Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Cohort Study of Metformin Exposure and Survival in Patients with Stage I–III Colorectal Cancer

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Abstract

Background: Preclinical evidence suggests a beneficial effect of metformin in colorectal cancer. This study aimed to investigate associations between metformin exposure and colorectal cancer–specific survival using population-level data.

Methods: Adult patients with stage I–III colorectal cancer diagnosed from 2001 to 2006 were identified from the National Cancer Registry Ireland. Use of metformin and other antidiabetic medications was determined from a linked national prescription claims database. Multivariate Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for associations between prediagnostic metformin exposure (versus nonmetformin antidiabetic drugs) and colorectal cancer–specific mortality. Models were stratified by antidiabetic drug coprescription and intensity of metformin exposure.

Results: The cohort included 207 diabetics who received metformin, 108 diabetics not exposed to metformin, and 3,501 nondiabetic patients. In multivariate analyses, a nonsignificant reduction in colorectal cancer–specific mortality was observed for metformin-exposed patients relative to other treated diabetics (HR, 0.61; 95% CI, 0.37–1.01). In stratified analyses, no significant association was observed for patients receiving low-intensity metformin or metformin in combination with other antidiabetic drugs. High-intensity exclusive metformin use was associated with a significant reduction in colorectal cancer–specific mortality (HR, 0.44; 95% CI, 0.20–0.95).

Conclusions: Significant associations between metformin exposure and colorectal cancer–specific mortality were observed only for high-intensity exclusive metformin use in the diabetic cohort.

Impact: This study provides moderate evidence of an association between metformin exposure and improved colorectal cancer survival in a diabetic population. Additional studies in larger cohorts, with detailed information on diabetes severity, are required to confirm these results. *Cancer Epidemiol Biomarkers Prev; 22(8); 1364–73. ©2013 AACR.*

Introduction

Metformin is an oral hypoglycaemic drug with a well-established safety profile and is recommended as first-line therapy in type II diabetes management (1). Evidence from preclinical studies has also identified a possible role for metformin in the treatment of colorectal cancer as it has been found to inhibit tumor growth and reduce the tumor-promoting effect of a high-fat diet (2–7). Putative mechanisms of action for anticancer properties of metformin include direct effects through inhibition of the mTOR pathway and indirect effects through reduction of insulin levels; these have been reviewed extensively (8–10). In addition to this preclinical evidence, a number of epidemiologic studies have suggested the possibility of an association between metformin use and reduced cancer mortality among diabetic patients taking metformin (11–16). Results from two previous single-institution observational studies have reported significant associations between metformin exposure and improved survival among colorectal cancer patients with diabetes (15, 16). Although these results have suggested a beneficial effect of metformin, concerns regarding the presence of immortal time bias have been raised. Further studies, using appropriate methodologies have been called for to address these concerns and confirm these findings (17). This study aims to investigate associations between metformin exposure and cancer-specific survival using linked national prescribing and cancer datasets, and an intention to treat design within a cohort of patients with colorectal cancer (17).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Materials and Methods

Setting and data sources

All data used in this study were provided by the National Cancer Registry Ireland (NCRI) and comprised individual cancer patient records which have been linked

to national prescription-dispensing data from Ireland's Health Services Executive (HSE)— Primary Care Reimbursement Services (PCRS) pharmacy claims database. The NCRI collects comprehensive details on all incident cancers in the population usually resident in Ireland. Multiple sources of information, including pathology and radiology reports, treatment records, and death certificates are collated by trained, hospital-based, tumor registration officers to identify new cancers. The HSE-PCRS General Medical Services (GMS) scheme provides taxpayer-funded universal healthcare, including medicines, to approximately 38% (1.6 million) of the Irish population (18). Eligibility for the GMS scheme was through means test in those under 70 years and universal for those aged 70 and older during the period of the study. The GMS pharmacy claims database contains detailed prescription claims information (drugs coded using the WHO Anatomical Therapeutic Chemical, ATC, classification system; ref. 19) for all patients with eligibility for the scheme. The use for research of anonymized data held by the NCRI is covered by the Health (Provision of Information) Act 1997.

Study design

Patients over the age of 18 were eligible for inclusion in this retrospective cohort study if they had a diagnosis of TNM stage I–III (pathologic or clinical staging; ref. 20) colorectal cancer (ICD-10, C18–C20) between January 1, 2001 and December 31, 2006 inclusive. Stage IV (metastatic) patients were excluded from the main analyses due to a lack of benefit observed in these patients in previous studies (15, 16), but were included as part of sensitivity analyses (see below). Patients were excluded from the cohort if their colorectal cancer was diagnosed at autopsy, if they had a prior history of an invasive cancer other than nonmelanoma skin cancer, or if they did not have GMS eligibility for the full year before the diagnosis of colorectal cancer.

Cohort members were classified into two groups: "diabetic" and "nondiabetic". Individuals were classified as diabetic if they were identified through the GMS claims data to have received a supply of at least one antidiabetic drug (ADD; WHO ATC therapeutic subgroup A10; ref. 19) in the year before the diagnosis of colorectal cancer. All other patients were classified as nondiabetic. The main analyses were nested within the diabetic subgroup and considered diabetics not receiving metformin as the reference group. Analyses were subsequently repeated in the full cohort where the reference group was nondiabetics. These analyses were carried out to address the possibility that studies nested within a diabetic population may be biased due to differences in the severity of diabetes or the effectiveness of diabetes control between patients receiving metformin versus nonmetformin ADDs (21, 22).

Exposure definition

Metformin exposure was identified from linked prescription refill data using WHO ATC drug codes (Supplementary File 1). Exposure (yes/no) was defined according to whether or not the individual had a supply of metformin available at any point in the year before the diagnosis of colorectal cancer. Metformin dosing intensity was calculated as the proportion of days covered (PDC) in the year before the diagnosis of colorectal cancer for which a supply of metformin was available (23). This was stratified as 'low' or 'high' at the median.

Outcomes

The primary outcome was colorectal cancer–specific survival; overall survival was also examined in secondary analyses (24). The date and cause of death for each patient was identified using linked death certificate information from the NCRI database. Colorectal cancer–specific deaths were identified using the ICD-10 cause of death codes C18–C21 and ICD-9 codes 153 and 154 in earlier years. Survival time was calculated from the date of colorectal cancer diagnosis to the first of death or end of follow-up (December 31, 2010).

Covariates

Sociodemographic information and tumor and treatment details of patients were abstracted from the NCRI database. Patient information included age at diagnosis (years), gender, smoking status at diagnosis (current, former, never, or unspecified), and a census-based indicator of socioeconomic status (25). Tumor details included AJCC summary stage (I, II, or III; ref. 20), tumor grade (well/moderately differentiated, poorly differentiated, or unspecified), site (colon or rectum; Supplementary File 1), morphology (adenocarcinoma or other; Supplementary File 1), and year of diagnosis (categorical). Receipt of tumor-directed surgery, chemotherapy, and/or radiation in the year following diagnosis, and corresponding treatment commencement dates, were also abstracted. Linked prescription refill data was used to identify exposure (yes, no; Supplementary File S1) to nonmetformin ADDs (sulfonylureas, insulin, and other ADDs such as thiazolidinediones, DPP4 inhibitors, meglitinides, and α-glucosidase inhibitors) in the year before diagnosis. Exposure to aspirin was also identified due to increasing evidence of an effect for the drug in colorectal cancer (26). A comorbidity score was calculated for each patient on the basis of the number of distinct drug classes (level 5 ATC codes) to which the patient was exposed in the year before the diagnosis (27).

Statistical analysis

Patient characteristics were tabulated for diabetics according to metformin exposure status (yes or no) and for these groups versus nondiabetics, and potential differences between the exposure groups were explored using the Wilcoxon rank-sum test for continuous variables and Pearson χ^2 test for categorical variables. Crude survival rates for colorectal cancer–specific and overall survival were calculated as deaths per 1,000 person-years.

Within the diabetic subgroup, univariate and adjusted Cox proportional hazards models (SAS PROC PHREG) were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for associations between metformin exposure and colorectal cancer–specific survival. Direct adjusted Kaplan–Meier curves were also estimated (28). Prior knowledge, literature review, and causal diagrams were used to identify potential covariates from among the available patient, tumor, and treatment variables for inclusion in the multivariate model of colorectal cancer–specific survival (29, 30). Cancer treatment variables were included as time-varying covariates. The final multivariate model was selected using backward elimination on the basis of a maximum cumulative change in the risk estimates of 10% (31, 32). Analyses were also conducted stratifying by metformin dosing intensity (low/high) and by receipt of metformin exclusively or in combination with nonmetformin ADDs. This process was repeated for overall (all-cause) survival. Finally, analyses were repeated as above in the full cohort, that is, with the inclusion of nondiabetic patients as the reference group in place of diabetic patients who did not receive metformin.

All analyses were conducted using SAS, version 9.2 (SAS Institute Inc). A two-sided *P* value of less than 0.05 was considered statistically significant.

Sensitivity analyses

Sensitivity analyses were carried out to explore the effect of different classifications of recorded cause of death as follows. Analyses of colorectal cancer–specific survival were repeated with the inclusion of: (i) all deaths where colorectal cancer was identified as a secondary/contributory cause of death ('Definition 2'); and (ii) deaths due to malignant neoplasms of other/ill-defined digestive organs (C26), ill-defined cancer sites (C76.1, C80), secondary cancer sites (C77–79), cancers of uncertain or unknown behavior (D48.6, D48.9), and unspecified causes of death ('Definition 3'). Sensitivity analyses were also carried out including patients with stage IV or unspecified-stage colorectal cancer. Finally, an additional analysis was carried out comparing patients with *de novo* metformin exposure (i.e., receiving metformin for the first time) in the year following diagnosis to other diabetics not receiving metformin, with follow-up commencing from 1 year post diagnosis.

Results

Characteristics of the study cohort

A flowchart outlining selection of the cohort is presented in Fig. 1. Patient characteristics for the diabetic subgroup, classified as metformin exposed ($n = 207$) or unexposed (n = 108) are summarized in Table 1. No significant differences were found between the 2 metformin exposed and unexposed groups in terms of tumor stage, grade, or other tumor-related or sociodemographic factors. There was a nonsignificant higher prevalence of radiation therapy (16% versus 8%, $P = 0.06$) and aspirin use (70% versus 60%, $P = 0.09$) within the metformin-exposed group. Among metformin users, 52% of patients also received a sulfonylurea drug, while 72% of metformin-unexposed patients received sulfonylurea drugs. Insulin use was also significantly higher in the nonmetformin group (28% versus 9%), although use of other ADDs (e.g. thiazolidinediones) was more prevalent in the metformin group. The median metformin dosing intensity in the year before diagnosis was 0.92 [interquartile range (IQR) 0.55–1.00].

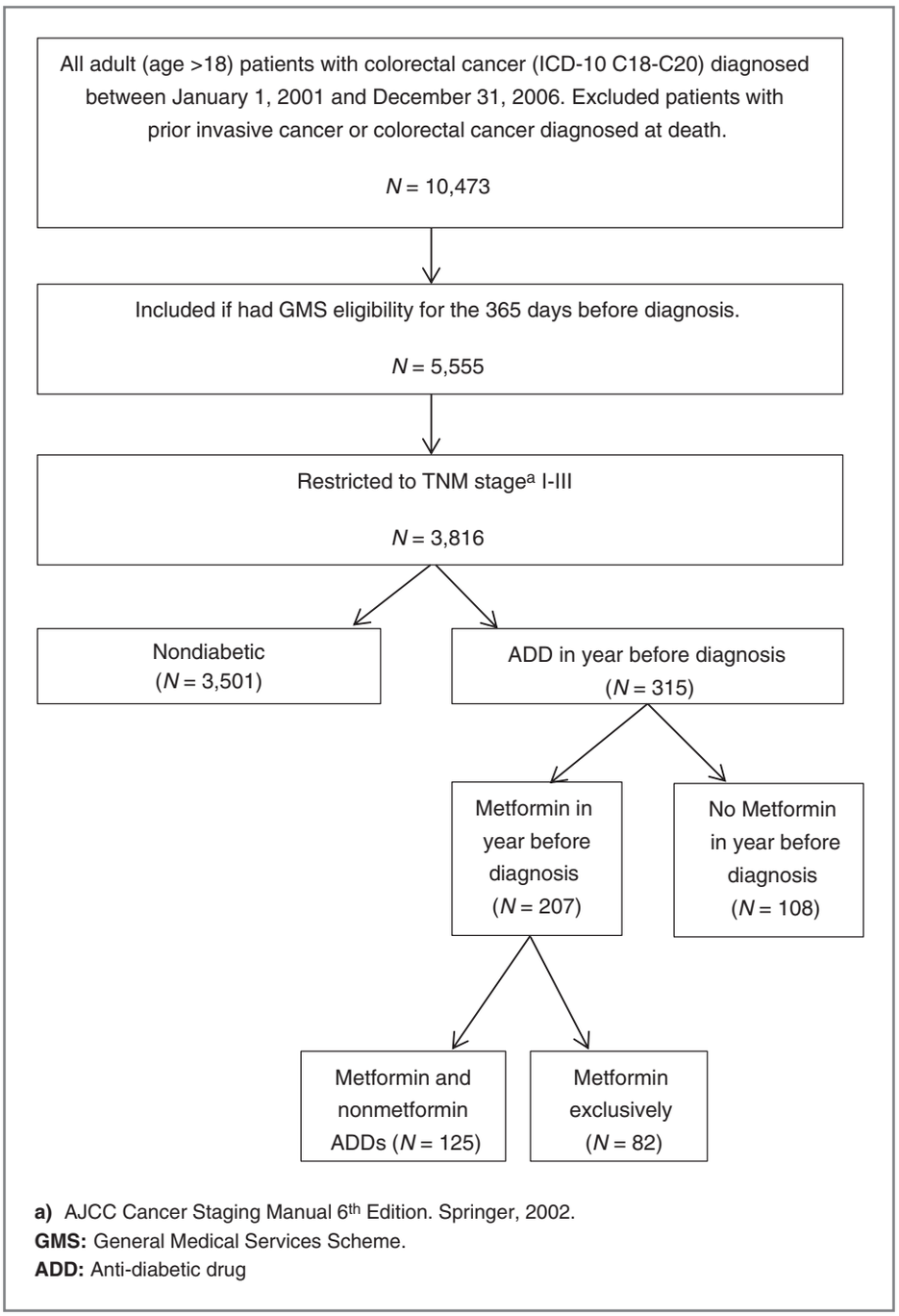
Survival analyses: diabetic subgroup

The results from analyses of stages I–III colorectal cancer patients with diabetes are presented in Table 2. Person-time contributed by the overall diabetic subgroup totaled 1,194 person-years; the crude colorectal cancer–specific mortality rates for metformin-exposed and -unexposed patients were 70 and 97 deaths per 1,000 person-years, respectively. In multivariate analyses, exposure to metformin was associated with a lower risk of colorectal cancer–specific mortality, and this approached statistical significance (HR, 0.61; 95% CI, 0.37–1.01; Table 2, Fig. 2). This result was not found to differ significantly according to gender ($P_{\text{interaction}} = 0.41$). Associations of a similar magnitude, although not statistically significant, were observed between metformin exposure and colorectal cancer–specific mortality for high and low exposure intensities (Table 2). When deaths from all causes were considered, metformin exposure was associated with a significantly lower risk of death (HR, 0.69; 95% CI, 0.49–0.97; Table 2).

In analyses stratified by coprescription with nonmetformin ADDs, metformin exposure, exclusively or co-prescribed, was associated with 39% and 30% lower risk of colorectal cancer–specific mortality respectively, but these estimates were not statistically significant (Table 2, Fig. 3). Significant associations between metformin use and colorectal cancer–specific mortality were observed in analyses stratified by both metformin dosing intensity and co-prescription with nonmetformin ADDs. In comparison with diabetics not receiving metformin, the risk of colorectal cancer–specific mortality was significantly lower in patients receiving metformin exclusively at high intensity (HR, 0.44; 95% CI, 0.20–0.95). Use of metformin exclusively at low intensity was not associated with a lower risk of colorectal cancer–specific mortality (HR, 0.81; 95%CI, 0.41–1.58). No significant associations were observed for metformin exposure at either high or low intensity when co-prescribed with nonmetformin ADDs. The interaction between metformin dosing intensity and co-prescription with nonmetformin ADDs was not statistically significant ($P_{\text{interaction}} = 0.16$).

Survival analyses: full cohort

Results from analyses including nondiabetic patients as the reference group are presented in Table 3. Characteristics of nondiabetic patients, and metformin-exposed



a) AJCC Cancer Staging Manual 6th Edition. Springer, 2002.
GMS: General Medical Services Scheme.
ADD: Anti-diabetic drug

Figure 1. Flowchart – study population.

and -unexposed diabetic patients, are compared in Supplementary Table S1. In these analyses, diabetic patients receiving metformin had a nonsignificantly lower risk of colorectal cancer–specific mortality compared with nondiabetic patients (HR, 0.84; 95% CI, 0.58–1.20). Results from analyses stratified by dosing intensity and co-prescription with nonmetformin ADDs followed similar trends to those observed in the analyses including only the diabetic subgroup.

Sensitivity analyses

The results from sensitivity analyses exploring the impact on the result of different classifications of cause of death are presented in Supplementary Table S2. Associations between metformin exposure and colorectal cancer–specific mortality did not differ appreciably from those found in the primary analysis when either of the 2 alternative definitions of colorectal cancer–specific mortality was applied. However, using the broadest

Table 1. Characteristics of the diabetic subgroup

Characteristic		Any metformin exposure in year before diagnosis: Unexposed ($n = 108$)	Any metformin exposure in year before diagnosis: Exposed ($n = 207$)	*P*
Patient details				
Age—median (IQR)	Years	76 (71, 79)	74 (71, 80)	0.80
Comorbidity—median (IQR)	Number of drug classes	14 (10, 20)	15 (11, 19)	0.39
Gender (%)	Male	67 (62.0)	127 (61.4)	0.91
Smoking status (%)	Current	10 (9.3)	17 (8.2)	0.96
	Former	49 (45.4)	100 (48.3)	
	Never	26 (24.1)	49 (23.7)	
	Unspecified	23 (21.3)	41 (19.8)	
Socioeconomic status (%)	Least deprived	10 (9.3)	21 (10.1)	0.79
		13 (12.0)	26 (12.6)	
		18 (16.7)	26 (12.6)	
		19 (17.6)	28 (13.5)	
	Most deprived	40 (37.0)	89 (43.0)	
	Unspecified	8 (7.4)	17 (8.2)	
Tumor details				
TNM stage (%)	I	23 (21.3)	36 (17.4)	0.49
	II	38 (35.2)	86 (41.6)	
	III	47 (43.5)	85 (41.1)	
Grade differentiation (%)	Well/moderate	75 (69.4)	159 (76.3)	0.41
	Poorly differentiated	17 (15.7)	24 (11.6)	
	Unspecified	16 (14.8)	25 (12.1)	
Site (%)	Colon (vs. rectum)	81 (75.0)	147 (71.0)	0.45
Morphology (%)	Adenocarcinoma	93 (86.1)	179 (86.5)	0.93
	Other	15 (13.9)	28 (13.5)	
Treatment[a] (%)	Surgery	104 (96.3)	192 (92.8)	0.21
	Chemotherapy	22 (20.4)	59 (28.5)	0.12
	Radiation	9 (8.3)	33 (15.9)	0.06
Year of diagnosis (%)	2001	15 (13.9)	20 (9.7)	0.46
	2002	18 (16.7)	25 (12.1)	
	2003	19 (17.6)	37 (17.9)	
	2004	12 (11.1)	38 (18.4)	
	2005	21 (19.4)	42 (20.3)	
	2006	23 (21.3)	45 (21.7)	
Drug exposures[b] – (%)				
Sulfonylurea		78 (72.2)	108 (52.2)	<0.001
Insulin		30 (27.8)	18 (8.7)	<0.001
Other ADDs		9 (8.3)	31 (15.0)	0.09
Aspirin		65 (60.2)	144 (69.6)	0.09
Metformin Exposure Details				
Dosing Intensity – median (IQR)[c]		-	0.92 (0.55, 1.0)	
Mean daily dose – median (IQR)[d]	mg/day	-	1148 (682, 4318)	
Exposure to metformin following diagnosis - (%)		20 (18.5)	178 (86.0)	

[a]Refers to treatment received in year post diagnosis.
[b]Exposures in year before diagnosis.
[c]Exposure intensity calculated as number of days with supply available in year prior to diagnosis, divided by 365.
[d]Mean daily dose calculated as cumulative dose in year prior to diagnosis, divided by 365.
IQR, interquartile range.

Table 2. Univariate and multivariate HRs for metformin exposure and mortality; diabetic subgroup, stages I–III colorectal cancer

Exposure Information			Colorectal cancer–specific survival			Overall survival		
Main analysis[a]	**(*n* = 315)**	**Person-years**	**Deaths (crude rate)[c]**	**Univariate HR (95% CI)**	**Adjusted HR (95% CI)**	**Deaths (crude rate)[c]**	**Univariate HR (95% CI)**	**Adjusted HR (95% CI)**
No metformin	108	361	35 (97)	**(Ref)**	**(Ref)**	74 (205)	**(Ref)**	**(Ref)**
Any metformin	207	833	58 (70)	0.72 (0.48–1.10)	0.61 (0.37–1.01)	122 (146)	0.73 (0.55–0.97)	0.69 (0.49–0.97)
Stratified analyses								
Dosing intensity[a]								
Any metformin (low)	103	406	31 (76)	0.79 (0.49–1.28)	0.62 (0.35–1.10)	68 (168)	0.83 (0.59–1.15)	0.76 (0.52–1.10)
Any metformin (high)	104	427	27 (63)	0.66 (0.40–1.09)	0.60 (0.33–1.07)	54 (126)	0.64 (0.45–0.90)	0.62 (0.42–0.93)
Co-prescription[b]								
Metformin + co-Rx ADDs	125	483	35 (73)	0.75 (0.47–1.19)	0.70 (0.43–1.15)	76 (157)	0.78 (0.57–1.07)	0.77 (0.55–1.08)
Metformin exclusively	82	350	23 (66)	0.69 (0.41–1.17)	0.61 (0.35–1.06)	46 (131)	0.66 (0.46–0.96)	0.56 (0.38–0.82)
Dosing intensity and coprescription[b]								
Metformin (low) + Co-Rx ADDs	65	259	17 (66)	0.68 (0.38–0.22)	0.60 (0.32–1.10)	41 (158)	0.78 (0.53–1.14)	0.74 (0.49–1.12)
Metformin (high) + co-Rx ADDs	60	223	18 (81)	0.81 (0.46–1.44)	0.82 (0.45–1.49)	35 (157)	0.78 (0.52–1.17)	0.79 (0.52–1.19)
Metformin (low) exclusively	38	146	14 (96)	0.97 (0.52–1.80)	0.81 (0.41–1.58)	27 (185)	0.91 (0.59–1.42)	0.74 (0.46–1.20)
Metformin (high) exclusively	44	204	9 (44)	0.48 (0.23–1.00)	0.44 (0.20–0.95)	19 (93)	0.48 (0.29–0.79)	0.41 (0.24–0.70)

[a]Adjusted for age, tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, exposure to nonmetformin ADDs (sulfonylureas yes/no, insulin yes/no, other ADDs yes/no), socioeconomic status, and radiation therapy.

[b]Adjusted for age, tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, socioeconomic status, radiation therapy. 'Co-Rx' ADDs include sulfonylureas, insulin, and/or other ADDs.

[c]Rate calculated as deaths per 1,000 person-years.

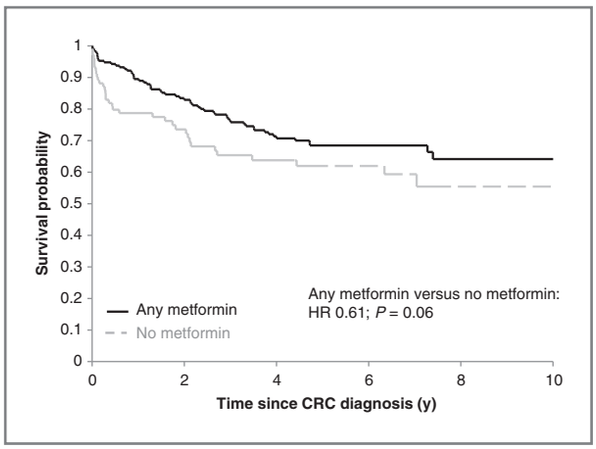


Figure 2. Direct adjusted survival curve. Adjusted cumulative incidences of colorectal cancer–specific mortality for metformin users and nonusers in diabetic patients with stages I–III colorectal cancer. Cumulative incidences are adjusted for tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, exposure to nonmetformin ADDs (sulfonylureas yes/no, insulin yes/no, and/or other ADDs yes/no), socioeconomic status, and radiotherapy.

definition (Definition 3), overall exposure to metformin was associated with a significantly lower risk of colorectal cancer–specific mortality. This effect was also significant for patients receiving metformin exclusively or at high dosing intensity, or under both of these conditions.

The results from sensitivity analyses including patients with stage IV colorectal cancer or unspecified staging are presented in Supplementary Table S3. In general, associations between metformin exposure and colorectal cancer–specific mortality were closer to the null than those observed in the analyses of stage I–III patients, and no results reached statistical significance.

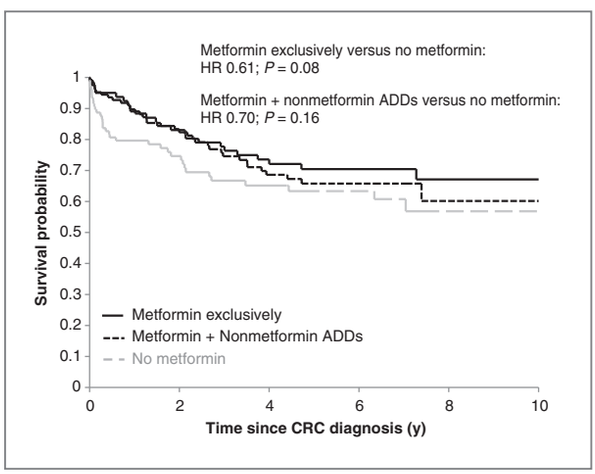


Figure 3. Direct adjusted survival curve. Adjusted cumulative incidences of colorectal cancer–specific mortality for metformin users and nonusers in diabetic patients with stages I–III colorectal cancer; stratified by co-prescription with nonmetformin ADDs. Cumulative incidences are adjusted for tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, socioeconomic status, and radiotherapy.

The results from analyses of *de novo* postdiagnostic metformin exposure are presented in Supplementary Table S4. Compared with patients who received a non-metformin antidiabetic drug in the year before or post cancer diagnosis, no association with colorectal cancer mortality was observed for *de novo* postdiagnostic metformin exposure.

Discussion

This study examined associations between metformin exposure and colorectal cancer–specific mortality among patients with stage I–III colorectal cancer receiving treatment for diabetes. For overall metformin exposure, the risk of colorectal cancer–specific mortality was 39% lower in metformin-treated diabetics, versus diabetics not receiving metformin, but did not reach the conventional threshold for statistical significance ($P = 0.06$).

This result is consistent with the findings from 2 previous single-center studies of metformin exposure and survival in colorectal cancer (15, 16). In a study of diabetic patients with stage I–IV disease by Lee and colleagues, metformin exposure for a minimum of 6 months was associated with a significant 34% lower risk of colorectal cancer–specific mortality (16). The results from this study have, however, been questioned due to the possible presence of immortal time bias (17).

In a study by Garrett and colleagues, of diabetic patients with stage I–IV colorectal cancer, metformin exposure at diagnosis was associated with a significant 40% lower risk of overall mortality (associations with colorectal cancer–specific mortality were not reported; ref. 15). A significant association of a similar magnitude between metformin exposure and overall mortality in patients with colorectal cancer was also observed in the present study. However, these results should be interpreted with caution as the risk of non–cancer-related deaths is likely to be lower in diabetic patients receiving metformin, a common first-line choice for diabetes treatment, in comparison with diabetic patients receiving second- and third-line treatments, which served as the comparator in these analyses. In the present study, attenuated associations between metformin exposure and colorectal cancer–specific survival were observed after the inclusion of patients with stage IV disease in the study cohort. This is consistent with the results from Lee and colleagues and Garrett and colleagues, both of which reported no association between metformin exposure and mortality in univariate analyses of patients with stage IV colorectal cancer (15, 16).

The present study and previous studies (15, 16) have examined associations between metformin exposure and outcomes in colorectal cancer patients with diabetes. However, it has been suggested that the results from studies nested within a diabetic population may be biased due to differences in the severity of diabetes or the effectiveness of diabetes control between patients receiving

Table 3. Univariate and multivariate HRs for metformin exposure and mortality; full cohort, stages I–III colorectal cancer

Exposure Information			Colorectal cancer–specific survival			Overall survival		
Main analysis[a]	**(*n* = 3,816)**	**Person-years**	**Deaths (crude rate)[c]**	**Univariate HR (95% CI)**	**Adjusted HR (95% CI)**	**Deaths (crude rate)[c]**	**Univariate HR (95% CI)**	**Adjusted HR (95% CI)**
Nondiabetic	3,501	15,912	1,082 (68)	**(Ref)**	**(Ref)**	1,897 (119)	**(Ref)**	**(Ref)**
Diabetic - No metformin	108	361	35 (97)	1.27 (0.91–1.78)	1.22 (0.69–2.14)	74 (205)	1.54 (1.22–1.95)	1.19 (0.82–1.74)
Any metformin	207	833	58 (70)	0.91 (0.70–1.18)	0.84 (0.58–1.20)	122 (146)	1.11 (0.92–1.33)	0.90 (0.69–1.17)
Stratified analyses								
Dosing intensity[a]								
Any metformin (low)	103	406	31 (76)	0.99 (0.70–1.42)	0.87 (0.56–1.37)	68 (168)	1.26 (0.99–1.61)	0.99 (0.72–1.35)
Any metformin (high)	104	427	27 (63)	0.83 (0.56–1.21)	0.80 (0.51–1.26)	54 (126)	0.96 (0.73–1.26)	0.82 (0.60–1.13)
Coprescription[b]								
Metformin + co-Rx ADDs	125	483	35 (73)	0.93 (0.67–1.31)	0.82 (0.58–1.16)	76 (157)	1.18 (0.94–1.48)	1.04 (0.82–1.32)
Metformin exclusively	82	350	23 (66)	0.87 (0.58–1.32)	0.73 (0.48–1.11)	46 (131)	1.01 (0.75–1.35)	0.82 (0.61–1.10)
Dosing intensity and coprescription[b]								
Metformin (low) + co-Rx ADDs	65	259	17 (66)	0.86 (0.53–1.39)	0.74 (0.45–1.20)	41 (158)	1.20 (0.88–1.63)	1.04 (0.76–1.43)
Metformin (high) + co-Rx ADDs	60	223	18 (81)	1.01 (0.64–1.62)	0.93 (0.58–1.49)	35 (157)	1.16 (0.83–1.62)	1.04 (0.74–1.45)
Metformin (low) exclusively	38	146	14 (96)	1.22 (0.72–2.07)	0.93 (0.55–1.59)	27 (185)	1.37 (0.94–2.01)	1.02 (0.69–1.50)
Metformin (high) exclusively	44	204	9 (44)	0.60 (0.31–1.16)	0.54 (0.28–1.05)	19 (93)	0.73 (0.46–1.15)	0.64 (0.41–1.01)

[a]Adjusted for age, tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use, exposure to nonmetformin ADDs (sulfonylureas yes/no, insulin yes/no, and other ADDs yes/no).

[b]Adjusted for age, tumor stage, tumor grade, year of diagnosis, comorbidity score, aspirin use. 'Co-Rx' ADDs include sulfonylureas, insulin, and/or other ADDs.

[c]Rate calculated as deaths per 1,000 person-years.

metformin versus nonmetformin ADDs (21, 22). In addition, it has also been suggested that any apparent benefit of metformin exists only relative to potential harmful effects of comparator diabetes treatments (33). To explore this possibility, we also assessed associations between metformin exposure and colorectal cancer–specific mortality with reference to nondiabetic patients. Although associations were nonsignificant, the risk of colorectal cancer–specific mortality in diabetes patients treated with metformin was lower in comparison with nondiabetics. These results should not, however, be taken to suggest that associations between metformin and cancer survival in diabetics are generalizable to a nondiabetic population. Ongoing and upcoming clinical trials of the effects of metformin in nondiabetic cancer patients will explore this possibility (34).

This study is the first, to the authors' knowledge, to assess the presence of an exposure response effect between increasing metformin use and colorectal cancer outcomes. In analyses stratified by metformin exposure intensity, there was little difference in associations between low- and high-intensity metformin exposure and colorectal cancer–specific mortality. However, there was a suggestion that a stronger association was present for high intensity metformin use among those patients receiving metformin exclusively. In this subgroup, low and high metformin exposure intensity were associated with a 19% and 56% lower risk of colorectal cancer–specific mortality, respectively. The latter of these was statistically significant and approached significance in analyses with nondiabetics as the reference group. It should be noted, however, that the number of patients in these subgroup analyses was small; therefore, these results require further confirmation in larger studies. Further caution is also required in the interpretation of the results from this study as sensitivity analyses showed no association between *de novo* metformin use in the year post diagnosis and colorectal cancer mortality.

This study has a number of additional strengths. It is the first study of associations between metformin exposure and colorectal cancer survival using national, prospectively collected linked cancer and prescribing data. Access to pharmacy claims data in these analyses provided detailed, objective, longitudinal exposure data, which is not influenced by recall bias. Although noncompliance with received treatment (about which information is not available) will have resulted in exposure misclassification, this would usually bias results toward the null. Finally, this study was conducted using an intention-to-treat–based analysis, with metformin exposure defined before the beginning of follow-up. This study design is not influenced by time-related biases (17), although it should be noted that the results of intention-to-treat analyses may be biased toward the null due to postdiagnostic treatment crossover. Of patients who did not receive metformin before diagnosis, 18.5% received the drug following their diagnosis. Of those patients who received metformin before diagnosis, 14% discontinued therapy following colorectal cancer diagnosis.

Additional study limitations include a limited sample size (although similar to previous studies of metformin and colorectal cancer outcomes), which restricted the power to detect significant differences in survival, and a lack of clinical information regarding severity or duration of diabetes. Data regarding obesity, such as BMI, were also not available in this study. However, previous research has suggested that BMI is not a strong predictor of colorectal cancer–specific survival (35–37) and it has not been shown to be a confounder in previous studies of metformin and colorectal cancer outcomes (15). Finally, as this study largely comprised elderly Irish participants, results may not be generalizable to an ethnically diverse population.

In conclusion, this study examined varying levels of metformin exposure and associations with colorectal cancer–specific mortality. Evidence for a significant association between overall metformin exposure and colorectal cancer–specific mortality was inconclusive, which is broadly consistent with previous studies. However, significant associations were observed in stratified analyses of high-intensity, exclusive metformin usage and the results also suggest that metformin exposure may potentially improve survival relative to nondiabetic patients. Additional studies in larger population-based cohorts are required to further explore the influence of varying exposure levels and timing and to determine if any patient subgroups are more likely to benefit from metformin.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of these data are the responsibility of the authors and should, in no way, be seen as the official policy or interpretation of the National Cancer Registry Ireland or the Irish Health Services Executive Primary Care Reimbursements Services. The Irish Cancer Society and the Health Research Board Ireland had no role in the study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit the article for publication.

Authors' Contributions

Conception and design: S.C. Spillane, L. Sharp, T.I. Barron
Development of methodology: S.C. Spillane, T.I. Barron
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Bennett, L. Sharp, T.I. Barron
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.C. Spillane, L. Sharp, T.I. Barron
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