11.4)	80 (13.8)
Medication after diagnosis					
Low-dose aspirin[1]	651 (54.4)	405 (60.0)	246 (47.1)	348 (56.4)	303 (52.2)
Statins[1]	805 (67.3)	466 (69.0)	235 (45.0)	413 (66.9)	288 (49.7)
Anti-diabetic medication after diagnosis					
Metformin[1]	675 (100)	675 (100)	0 (0)	426 (69.0)	249 (42.9)
Sulfonylureas[1]	617 (51.6)	426 (63.1)	191 (36.6)	617 (100)	0(0)
Insulin[1]	225 (18.8)	139 (20.6)	86 (16.5)	99 (16.1)	126 (21.7)
Other ADDs[1]	219 (18.3)	187 (27.7)	32 (6.1)	173 (28.0)	46 (7.9)
HbA1c level in year prior to diagnosis					
Mean % (SD)	13 (16.7)	15 (0.7)	11 (0.7)	14 (0.8)	12 (0.7)
≤6.5%	334 (27.9)	146 (21.6)	188 (36.0)	140 (22.7)	194 (33.5)
>6.5%	729 (60.9)	491 (72.7)	238 (45.6)	445 (72.1)	284 (49.0)
Missing	134 (11.2)	38 (5.6)	96 (18.4)	32 (5.2)	102 (17.6)

[1]After diagnosis in exposure period.
ADD = anti-diabetic drug

comorbidities generally appeared to be similar between the groups. Patient characteristics of users of insulin and other anti-diabetic medications are listed in Supporting Information Table 1.

Association between metformin use and survival

Associations between anti-diabetic medications and colorectal cancer-specific mortality are shown in Table 2. Compared with non-users, metformin use was not associated with colorectal cancer-specific mortality (HR 0.83, 95% CI 0.67, 1.02) and after adjustment for potential confounders, the association was further attenuated (adjusted HR 1.06, 95% CI 0.80, 1.40). There was no evidence of a dose-response relationship between colorectal cancer-specific mortality and metformin use by increasing number of prescriptions and increasing DDDs. There was also no evidence of association between

Table 2. Association between anti-diabetic medication usage and cancer mortality in colorectal patients with type 2 diabetes before cancer diagnosis

Medication usage after diagnosis	Cancer-specific mortality	All patients	Person years	Unadjusted HR (95%CI)	p	Adjusted[1] HR (95%CI)	p	Fully adjusted[2] HR (95%CI)	p
Number of patients				*(1,197)*		*(1,197)*		*(919)*	
Metformin									
Metformin non-user	221	522	1,872	1.00		1.00		1.00	
Metformin user[3]	161	675	2,193	0.83 (0.67, 1.02)	0.07	1.06 (0.85, 1.33)	0.59	1.06 (0.80, 1.40)	0.68
Metformin non-user	221	522	1,872	1.00		1.00		1.00	
Metformin user 1-11 prescriptions[4]	95	226	947	0.78 (0.61, 0.99)	0.04	1.01 (0.78, 1.31)	0.94	0.94 (0.68, 1.30)	0.69
Metformin user ≥12 prescriptions[4]	66	449	1,246	0.93 (0.68, 1.28)	0.66	1.19 (0.86, 1.66)	0.30	1.22 (0.83, 1.78)	0.31
Metformin non-user	221	522	1,872	1.00		1.00		1.00	
Metformin user 1-365 DDDs[4]	107	270	1,056	0.84 (0.66, 1.06)	0.13	1.09 (0.85, 1.39)	0.52	0.97 (0.71, 1.32)	0.85
Metformin user ≥365 DDDs[4]	54	405	1,138	0.80 (0.58, 1.12)	0.20	1.01 (0.71, 1.44)	0.94	1.18 (0.79, 1.77)	0.42
Sulfonylureas									
Sulfonylurea non-user	219	580	1,986	1.00		1.00		1.00	
Sulfonylurea user[3]	163	617	2,080	0.97 (0.79, 1.19)	0.76	0.98 (0.78, 1.23)	0.88	1.14 (0.86, 1.51)	0.37
Sulfonylurea non-user	219	580	1,986	1.00		1.00		1.00	
Sulfonylurea user 1-11 prescriptions[4]	100	210	781	1.01 (0.79, 1.28)	0.95	1.01 (0.78, 1.31)	0.93	1.21 (0.89, 1.66)	0.23
Sulfonylurea user ≥12 prescriptions[4]	63	407	1300	0.90 (0.65, 1.23)	0.50	0.91 (0.66, 1.27)	0.59	0.96 (0.64, 1.44)	0.84
Sulfonylurea non-user	219	580	1,986	1.00		1.00		1.00	
Sulfonylurea user 1-365 DDDs[4]	64	133	465	1.03 (0.77, 1.36)	0.86	1.03 (0.77, 1.38)	0.85	1.28 (0.89, 1.83)	0.19
Sulfonylurea user ≥365 DDDs[4]	99	484	1,615	0.93 (0.72, 1.20)	0.57	0.93 (0.71, 1.23)	0.62	1.01 (0.73, 1.42)	0.93
Insulin									
Insulin non-user	321	972	3,480	1.00		1.00		1.00	
Insulin user[3]	61	225	286	1.32 (1.00, 1.74)	0.05	1.28 (0.95, 1.71)	0.10	1.35 (0.95, 1.93)	0.10
Other ADDs									
Other ADD non-user	354	978	3,393	1.00		1.00		1.00	
Other ADD user[3]	28	219	673	0.59 (0.40, 0.87)	0.01	0.68 (0.45, 1.02)	0.06	0.73 (0.46, 1.14)	0.17

[1]Adjusted for gender, year of diagnosis, age at diagnosis, deprivation (in fifths), site (colon or rectum), surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, comorbidities (prior to diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease), other anti-diabetic medication usage (after diagnosis, as time varying covariates, including metformin, sulfonylureas, insulin and other ADDs) and other medication usage (after diagnosis, as time varying covariates, including low dose aspirin and statins).
[2]Adjusted for all variables in "[1]", additionally adjusted for cancer stage in individuals with non-missing values.
[3]Medication use modeled as a time varying covariate. An individual was considered a nonuser prior to 6 months after first medication usage and a user after this time, excludes deaths in the 6 months after cancer diagnosis.
[4]Medication use modeled as a time varying covariate. An individual was considered a nonuser prior to 6 months after first medication usage, a short-term user from 6 months after first prescription to 6 months after the 12th prescription (or 365 DDDs), and a longer-term user after this time, excludes deaths in the 6 months after cancer diagnosis.
ADD = Anti-diabetic drug.

Table 3. Association between anti-diabetic medication usage and death from any cause in colorectal patients with type 2 diabetes before cancer diagnosis

Medication usage after diagnosis	Cancer-specific mortality	All patients	Person years	Unadjusted HR (95%CI)	*p*	Adjusted[1]HR (95%CI)	*p*	Fully adjusted[2] HR (95%CI)	*p*
Number of patients				*(1,197)*		*(1,197)*		*(919)*	
Metformin									
Metformin non-user	307	522	1,872	1.00		1.00		1.00	
Metformin user[3]	259	675	2,193	0.82 (0.69, 0.98)	0.03	1.05 (0.87, 1.27)	0.61	1.03 (0.83, 1.29)	0.79
Metformin non, user	307	522	1,872	1.00		1.00		1.00	
Metformin user 1-11 prescriptions[4]	132	226	947	0.81 (0.66, 1.00)	0.05	1.04 (0.83, 1.30)	0.73	1.00 (0.76, 1.30)	0.97
Metformin user ≥12 prescriptions[4]	127	449	1,246	0.84 (0.67, 1.06)	0.15	1.05 (0.82, 1.35)	0.68	1.06 (0.80, 1.40)	0.69
Metformin non-user	307	522	1,872	1.00		1.00		1.00	
Metformin user 1-365 DDDs[3]	151	270	1,055	0.86 (0.71, 1.05)	0.15	1.09 (0.89, 1.35)	0.39	1.01 (0.79, 1.31)	0.91
Metformin user ≥365 DDDs[3]	108	405	1,138	0.76 (0.59, 0.97)	0.03	0.96 (0.74, 1.24)	0.74	1.04 (0.77, 1.40)	0.79
Sulfonylureas									
Sulfonylurea non-user	294	580	1,986	1.00		1.00		1.00	
Sulfonylurea user[3]	272	617	2,080	1.03 (0.87, 1.22)	0.74	1.05 (0.87, 1.26)	0.64	1.22 (0.98, 1.52)	0.08
Sulfonylurea non, user	294	580	1,986	1.00		1.00		1.00	
Sulfonylurea user 1-11 prescriptions[3]	132	210	781	1.06 (0.86, 1.30)	0.60	1.08 (0.86, 1.34)	0.51	1.30 (1.00, 1.69)	0.05
Sulfonylurea user ≥12 prescriptions[3]	140	407	1,300	1.00 (0.79, 1.26)	0.97	1.00 (0.78, 1.27)	0.99	1.10 (0.83, 1.47)	0.50
Sulfonylurea non, user	294	580	1,986	1.00		1.00		1.00	
Sulfonylurea user 1-365 DDDs[3]	86	133	465	1.11 (0.87, 1.42)	0.41	1.12 (0.87, 1.44)	0.38	1.39 (1.03, 1.88)	0.03
Sulfonylurea user ≥365 DDDs[3]	186	484	1,615	0.99 (0.81, 1.21)	0.90	1.00 (0.81, 1.24)	0.99	1.12 (0.87, 1.44)	0.38
Insulin									
Insulin non-user	460	972	3,480	1.00		1.00		1.00	
Insulin user[3]	106	225	586	1.49 (1.21, 1.85)	<0.001	1.31 (1.04, 1.66)	0.02	1.50 (1.14, 1.97)	<0.01
Other ADDs									
Other ADD non-user	504	978	3,393	1.00		1.00		1.00	
Other ADD user[3]	62	219	673	0.72 (0.55, 0.95)	0.02	0.87 (0.65, 1.15)	0.32	0.89 (0.65, 1.22)	0.48

[1]Adjusted for gender, year of diagnosis, age at diagnosis, deprivation (in fifths), site (colon or rectum), surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, comorbidities (prior to diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease), other anti-diabetic medication usage (after diagnosis, as time varying covariates, including metformin, sulfonylureas, insulin and other ADDs) and other medication usage (after diagnosis, as time varying covariates, including low dose aspirin and statins).
[2]Adjusted for all variables in "[1]," additionally adjusted for cancer stage in individuals with non-missing values.
[3]Medication use modelled as a time varying covariate. An individual was considered a nonuser prior to 6 months after first medication usage and a user after this time, excludes deaths in the 6 months after cancer diagnosis.
ADD = Anti-diabetic drug.

Table 4. Sensitivity analyses for association between metformin and sulfonylurea use and cancer-specific mortality in colorectal patients with type 2 diabetes before cancer diagnosis

				Metformin			Sulfonylureas		
Analysis	Cancer-specific deaths (*n*)	All patients (*n*)	Person years	Adjusted[1] HR (95%CI)	*p*	*p* for interaction	Adjusted[1] HR (95%CI)	*p*	*p* for interaction
Main analysis: ADD user versus non-user after diagnosis	260	919	3,313	1.06 (0.80, 1.40)	0.68		1.14 (0.86, 1.51)	0.37	
Sub group analyses: ADD user versus non-user after diagnosis, restricted to:									
Colon cancer patients	174	638	2,264	1.00 (0.70, 1.41)	0.98	0.25	1.25 (0.89, 1.76)	0.19	0.90
Rectal cancer patients (inc. rectosigmoid junct.)	86	281	1,049	1.26 (0.73, 2.19)	0.41		0.82 (0.48, 1.40)	0.46	
Males	180	594	2,093	1.09 (0.77, 1.54)	0.63	0.20	1.19 (0.84, 1.69)	0.34	0.89
Females	80	325	1,220	0.78 (0.45, 1.34)	0.37		1.26 (0.74, 2.13)	0.40	
Stages I,II, III	200	850	3,239	1.00 (0.73, 1.37)	0.99	0.18	1.15 (0.84, 1.58)	0.39	0.79
Stage IV	60	68	71	2.64 (1.16, 6.00)	0.02		0.78 (0.33, 1.83)	0.57	
Pre-diagnosis ADD use non-users[2]	127	427	1,636	1.24 (0.71, 2.20)	0.45	0.16	1.05 (0.68, 1.61)	0.84	0.37
Pre-diagnosis ADD users[2]	109	420	1,365	0.82 (0.46, 1.46)	0.50		1.17 (0.72, 1.90)	0.51	
BMI before diagnosis, $\leq$25 kg m^{-2}	50	205	768	0.60 (0.28, 1.29)	0.19	0.05	0.71 (0.31, 1.61)	0.42	0.11
BMI before diagnosis, $>$25 kg m^{-2}	210	714	2,546	1.15 (0.84, 1.58)	0.39		1.23 (0.90, 1.68)	0.20	
HbA1c $\leq$6.5%[3]	85	288	1,007	1.24 (0.73, 2.09)	0.42	0.72	0.59 (0.33, 1.07)	0.08	0.02
HbA1c $>$6.5%[3]	175	631	2,306	0.89 (0.60, 1.31)	0.54		1.53 (1.04, 2.24)	0.03	
$\geq$5 years follow-up after diagnosis	19	288	728	2.26 (0.60, 8.49)	0.23		2.54 (0.65, 9.95)	0.18	
$<$5 years follow-up after diagnosis	241	919	2,583	1.05 (0.78, 1.40)	0.76		1.09 (0.81, 1.46)	0.57	
Sensitivity analyses: ADD user versus non-user after diagnosis									
Increasing lag to 1 year[4]	190	821	3,289	1.14 (0.82, 1.58)	0.43		0.99 (0.71, 1.38)	0.96	
Increasing lag to 2 years[5]	105	697	2,119	1.46 (0.96, 2.24)	0.08		1.02 (0.65, 1.60)	0.93	
BMI prior to diagnosis available (and adjusted for)[6]	244	884	3,181	1.05 (0.78, 1.40)	0.76		1.14 (0.85, 1.52)	0.38	
Smoking prior to diagnosis available (and adjusted for)[7]	241	862	3,057	1.09 (0.82, 1.47)	0.55		1.12 (0.83, 1.50)	0.46	
Grade prior to diagnosis available (and adjusted for)[8]	226	842	3,092	1.03 (0.77, 1.40)	0.82		1.21 (0.90, 1.64)	0.21	

Table 4. Sensitivity analyses for association between metformin and sulfonylurea use and cancer-specific mortality in colorectal patients with type 2 diabetes before cancer diagnosis (Continued)

				Metformin			Sulfonylureas		
Analysis	Cancer-specific deaths (*n*)	All patients (*n*)	Person years	Adjusted[1] HR (95%CI)	*p*	*p* for interaction	Adjusted[1] HR (95%CI)	*p*	*p* for interaction
ADD user status based on ≥36 prescriptions	260	919	3,313	1.07 (0.32, 1.28)	0.21		1.43 (0.72, 2.82)	0.31	
Excluding patients who died within 3 months of their diagnosis[9]	306	986	3,548	1.00 (0.77, 1.30)	0.98		1.04 (0.81, 1.35)	0.74	
Based upon first year after diagnosis[10]	190	821	3,289	1.10 (0.80, 1.51)	0.55		0.98 (0.71, 1.36)	0.92	
Pre-diagnosis ADD use[11]	398	1,085	3,001	1.08 (0.85, 1.36)	0.52		0.82 (0.65, 1.04)	0.11	
Additionally adjusted for pre-diagnosis ADD use[2]	236	847	3,001	1.03 (0.69, 1.53)	0.89		1.37 (0.90, 2.08)	0.14	
Additionally adjusted for type 2 diabetes duration[12]	177	625	2,036	1.15 (0.80, 1.63)	0.45		1.03 (0.73, 1.47)	0.85	
HbA1c level prior to diagnosis available (and adjusted for)[3]	237	833	2,875	1.06 (0.79, 1.42)	0.70		1.18 (0.88, 1.59)	0.26	
Imputing stage (based upon first year after diagnosis)[13]	262	1,040	4,549	1.03 (0.75, 1.40)	0.87		0.80 (0.60, 1.07)	0.14	

[1]Except where otherwise stated, all analyses adjusted for gender, year of diagnosis, age at diagnosis, deprivation (in fifths), site (colon or rectum), surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, comorbidities (prior to diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease), other anti-diabetic medication usage (after diagnosis, as time varying covariates, including metformin, sulfonylureas, insulin and other ADDs), other medication usage (after diagnosis, as time varying covariates, including low dose aspirin and statins) and stage at diagnosis.
[2]Pre-diagnosis use based on one or more prescriptions in the year before diagnosis, restricted to individuals with 1 year of records before colorectal cancer diagnosis.
[3]Based upon GP-recorded HbA1c levels in the year prior to diagnosis.
[4]Increasing lag to 1 year among individuals living more than 1 year after cancer diagnosis.
[5]Increasing lag to 2 year among individuals living more than 2 years after cancer diagnosis.
[6]Adjusted model contains all variables in "[1]" along with BMI prior to diagnosis (in individuals with BMI available).
[7]Adjusted model contains all variables in "[1]" along with smoking prior to diagnosis (in individuals with smoking available).
[8]Adjusted model contains all variables in "[1]"along with tumour grade prior to diagnosis (in individuals with grade available).
[9]Medication usage lagged by 3 months, to remove prescriptions in the last three months prior to death.
[10]Simplified analysis, not requiring time varying covariate use, comparing metformin users to metformin non-users in the first year after diagnosis in individuals living more than 1 year after cancer diagnosis, adjusted for all confounders in [a] but other medication use also restricted to first year after diagnosis.
[11]Based on one or more prescriptions in the year before diagnosis, restricted to individuals with 1 year of records before colorectal cancer diagnosis, does not exclude deaths in the first 6 months after diagnosis. Adjusted analysis includes all variables used in (a) and other medication use (including low-dose aspirin, ACEIs, and metformin), which are adjusted in the year before diagnosis. Stage is not adjusted for as this could be on causal pathway.
[12]Type 2 diabetes duration categorised as <1 year, 1–2 years, 3–5 years and >5 years, restricted to individuals with at least 5 years of records before colorectal cancer diagnosis.
[13]Analysis based upon model in footnote "[10]." An ordinal logistic regression model was used to impute stage with explanatory variables including cumulative hazard, death status, ADD use within 1 year and all confounders in footnote 'a' with other medication use restricted to first year after diagnosis. Ten imputations were conducted, and results were combined using Rubin's rules.
ADD = Anti-diabetic drug.

sulfonylureas use and cancer-specific mortality and no demonstrable dose-response relationship was evident. There was evidence of a slight increase in colorectal cancer mortality among users of insulin after diagnosis but this was attenuated after adjustment (adjusted HR 1.21, 95% CI 0.90, 1.64). Finally, there was evidence of a reduction in cancer-specific mortality in users of other anti-diabetic medications but again this was attenuated after accounting for potential confounders (adjusted HR 0.73, 95% CI 0.46, 1.14). Results for metformin and sulfonylureas were similar in analysis of all-cause mortality, Table 3.

Sensitivity/secondary analyses

The findings from sensitivity/secondary analyses are shown in Table 4. The association between metformin use and colorectal cancer mortality remained relatively similar after stratification by cancer site, sex, cancer stage at diagnosis, pre-diagnosis metformin use or HbA1c level. Prior to adjustment for stage, results remained largely unchanged for metformin use and CRC specific mortality in the first 5 years after diagnosis (adjusted HR = 1.12, 95% CI 0.41, 3.10) and in the period 5 or more years after diagnosis (adjusted HR = 1.10, 95% CI 0.86, 1.39). Results did not materially alter from the main analysis when the lag was increased to 1 or 2 years, in simplified analysis of drug exposure in the year after diagnosis and after additionally controlling for BMI, grade, smoking, pre-diagnosis metformin use, type 2 diabetes duration and HbA1C levels. Estimates also did not change considerably when the exposure definition was based upon 36 prescriptions (~3 years of use), when analysis imputing for missing stage was conducted or when a nested case-control analysis was applied (Supporting Information Table 2). Findings from sensitivity/secondary analyses of sulfonylurea usage also did not materially differ to the main analysis, Table 4.

Discussion

The findings from this UK population-based study do not support a protective association between post-diagnostic metformin use and survival in a large cohort of colorectal cancer patients with type 2 diabetes. There was also no evidence of an association in dose-response analysis and in analysis of all-cause mortality.

Only one study has previously examined the impact of post-diagnostic metformin use on colorectal cancer-specific mortality. In a cohort of 595 individuals diagnosed in a single institution in Korea, evidence of a protective association between metformin use after colorectal cancer diagnosis and cancer-specific mortality was observed.[8] These findings however have been attributed to immortal time bias as previously explained.[9] Our analysis avoided this particular bias by treating all drug exposures as time-varying covariates with cohort follow-up beginning after the first prescription (with a 6 month lag). In a separate analysis of 212 postmenopausal women with colorectal cancer and type 2 diabetes, no statistically significant difference in colorectal cancer-specific survival was observed among users of metformin compared to non-users (HR 0.75, 95% CI 0.40–1.38) although unfortunately, the authors of this study were unable to obtain data on the timing of metformin use in relation to colorectal cancer diagnosis.[28] Other epidemiological studies investigating metformin use after colorectal cancer diagnosis and all-cause mortality and have indicated a beneficial effect with metformin use,[11,12] however these investigations are limited by small sample size and the use of only one exposure timepoint. Moreover, findings from studies which only examine the impact of metformin on all-cause mortality may be reflective of non-cancer mortality.

Our study had several strengths. It is the largest to examine the impact of metformin on cancer-specific mortality and benefitted from long follow-up of up to 14 years. Robust verification of colorectal cancer cases and deaths was enabled by utilising NCDR and ONS data, respectively. We used drug information based on robust GP-prescription records of documented high quality[18] which allowed for detailed investigation of the timing of drug exposure and for analyses into number of prescriptions and cumulative dose. Moreover, drug exposures were treated as time-dependent which therefore did not incur immortal time bias to our findings. This study benefitted from a long follow-up period of up to 14 years and included a comprehensive and simultaneous examination of all anti-diabetic medications and colorectal cancer-specific mortality. Furthermore, anti-diabetic drugs are not available over the counter in the UK; hence misclassification due to over-the-counter drug use is unlikely.

We did not have data on anti-diabetic drug adherence but similar associations were observed among patients who received multiple prescriptions in whom drug adherence may be more likely. A further weakness may be that despite being the largest study to date, we cannot rule out Type 2 error, particularly in the analyses of subgroups such as early stage colorectal cancer patients. Misclassification of colorectal cancer deaths may have occurred, however methodological studies have suggested that in comparative studies where differential misclassification of death is unlikely, as in our study, effect estimates are unlikely to be effected.[29] Finally, although we controlled for a wide range of potential confounders, and analyses imputing for missing stage resulted in similar estimates, residual confounding caused by unrecorded or incomplete data (*e.g.*, cancer stage) cannot be ruled out. In conclusion, the findings from this UK population-based study, which is the largest to date and used individual cancer registry data, do not support a significant protective association between metformin and colorectal cancer mortality.

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