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# A retrospective study on the role of diabetes and metformin in colorectal cancer disease survival

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## ABSTRACT

**Background** Recent studies have suggested an effect of metformin on mortality for patients with both diabetes and colorectal cancer (CRC). However, the literature is contradictory, with both positive and negative effects being identified. We set out to determine the effect of metformin with respect to prognosis in CRC patients.

**Methods** After a retrospective chart review of CRC patients treated at the Cancer Centre of Southeastern Ontario, Kaplan–Meier analyses and Cox proportional hazards regression models were used to compare overall survival (OS) in patients with and without diabetes.

**Results** We identified 1304 CRC patients treated at the centre. No significant differences between the diabetic and nondiabetic groups were observed with respect to tumour pathology, extent of metastatic disease, time or toxicity of chemotherapy, and the OS rate (1-year OS: 85.6% vs. 86.4%, $p = 0.695$; 2-year OS: 73.6% vs. 77.0%, $p = 0.265$). In subgroup analysis, diabetic patients taking metformin survived significantly longer than their counterparts taking other diabetes treatments (OS for the metformin group: 91% at 1 year; 80.5% at 2 years; OS for the group taking other treatments, including diet control: 80.6% at 1 year, 67.4% at 2 years). Multivariate analysis suggests that patients with diabetes taking treatments other than metformin experience worse survival ($p = 0.025$).

**Conclusions** Our results suggest that CRC patients with diabetes, excluding those taking metformin, might have a worse CRC prognosis. Taking metformin appears to have a positive association with prognosis. The protective nature of metformin needs further evaluation in prospective analyses.

**Key Words** Colorectal neoplasms, diabetes mellitus, metformin, insulin, mortality

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## INTRODUCTION

Colorectal cancer (CRC) is the 3rd most common malignancy worldwide after lung and breast cancer[1]. In Canada, close to 24,000 new cases of CRC were expected to be diagnosed in 2013[2]. A statistically significant association between diabetes and the incidence of CRC is well established[3,4]. Compared with nondiabetic patients, patients with type 2 diabetes tend to be younger at presentation, to have more right-sided tumours, and to experience poorer 5-year overall survival (OS)[5]. Those data accord with early studies that suggested a higher rate of overall mortality in patients with both CRC and diabetes[6]. To date, few reports have considered the level of glycemic control achieved or the antihyperglycemic regimens used by patients experiencing poor outcomes.

Metformin is the antihyperglycemic medication recommended as first-line pharmacologic therapy for all patients with type 2 diabetes in Canada[7]. Recently, studies have shown that metformin can inhibit the growth of cancer cells both *in vitro* and *in vivo*[8–10]. Additionally, observational studies have identified a potential role for metformin in slowing cancer progression[11]. A trend in such risk reduction has been well described in breast cancer, CRC, and pancreatic cancer[12–14].

Although strong evidence supports the association of diabetes with CRC, and recent work has examined metformin as a prognostic factor in CRC, results are

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contradictory and tend to be related to specific patient populations[15–19]. In the present retrospective study, we set out to investigate whether metformin use in diabetic patients diagnosed with CRC was associated with survival. We compared 5-year survival and stage at diagnosis in CRC patients with and without diabetes and in CRC patients with diabetes taking metformin or using another antihyperglycemic regimen excluding metformin. We hoped to identify any potential association of metformin with disease burden and survival in this population of at-risk individuals.

## METHODS

### Study Design and Study Population

This retrospective cohort study involving a chart review of patients diagnosed with CRC was approved by the Queen's University institutional ethics board. We identified all patients 18 years of age and older with a pathology diagnosis of TNM stage I–IV CRC who had been seen during the period 1 January 2005 to 31 December 2011 at the Cancer Centre of Southeastern Ontario, the major cancer centre in southeastern Ontario. In total, 1304 patients were identified and confirmed using diagnosis codes from the *International Classification of Diseases,* 10th edition. Patients whose tumour pathology had been reviewed at the centre, but who had never personally been seen there, were excluded from the database.

### Definition of Diabetes Exposure

Diabetic treatments were identified from patient's oncology consult notes. Exposure (yes or no) was defined according to whether the patient was currently receiving antihyperglycemic therapy. Prior exposures to diabetes treatments were not captured, because that information was unavailable. For the purposes of the present study, patients who were taking multiple oral agents including metformin were classified as being treated with metformin. The definition of "other diabetes treatments" included diet control only, insulin, or oral agents excluding metformin. Diabetic complications identified through the chart review included nephropathy, retinopathy, neuropathy, chronic ulcerations, and cardiovascular disease.

### Data Collection and Outcomes Measured

Data were collected from baseline (the time of medical, radiation, and surgical oncology consult) until the end of the observation period (last visit or 6 July 2013). Sociodemographic, tumour, and radiographic and chemotherapy treatment details were abstracted from patient charts. Patient information included age at diagnosis, sex, smoking and alcohol status at diagnosis, comorbidities (cardiac, respiratory, renal, hematologic, and diabetic complications), family history of CRC, and body mass index (BMI). Radiology and clinic reports from our institution were reviewed for dates of recurrence and progression. Pathology reports were reviewed for tumour characteristics including location, size (both largest diameter and volume), grade, lymphovascular and perineural invasion status, and T and N staging (including total number of lymph nodes obtained and number of positive lymph nodes). Toxicity data were captured from treatment reports as "present" or "absent." Dates of death were obtained from hospital databases and obituaries. The primary outcome was overall survival time, calculated from the date of CRC pathology diagnosis to date of death or to last visit if still living.

### Statistical Analysis

Data were collected in Microsoft Excel and imported into the IBM SPSS Statistics software application (version 22.0 for Windows: IBM, Armonk, NY, U.S.A.) for statistical analysis. The statistical significance of between-cohort differences in categorical variables was evaluated using the chi-square test. Continuous data were compared using the two-sample t-test (diabetic vs. nondiabetic patients, and within the diabetic cohort, those taking metformin vs. those taking any other treatment). All tests were two-tailed, with a significance level of $p < 0.05$.

Kaplan–Meier curves were constructed to compare—from the day of diagnosis to death or to study end—nondiabetic patients, diabetic patients taking metformin, and diabetic patients taking any other treatment. A multivariate Cox proportional hazards regression analysis assessed time to death while controlling for known risk factors, including age, sex, comorbidities (cardiac, diabetic, renal, and respiratory), diabetes treatments (metformin or not), BMI (<25 vs. ≥25), smoking history, alcohol history, family history of CRC, location of cancer (rectum vs. colon), stage at diagnosis (I–IV), and differentiation (well, poorly, or moderately differentiated).

## RESULTS

### Patients Demographics and Clinical Characteristics

Table I summarizes patient demographics. Diabetic patients constituted 21.6% of the study population [median age: 71.2 years (range: 24–98 years)]. No statistically significant difference were observed between the groups with respect to average BMI, alcohol history, or family history. Compared with the nondiabetic population, the diabetic population had a larger percentage of individuals with at least 1 comorbidity other than diabetes (85.6% vs. 62.6%, $p < 0.0001$). Compared with the individuals in the nondiabetic group, the individuals in the diabetic group had significantly more cardiac ($p = 0.0001$) and renal comorbidities ($p = 0.0013$); they were also more likely to have a smoking history ($p = 0.0001$), and their rate of respiratory comorbidity fell just short of significance ($p = 0.0573$). In the diabetic group, neither the average HbA1c (0.079 in the metformin group, 0.075 in the other-treatment group), nor the percentage of members experiencing diabetic complications (42.9% in the metformin group, 43.1% in the other-treatment group) was significantly different, suggesting that the severity of diabetes was similar in the two groups.

Clinical characteristics in the study subgroups were subsequently compared (Table II). We observed no significant differences in tumour differentiation, T stage, average tumour size, perineural invasion, and location of the primary tumour. Additionally, the groups showed no differences in positive lymph node status, including average number of positive lymph nodes per patient and

**TABLE I** Demographics of the study patients

| Variable | Patient group[a] | | | |
|---|---|---|---|---|
| | Nondiabetic | Diabetic | | |
| | | Overall | Taking metformin | Taking other diabetes treatment |
| Patients (*n*) | 1027 | 277 | 133 | 144 |
| Average age (years) | 70.78 | **72.25** | 71.75 | 72.62 |
| Sex [*n* (%)] | | | | |
| Men | 581 (56.6) | **183 (66.1)** | **88 (66.2)** | **99 (68.8)** |
| Women | 446 (43.4) | **94 (33.9)** | **45 (33.8)** | **45 (31.3)** |
| Comorbidities [*n* (%)] | | | | |
| Cardiac | 547 (53.3) | **223 (80.5)** | **110 (82.7)** | **113 (78.5)** |
| Respiratory | 141 (13.7) | 52 (18.8) | 23 (17.3) | 29 (20.1) |
| Renal | 43 (4.2) | **28 (10.1)** | **10 (7.5)** | **18 (12.5)** |
| Liver | 20 (1.9) | 8 (2.9) | 3 (2.3) | 5 (3.5) |
| Average body mass index | 26.90 | 27.66 | 27.45 | 26.56 |
| Smoking history | | | | |
| Yes | 171 (16.7) | **153 (55.2)** | 74 (55.6) | 79 (54.9) |
| No | 847 (82.5) | 122 (44.0) | 59 (44.4) | 65 (45.1) |
| Unknown | 9 (0.9) | | — | — |
| Alcohol history | | | | |
| Yes | 638 (62.2) | 179 (64.6) | 88 (66.2) | 90 (62.5) |
| No | 372 (36.8) | 96 (34.7) | 44 (33.1) | 53 (36.8) |
| Unknown | 17 (1.7) | 2 (1.7) | 1 (0.7) | 1 (0.7) |
| Family history of colorectal cancer | | | | |
| Maternal | 138 (13.4) | 32 (11.6) | 16 (12.0) | 17 (11.8) |
| Paternal | 100 (9.7) | 20 (7.2) | 9 (6.8) | 11 (7.6) |
| Diabetes treatment | | | | |
| Metformin | 0 (0) | 130 (46.9) | 130 (97.7) | 0 (0) |
| Metformin and another oral agent | 0 (0) | 3 (1.1) | 3 (2.3) | 0 (0) |
| Diet | 0 (0) | 77 (27.8) | 0 (0) | 77 (53.5) |
| Oral agents | 0 (0) | 26 (9.4) | 0 (0) | 26 (18.1) |
| Insulin | 0 (0) | 41 (14.8) | 0 (0) | 41 (28.5) |

[a] Boldface type marks values that reach $p < 0.05$ in comparison with the nondiabetic group.

average percentage of positive lymph nodes per patient. Moreover, a comparison of patients with diabetes taking metformin only and those taking any other treatment showed no differences in any of the pathologic characteristics that were analyzed.

### Survival Estimates

Univariate analysis (Table III) comparing patients without and with diabetes demonstrated no statistically significant differences in 1-year OS (86.5% vs. 85.6% respectively, $p = 0.695$), 2-year OS (77.0% vs. 73.6%, $p = 0.265$), or 5-year OS (64.2% vs. 62.5%, $p = 0.622$). However, substantial differences in survival were observed in patients with diabetes depending on whether they were taking metformin or other diabetes treatments (1-year OS: 91% vs. 80.6% respectively, $p = 0.0163$; 2-year OS: 80.5% vs. 67.4%, $p = 0.0144$; 5-year OS: 72.2% vs. 53.5%, $p = 0.0018$). Among CRC patients with stage II and IV disease, prognosis was worse for patients with diabetes receiving non-metformin treatments than for nondiabetic patients and for diabetic patients taking metformin, suggesting a potential protective effect of metformin in those disease stages (Figure 1, $p = 0.002$). Multivariate Cox proportional hazards modelling of all patients (Table IV) suggested a worse prognosis for diabetic patients receiving non-metformin treatments (hazard ratio: 1.35; 95% confidence interval: 1.039 to 1.753; $p = 0.025$).

## DISCUSSION

Since the early 2000s, it has become clear that an association between diabetes and cancer exists. Although pancreatic cancer was one of the first cancers to be associated with diabetes, diabetes has also since been associated

**TABLE II** Tumour characteristics in the study cohort

| Characteristic | Patient group[a] | | | |
|---|---|---|---|---|
| | Nondiabetic | Diabetic | | |
| | | Overall | Taking metformin | Taking other diabetes treatment |
| Histology [*n* (%)] | | | | |
| Adenocarcinoma | 897 (87.3) | 234 (84.5) | 114 (85.7) | 120 (83.3) |
| Mucinous adenocarcinoma | 107 (10.4) | 40 (14.4) | 18 (13.5) | 22 (15.3) |
| Unknown | 23 (2.2) | 3 (1.1) | 1 (0.8) | 2 (1.4) |
| Location [*n* (%)] | | | | |
| Right-sided colon | 327 (31.8) | 93 (33.6) | 43 (32.3) | 50 (34.7) |
| Left-sided colon | 232 (22.6) | 56 (20.2) | 26 (19.5) | 30 (20.8) |
| Rectal | 410 (39.9) | 116 (41.9) | 59 (44.4) | 57 (39.6) |
| Unknown | 58 (5.6) | 12 (4.3) | 5 (3.8) | 7 (4.9) |
| Differentiation [*n* (%)] | | | | |
| Well-differentiated | 41 (4.0) | 7 (2.5) | 4 (3.0) | 3 (2.1) |
| Moderately differentiated | 802 (78.1) | 213 (76.9) | 98 (73.7) | 115 (79.9) |
| Poorly differentiated | 86 (8.4) | 34 (12.3) | 20 (15.0) | 14 (9.7) |
| Unknown | 98 (9.5) | 23 (8.3) | 11 (8.3) | 12 (8.3) |
| Stage [*n* (%)] | | | | |
| I | 76 (7.4) | 20 (7.2) | 10 (7.5) | 10 (6.9) |
| II | 323 (31.5) | 77 (27.8) | 36 (27.1) | 41 (28.5) |
| III | 370 (36.0) | 114 (41.2) | **60 (45.1)** | 54 (37.5) |
| IV | 253 (24.6) | 66 (23.8) | 27 (20.3) | 39 (27.1) |
| Unknown | 5 (0.5) | — | — | — |
| T Stage [*n* (%)] | | | | |
| 1 | 36 (3.5) | 11 (4.0) | 6 (4.5) | 5 (3.5) |
| 2 | 114 (11.1) | 38 (13.7) | 23 (17.3) | 15 (10.4) |
| 3 | 475 (46.3) | 135 (48.7) | 68 (51.1) | 67 (46.5) |
| 4 | 162 (15.8) | 46 (16.6) | 16 (12.0) | 30 (20.8) |
| Unknown | 240 (23.4) | 47 (17.0) | 20 (15.0) | 27 (18.8) |
| Average tumour size ($cm^3$) | 36.35 | 37.56 | 38.46 | 36.11 |
| N Stage [*n* (%)] | | | | |
| N0 | 440 (42.8) | 90 (32.5) | 43 (32.3) | 47 (32.6) |
| N1 | 202 (19.7) | 77 (27.8) | 36 (27.1) | 41 (28.5) |
| N2 | 132 (12.9) | 43 (15.5) | 23 (17.3) | 20 (13.9) |
| N3 | 43 (4.2) | 11 (4.0) | 6 (4.5) | 5 (3.5) |
| Unknown | 210 (20.4) | 56 (20.2) | 25 (18.8) | 31 (21.5) |
| LVI-positive [*n* (%)] | 183 (17.8) | 53 (19.1) | 27 (20.3) | 26 (18.1) |
| PNI–positive [*n* (%)] | 80 (7.8) | 15 (5.4) | 6 (4.5) | 9 (6.3) |

[a] Boldface type marks values that reach $p < 0.05$ in comparison with the nondiabetic group.
LVI = lymphovascular invasion; PNI = perineural invasion.

with colorectal cancer, hepatocellular carcinoma, breast cancer, and bladder cancer, among others[20–25]. Many hypotheses have been put forward about the role that diabetes might play in tumour development, including mechanisms arising from hyperinsulinemia, hyperglycemia, and insulin resistance[26]. Elevated insulin levels might promote cancer cell proliferation by activation of insulin-like growth factor 1–mediated pathways in which tumour cells seem to overexpress insulin-like growth factor 1 receptor and receive long-term proliferation signals related to elevated insulin levels, likely increasing tumour recurrence and progression[26,27].

It has additionally been suggested that in CRC, diabetes might adversely affect survival by affecting the biology of the disease, stage at presentation, and treatment duration and toxicities, in addition to its effect on comorbidities[28].

**TABLE III** Deaths and overall survival, by study group

| Study group | Pts (*n*) | Deaths [*n* (%)] | Overall survival at ... | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1 Year (%) | *p* Value | 2 Years (%) | *p* Value | 3 Years (%) | *p* Value |
| Nondiabetic | 1027 | 392 (38.2) | 86.5 | Reference | 77.0 | Reference | 64.2 | Reference |
| Diabetic | 277 | 114 (41.2) | 85.6 | 0.695 | 73.6 | 0.265 | 62.5 | 0.622 |
| Taking metformin | 133 | 43 (32.3) | 91.0 | 0.171 | 80.5 | 0.440 | 72.2 | 0.082 |
| Taking other diabetes treatment | 144 | 71 (49.3) | 80.6 | 0.074 | 67.4 | 0.016 | 53.5 | 0.016 |

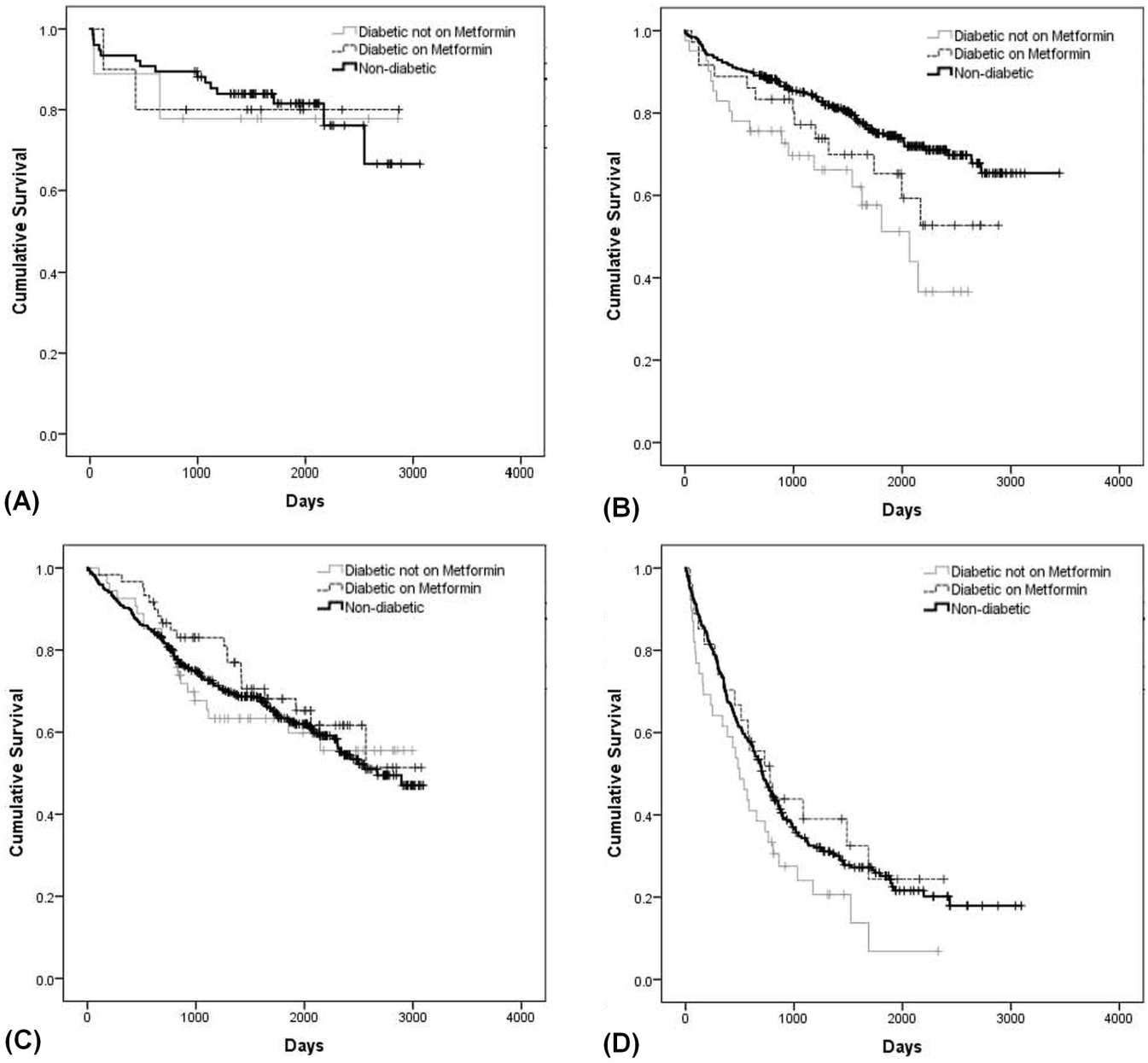


**FIGURE 1** Kaplan–Meier survival curves. Overall survival of patients by colorectal cancer stage, comparing nondiabetic patients (ND) with diabetic patients on all other treatments (DOT) and diabetic patients on metformin alone (DOM). (A) Stage I (76 ND, 10 DOT, 10 DOM; $p = 0.826$). (B) Stage II (323 ND, 41 DOT, 36 DOM; $p = 0.003$). (C) Stage III (370 ND, 54 DOT, 60 DOM; $p = 0.660$). (D) Stage IV (258 ND, 39 DOT, 27 DOM; $p = 0.020$).

**TABLE IV** All-stage Cox proportional hazards model

| Variable | Hazard ratio | 95% CI | *p* Value[a] |
|---|---|---|---|
| Sex | 0.903 | 0.756 to 1.078 | 0.260 |
| Age | 1.006 | 0.998 to 1.014 | 0.155 |
| Comorbidities | | | |
| Cardiac | 1.208 | 0.997 to 1.464 | 0.053 |
| Renal | 1.524 | 1.099 to 2.113 | **0.012** |
| Respiratory | 1.308 | 1.042 to 1.641 | **0.021** |
| Diabetic | | | |
| Taking metformin | 0.807 | 0.601 to 1.084 | 0.154 |
| Taking other diabetes Tx | 1.350 | 1.039 to 1.753 | **0.025** |
| Body mass index > 25 | 1.176 | 0.903 to 1.533 | 0.229 |
| Smoking history | 0.927 | 0.771 to 1.114 | 0.420 |
| Alcohol history | 0.907 | 0.752 to 1.096 | 0.313 |
| Family CRC history | 0.964 | 0.770 to 1.208 | 0.752 |
| Colon cancer | 1.362 | 0.961 to 1.929 | 0.082 |
| Tumour differentiation | | | |
| Moderate | 1.270 | 0.754 to 2.138 | 0.369 |
| Poor | 2.365 | 1.346 to 4.154 | **0.003** |
| Stage at diagnosis | 2.132 | 1.900 to 2.392 | **0.000** |

[a] Boldface type indicates significant results.
CI = confidence interval; Tx = treatment; CRC = colorectal cancer.

Our data suggest that the diabetic groups (whether taking metformin or not) and the nondiabetic group did not substantially differ with respect to patient characteristics, disease pathology, stage of disease (including extent of metastatic disease), and treatment duration and toxicities (data not shown), contradicting the published literature.

Previous studies have attempted to identify the effect of diabetes and metformin on both cancer-specific and overall mortality in CRC patients, but with varying results[17,29–32]. One focused on postmenopausal women only, another did not examine specific diabetes treatments, and the remaining studies did not provide a comparison to a nondiabetic control group[17–19,33,34]. Other studies, including a recent meta-analysis looking at the role of metformin with respect to cancer risk and mortality, suggested that metformin could reduce the risks, but did not assess the effect of tumour stage[35,36]. Our study adds further evidence of the negative effects of diabetes with respect to mortality, with the added observation that our patients on diabetes treatments other than metformin experienced worse survival than our nondiabetic patients. Compared with other studies, our study also looked at a more diverse population (which included nondiabetic and diabetic patients of both sexes, without an age limit) and examined tumour stage.

Our study provides potential evidence of the deleterious effects of diabetes treatments other than metformin on the diabetic CRC population, despite no identified differences in the extent of disease, time on treatment, or toxicity from chemotherapy. Our analysis therefore cannot determine the cause of the survival difference. Because of the nature of cancer treatment in our region, many patients are followed in the community after receiving treatment at our institution, and so progression or recurrence could not be fully captured. We were able to identify progression and recurrences in patients treated at our centre, but using those data would create bias because we would be limited to analyzing only patients treated at our institution. We consequently could not determine if the survival difference in patients taking metformin was the result of a difference in cancer progression or recurrence.

Although every attempt was made to minimize errors, our study has several limitations. Given the retrospective nature of the study, we were limited to the information available in consult notes, which at times was inconsistent or missing. Our multivariate analysis attempted to control for unrecorded information by including a category for "missing data" for each variable, which did not affect the overall results.

Although our study looked at all-cause mortality, we acknowledge that cancer-specific mortality would have been more appropriate. However, that information was not available because of restrictions in death certificate information (which is not stored in the hospital database) and lack of access to provincial databases. Although other studies have not controlled for BMI and for cardiac, respiratory, and renal comorbidities, we cannot conclude, based on our analysis, that the difference in the mortality observed in the diabetic patients taking metformin is strictly a result of differences in cancer-related death or of other factors. However, our observations do suggest a role of metformin in mortality.

Several important points about patients with diabetes have to be addressed. Because diabetes treatment was captured from consult notes, we could not address treatments used before the consult or determine whether treatments changed during the study interval. We could capture only a snapshot of any patient's treatment, potentially resulting in a time bias in the data. Additionally, the "other diabetes treatment" group included not only other oral and injectable agents, but also diet control, which might represent the earliest stage of diabetes. However, when we compared the diabetic populations taking metformin and taking other treatments, we found that the average HbA1c and the rate of diabetic complications were similar between the two groups, and yet a distinct difference in survival was evident, suggesting that the mortality difference might not be related to their glycemic control, but potentially to their oncologic diagnosis.

## CONCLUSIONS

Our study corroborates prior evidence that pre-existing diabetes increases all-cause mortality in CRC patients. Compared with nondiabetic patients, those with diabetes who are treated with any therapy other than metformin experience poorer survival, which did not appear to be secondary to differences in comorbidities or disease burden. Metformin might mitigate that survival disadvantage and might possibly even confer a survival advantage above that for nondiabetic patients with CRC. Taken together, our data suggest that, in the presence of diabetes as a comorbid condition, the use of metformin—especially in

the stage IV CRC population—might lower the risk of dying. The mechanism of mortality reduction in this population requires elucidation.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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