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ARTICLE

Diabetes and Clinical Outcome in Patients With Metastatic Colorectal Cancer: CALGB 80405 (Alliance)

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Abstract

Background: Diabetes is a prognostic factor for some malignancies, but its association with outcome in patients with advanced or metastatic colorectal cancer (CRC) is less clear.
Methods: This cohort study was nested within a randomized trial of first-line chemotherapy and bevacizumab and/or cetuximab for advanced or metastatic CRC. Patients were enrolled at 508 community and academic centers throughout the National Clinical Trials Network. The primary exposure was physician-documented diabetes at the time of enrollment. The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS) and adverse events. Tests of statistical significance were two-sided.
Results: Among 2326 patients, 378 (16.3%) had diabetes. The median follow-up time was 6.0 years. We observed 1973 OS events and 2173 PFS events. The median time to an OS event was 22.7 months among those with diabetes and 27.1 months among those without diabetes (HR = 1.27, 95% CI = 1.13 to 1.44; $P < .001$). The median time to a PFS event was 9.7 months among those with diabetes and 10.8 months among those without diabetes (HR = 1.16, 95% CI = 1.03 to 1.30; $P = .02$). Patients with diabetes were more likely to experience no less than grade 3 hypertension (8.1% vs 4.4%; $P = .054$) but were not more likely to experience other adverse events, including neuropathy.
Conclusions: Diabetes is associated with an increased risk of mortality and tumor progression in patients with advanced or metastatic CRC. Patients with diabetes tolerate first-line treatment with chemotherapy and monoclonal antibodies similarly to patients without diabetes.

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer, and the second most common cause of cancer death in the United States (1). Diabetes is also a leading cause of morbidity and mortality in the United States (2). Diabetes is associated with a 30% increased risk of developing CRC (3). At the time of diagnosis of CRC, one in six patients will have preexisting diabetes (4). Some studies, but not all, have demonstrated an association between diabetes and higher risk of disease recurrence and death in patients with localized or regional CRC (5–8). However, the clinical implications of diabetes in patients with advanced or metastatic CRC are less clear (9).

The biologic hallmark of type 2 diabetes is insulin resistance and hyperglycemia (10). This metabolic status is relevant because CRC cells express insulin receptors, and exposure to insulin and glucose promote cell proliferation, migration, and invasion (11). A fluoropyrimidine with oxaliplatin (FOLFOX) or

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irinotecan (FOLFIRI) are recommended as first-line chemotherapy regimens for metastatic CRC (12). In vitro studies demonstrate that hyperinsulinemia and hyperglycemia increase CRC cell resistance to fluoropyrimidine, oxaliplatin, and irinotecan therapies (13–15). Consequently, patients with metastatic CRC and diabetes may be at an increased risk of tumor progression and overall mortality compared with those patients with metastatic CRC without diabetes.

Moreover, peripheral neuropathy is a common adverse event of oxaliplatin (16). Patients with diabetes are susceptible to the development or exacerbation of diabetic-related neuropathy (17). Patients with diabetes develop neuropathy at lower cumulative doses of oxaliplatin (18), demonstrating the increased vulnerability of patients with diabetes to experience treatment-related adverse events (19). However, evidence describing the incidence of treatment-related adverse events in patients with diabetes receiving therapy for advanced or metastatic CRC is limited (20).

We prospectively examined the relationship between diabetes with clinical outcome in a cohort of patients with advanced or metastatic CRC who were enrolled in a National Cancer Institute–sponsored randomized clinical trial of first-line chemotherapy. In this trial, physicians selected FOLFOX or FOLFIRI as the backbone chemotherapy regimen and then patients were randomly assigned to targeted monoclonal antibody(s): cetuximab or bevacizumab or their combination (21). We hypothesized that diabetes at trial enrollment would be associated with lower physician selection of FOLFOX; shorter progression-free survival; shorter overall survival; and higher incidence of treatment-related adverse events, as compared with patients without diabetes.

Methods

Study Design

Patients in this study participated in the National Cancer Institute-sponsored Cancer and Leukemia Group B (CALGB; now part of the Alliance for Clinical Trials in Oncology) 80405 trial of chemotherapy plus biologic monoclonal antibodies for advanced or metastatic CRC. The initial clinical trial design compared chemotherapy plus cetuximab; chemotherapy plus bevacizumab; and chemotherapy plus cetuximab and bevacizumab (ClinicalTrials.gov NCT00265850). After 3 years of enrollment, the lack of efficacy for epidermal growth factor receptor antibodies in *KRAS*-mutated tumors and the failure of dual-antibody combination treatments resulted in two consecutive amendments that restricted eligibility to patients with *KRAS* wild-type tumors (*KRAS* amendment) and closure of the dual-antibody arm. The final clinical trial design compared chemotherapy plus cetuximab to chemotherapy plus bevacizumab (21). However, this analysis included all patients, irrespective of their *KRAS* status, who were randomly assigned to any of the original three treatment arms.

Patient Eligibility

Eligibility for the treatment trial has been described (21). Briefly, eligible patients had pathologically confirmed previously untreated locally advanced or metastatic CRC. Patients were aged 18 years and older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and normal hepatic, renal, and hematologic laboratory values. Patients had to be candidates for either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) chemotherapy regimens without known central nervous system metastases or no less than grade 2 peripheral neuropathy (neuropathy exclusion only applicable to patients whose physician chose FOLFOX). In addition, hypertension had to be well controlled (blood pressure $<$160/90 mm Hg with treatment) without concurrent congestive heart failure. Patients were recruited from 508 study sites in the United States and Canada. Institutional review board approval was required at all study centers, and all patients provided written informed consent.

Diabetes Assessment

At the time of enrollment into the clinical trial, research staff documented physician-diagnosed history of diabetes from the medical record utilizing a standardized form. A subset of participants also completed a self-reported questionnaire that assessed a history of "physician-diagnosed diabetes or high blood sugars" (see lifestyle substudy below for additional detail). The primary analysis implemented a hierarchical approach that used diabetes abstracted from the medical record and supplemented by the lifestyle substudy.

Study Endpoints

The primary endpoint of CALGB/SWOG 80405 (Alliance) and this companion study was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and treatment-related adverse events. OS was defined as the time from randomization until death from any cause. Patients without reported death were censored at their last known follow-up. PFS was defined as the time from random assignment until first documented evidence of tumor progression or death from any cause. Patients were evaluated every 8 weeks for response with radiologic imaging using the RECIST criteria [Version 1.0; (22)]. Tumor progression was determined by the treating physician. Patients alive without documented tumor progression were censored for progression at the most recent disease assessment. Adverse events were assessed by the treating physician or other qualified health-care provider every two weeks. Adverse events were graded and attribution was assigned according to the National Cancer Institute Common Terminology Criteria for Adverse Events [Version 3.0; (23)]. For each patient, the maximum grade for each toxicity was analyzed.

Covariates

Data for patient characteristics including age, sex, race, body mass index, ECOG performance status, primary tumor location, prior chemotherapy, prior radiotherapy, and primary tumor resection status were obtained from a combination of patient self-report, physician assessment, and the medical record. At the time of enrollment, patients could also optionally participate in an observational lifestyle substudy (described below).

Lifestyle Substudy

Patients who elected to enroll in the lifestyle substudy (1354 of 2334; 58%) were provided with a self-report questionnaire

within the first month after random assignment that obtained information regarding use of oral hypoglycemic medication and/or insulin for "diabetes mellitus or high blood sugars" and time since physician diagnosis of this condition. Patients who enrolled in the lifestyle substudy also provided data that were used as covariates in supplementary multivariable-adjusted analyses.

Statistical Analysis

The primary statistical analysis compared clinical outcome by diabetes status at the time of trial enrollment. The Wilcoxon rank-sum test was used to compare the distribution of continuous variables and χ^2 tests were used to compare the distribution of categorical variables. Concordance between diabetes abstracted from the medical record compared to self-reported diabetes in the lifestyle substudy was compared using kappa coefficient (24). Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) between diabetes status with OS or PFS (25). The proportional hazards assumption was examined by including time-dependent covariates in the regression models and visually inspecting log-log plots. Sensitivity analyses were conducted using Fine-Gray competing risk regression models (26). Subgroup effect modification was examined by testing the statistical interaction term between diabetes variable and subgroup. Logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval between diabetes status and treatment-related adverse events. All analyses are based on data freeze for long-term follow-up on January 8, 2018. Data collection was conducted by the Alliance Statistics and Data Center. A two-sided *P* value less than .05 was considered statistically significant.

Results

Patient Characteristics

This study was conducted between October 2005 and February 2012. Characteristics of the 2326 patients by diabetes status are presented in Table 1. Of the patients, 378 had a medical record of diabetes (16.3%). Patients with diabetes were older (63.0 vs 58.4 years; $P < .001$), had a higher body mass index (29.5 vs 26.7 kg/m^2; $P < .001$), and poorer ECOG performance status (46.8% vs 40.5% with ECOG PS 1–2; $P = .02$). Characteristics associated with participation in the lifestyle substudy (Figure 1; Supplementary Table 1, available online) and additional characteristics associated with diabetes are presented as supplementary material (Supplementary Tables 2 and 3, available online). Among participants who enrolled in the lifestyle substudy, the agreement between medical record documentation of diabetes and self-reported history of diabetes was high (Cohen $\kappa = 0.83$, 95% CI = 0.79 to 0.87).

Associations Between Physician Selection of Chemotherapy Regimen With Diabetes

Patients with diabetes were less likely to receive FOLFOX (72.6 vs 78.1%; multivariable-adjusted $P = .03$) as the physician-selected backbone chemotherapy regimen. This result was similar when restricted to patients who had not received prior postoperative chemotherapy (74.1% vs 82.9%; multivariable-adjusted $P < .001$).

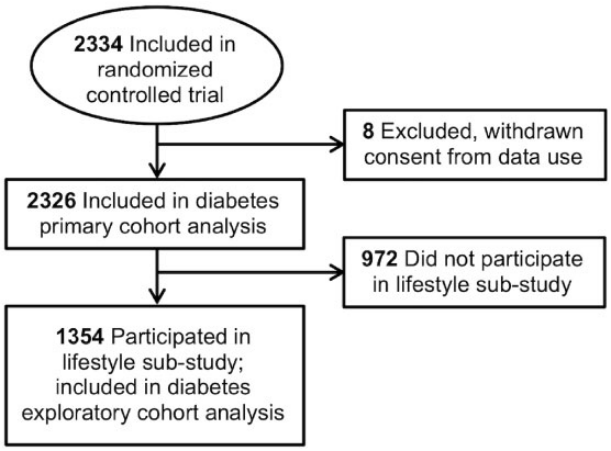

Figure 1. Consolidated Standards of Reporting Trials.

Associations Between Progression-Free and Overall Survival With Diabetes

The median follow-up time from randomization was 6.0 years. During follow-up, we observed 2173 PFS events and 1973 OS events. The associations between diabetes with PFS and OS are presented in Table 2. Patients with diabetes experienced shorter OS than those without diabetes; the median OS was 22.7 months among those with diabetes and 27.1 months among those without diabetes (multivariable-adjusted HR = 1.27, 95% CI = 1.13 to 1.44; $P < .001$). Results were similar in competing-risk regression models (Supplementary Table 4, available online). Patients with diabetes experienced shorter PFS than those without diabetes; the median PFS was 9.7 months among those with diabetes and 10.8 months among those without diabetes (multivariable-adjusted HR = 1.16, 95% CI = 1.03 to 1.30, $P = .02$). In subgroup analyses, performance status modified the association between diabetes and PFS ($P_{interaction} = .02$) but not OS ($P = .30$; Figure 2). Patients with diabetes had a higher risk of PFS with a poorer performance status (eg, ECOG $\geq$1). The above described results were not substantively different when additionally adjusted for covariates measured in the lifestyle substudy that included physical activity, weight history, smoking history, comorbid health conditions, and use of pharmacotherapy for hyperlipidemia and hypertension (Supplementary Table 5, available online).

Among those treated with FOLFOX, the proportion receiving no less than 70% relative dose intensity of oxaliplatin did not differ between patients with and without diabetes (65.5% vs 65.9%; multivariable-adjusted $P = .92$). Among those initially treated with FOLFIRI, the proportion who received FOLFOX as a second-line therapy was lower among patients with vs without diabetes (48.9% vs 64.1%; multivariable-adjusted $P < .001$).

Associations Between Treatment-Related Adverse Events With Diabetes

The associations between diabetes and adverse events are presented in Table 3. Patients with diabetes were more likely to experience no less than grade 3 hypertension at least possibly related to treatment (8.1% vs 4.4%; multivariable-adjusted $P = .054$). Patients with diabetes experienced similar rates of no less than grade 2 neuropathy (36.6% vs 36.3%; multivariable-adjusted $P = .99$). Results were similar in analyses that were

Table 1. Baseline characteristics by diabetes status*

Characteristic	No. (%) no diabetes (n = 1948; 83.7%)	No. (%) diabetes (n = 378; 16.3%)	P
Age, median (IQR), y	58.4 (50.2–66.8)	63.0 (55.2–70.6)	<.001
Sex			.37
Male	1127 (57.9)	228 (60.3)	
Female	821 (42.1)	150 (39.7)	
Race			.30
White	1595 (81.9)	301 (79.6)	
Black	224 (11.5)	54 (14.3)	
Other/missing	129 (6.6)	23 (6.1)	
Body mass index, median (IQR), kg/m^2	26.7 (23.5–30.5)	29.5 (26.1–33.6)	<.001
ECOG performance status			.02
0	1160 (59.5)	201 (53.2)	
1–2	788 (40.5)	177 (46.8)	
Colorectal tumor location			.12
Left	513 (26.3)	103 (27.2)	
Transverse	136 (7.0)	33 (8.7)	
Right	1136 (58.3)	200 (52.9)	
Multiple or unknown	163 (8.4)	42 (11.1)	
Protocol chemotherapy			.001
FOLFIRI	420 (21.6)	110 (29.1)	
mFOLFOX6	1528 (78.4)	268 (70.9)	
Prior chemotherapy	277 (14.2)	57 (15.1)	.66
Prior radiotherapy	165 (8.5)	40 (10.6)	.19
Primary tumor unresected at study entry	450 (23.1)	81 (21.4)	.48
KRAS amendment status			.28
Pre-amendment	1197 (61.4)	221 (58.5)	
Postamendment	751 (38.6)	157 (41.5)	
Randomized treatment arm			.60
Bevacizumab	743 (38.1)	154 (40.7)	
Cetuximab	754 (38.7)	143 (37.8)	
Bevacizumab + Cetuximab	451 (23.2)	81 (21.4)	
KRAS status			.98
Wild-type	1088 (55.9)	211 (55.8)	
Mutated	348 (17.9)	69 (18.3)	
Unknown	512 (26.3)	98 (25.9)	
Lifestyle substudy			.21
Enrolled	1123 (57.6)	231 (61.1)	
Declined	825 (42.4)	147 (38.9)	

*ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, irinotecan; IQR = interquartile range; mFOLFOX6 = 5-fluorouracil, leucovorin, oxaliplatin.

additionally adjusted for covariates measured in the lifestyle substudy (Supplementary Table 6 available online).

Associations Between Progression-Free and Overall Survival With Diabetes, Stratified by Diabetes Therapy and Duration of Diagnosis

The associations between diabetes with PFS and OS stratified by patients who did and did not use insulin are presented in Supplementary Table 7 (available online). The associations between duration of diabetes status with PFS and OS are presented in Supplementary Table 8 (available online).

Discussion

Physicians were more likely to select an irinotecan-containing regimen (FOLFIRI) as a first-line chemotherapy backbone for patients with diabetes when compared with patients without diabetes; nevertheless, 72.6% of patients with diabetes were treated with an oxaliplatin-containing regimen (FOLFOX). Patients with advanced or metastatic CRC and diabetes experienced a shorter time to tumor progression and overall mortality when compared with patients without diabetes. These associations persisted after adjustment for established prognostic factors of tumor progression and survival. Except for hypertension, patients with diabetes experienced a similar rate of treatment-related adverse events compared with patients without diabetes.

Diabetes is associated with the risk of developing and dying from a variety of cancers, including CRC (27). In a systematic review and meta-analysis of 26 studies of patients with CRC, diabetes was associated with a 17% increased risk of overall mortality when compared with patients without diabetes (8). However, studies conducted to date have often included smaller sample sizes, with data obtained retrospectively from single institution hospital records or from registry and administrative claims data. Moreover, studies often combine patients with nonmetastatic and metastatic CRC, inconsistently measure outcome events, and are limited in their ability to adjust for prognostic or confounding variables, such as age, sex, performance status, and body mass index (8,28).

Table 2. Progression-free survival and overall survival estimates by diabetes status

Outcome and exposure category	No. of events	No. at risk	Median time-to-event (IQR) months	Unadjusted		Multivariable adjusted*	
				HR (95% CI)	*P*	HR (95% CI)	*P*
Progression-free survival							
No diabetes	1816	1948	10.8 (10.4–11.1)	1.00 (Referent)	—	1.00 (Referent)	—
Diabetes	357	378	9.7 (9.2–10.5)	1.15 (1.02 to 1.29)	.02	1.16 (1.03 to 1.30)	.02
Overall survival							
No diabetes	1638	1948	27.1 (25.9–28.5)	1.00 (Referent)	—	1.00 (Referent)	—
Diabetes	335	378	22.7 (20.0–24.6)	1.27 (1.13 to 1.43)	<.001	1.27 (1.13 to 1.44)	<.001

*The multivariable-adjusted regression model is adjusted for age, sex, race, body mass index, Eastern Cooperative Oncology Group performance status, colorectal tumor location, protocol chemotherapy, prior chemotherapy, prior radiotherapy, intact primary tumor, randomized treatment arm, and KRAS status. CI = confidence interval; HR = hazard ratio; IQR = interquartile range.

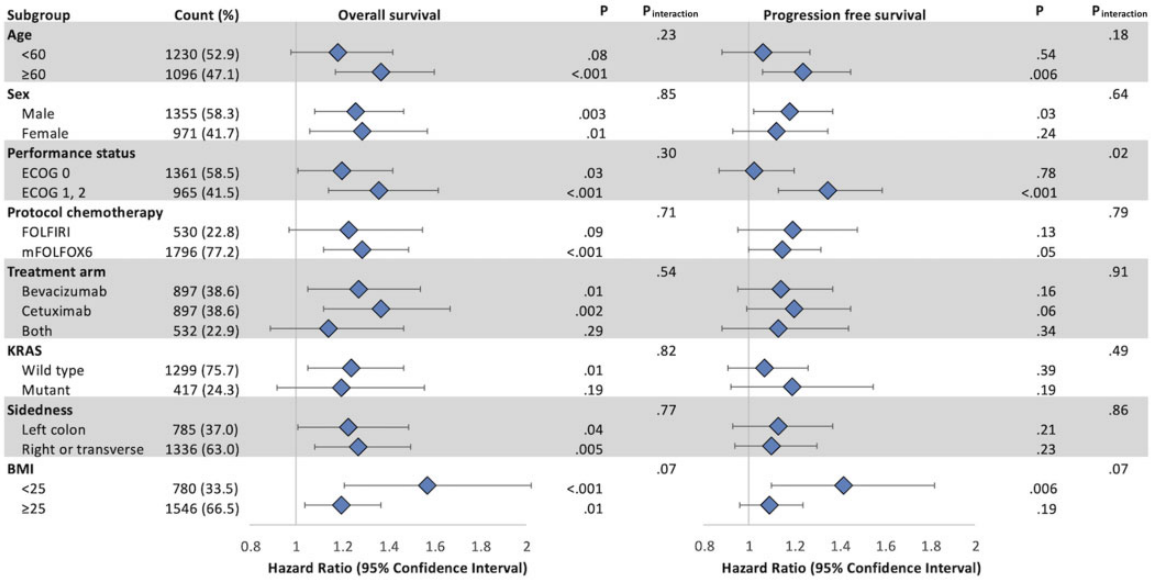

Figure 2. Subgroup analyses of progression-free survival and overall survival estimates by diabetes status. BMI, kg/m^2. BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, irinotecan; mFOLFOX6 = 5-fluorouracil, leucovorin, oxaliplatin.

Nesting a cohort study within a clinical trial to examine the association of diabetes with clinical outcome offers several advantages over the use of other data sources. First, our prospective study included 2326 patients who were recruited from 508 community and academic study sites throughout the United States and Canada, which improves the representation of this trial population over prior studies. Second, because of uniform enrollment criteria, disease status of study participants was well characterized, thereby reducing unmeasured heterogeneity. Third, because this analysis was conducted within the context of a therapeutic trial, treatment, follow-up care, and endpoint ascertainment were conducted according to a standardized protocol, and the date of tumor progression was prospectively recorded, allowing for consistent definition of PFS. Last, detailed information on confounding variables such as age, sex, performance status, and body mass index were collected from all participants. Supplementary analyses of patients who enrolled in the lifestyle substudy allowed for additional adjustment of potential confounding variables such as physical activity, weight history, smoking history, comorbid health conditions, and select medication use.

There are several important limitations of the current study. Patients who enroll in a clinical trial may differ from the underlying population (29), thereby influencing the generalizability of our findings. Patients with no less than preexisting grade 2 peripheral neuropathy at baseline were excluded from study enrollment if their physician desired to use FOLFOX, potentially reducing the generalizability of our findings. However, because our study population included patients recruited throughout the United States and Canada in community and academic sites, we believe that our findings may reflect the general population of CRC patients who are appropriate candidates for systemic therapy. Moreover, the 16.3% prevalence of diabetes at enrollment is consistent with population-based estimates in cancer patients (4). Diabetes status was obtained from the medical record at the time of trial enrollment. It is possible that there is misclassification of diabetes as our exposure measure. However, we would expect this misclassification to be nondifferential with respect to clinical outcome and bias our effect estimates toward the null. Because of the observational study design, we cannot rule out the possibility of residual confounding. However, the primary study endpoint, OS, was robust to adjustment for a variety of demographic-, clinical-, and

Table 3. Adverse events by diabetes status

Adverse event*	No. (%) no diabetes (n = 1948; 83.7%)	No. (%) diabetes (n = 378; 16.3%)	Odds ratio (95% CI)§	P§
Blood and/or bone marrow				
Neutropenia	621 (31.9)	114 (30.2)	0.91 (0.71 to 1.19)	.50
Anemia	36 (1.8)	7 (1.9)	0.80 (0.34 to 1.90)	.61
Gastrointestinal				
Diarrhea	210 (10.8)	52 (13.8)	1.15 (0.81 to 1.62)	.44
Dehydration	90 (4.6)	12 (3.2)	0.58 (0.31 to 1.10)	.09
Nausea	57 (2.9)	16 (4.2)	1.38 (0.76 to 2.52)	.29
Vomiting	59 (3.0)	14 (3.7)	1.28 (0.69 to 2.39)	.44
Anorexia	60 (3.1)	10 (2.6)	0.73 (0.36 to 1.48)	.39
Neurologic				
Neuropathy†	555 (36.3)	98 (36.6)	1.00 (0.76 to 1.32)	.99
Other				
Fatigue	186 (9.5)	37 (9.8)	0.92 (0.62 to 1.36)	.67
Severe weight loss	28 (1.4)	2 (0.5)	0.32 (0.07 to 1.40)	.13
Hypertension‡	52 (4.4)	19 (8.1)	1.78 (0.99 to 3.20)	.054
Pain	95 (4.9)	16 (4.2)	0.76 (0.43 to 1.33)	.34
Any AE as defined above	1207 (62.0)	228 (60.3)	0.94 (0.74 to 1.20)	.63

*Adverse events (AE) were included if they were grade ≥3, judged as being possibly, probably, or definitely related to treatment. CI = confidence interval.
†Neuropathy was included if it was grade ≥2, judged as being possibly, probably, or definitely related to treatment and were treated with mFOLFOX6.
‡Hypertension was included if it was grade ≥3, judged as being possibly, probably, or definitely related to treatment and were treated with bevacizumab.
§The multivariable-adjusted regression model and corresponding P values are adjusted for age, sex, race, body mass index, Eastern Cooperative Oncology Group performance status, colorectal tumor location, protocol chemotherapy, prior chemotherapy, prior radiotherapy, intact primary tumor, randomized treatment arm, and KRAS status.

treatment-related covariates. In supplementary analyses, these results persisted after multivariable adjustment for multiple behavioral and lifestyle factors. This study was designed prior to seminal reports that described the antineoplastic properties of metformin (30,31). Consequently, our questionnaire did not specifically inquire about the class of antidiabetic oral medication precluding our ability to replicate this prior finding. Participants who enrolled in the observational lifestyle substudy differed from those who did not enroll on several demographic-, clinical-, and treatment-related factors, which may limit generalizability of these; however, the prevalence of diabetes did not differ (P = .21).

If the association between diabetes and clinical outcome is causal, there are several plausible biologic pathways. The physiologic mechanisms that link diabetes with cancer outcomes may include hyperinsulinemia (including insulin-like growth factors and their binding proteins), hyperglycemia, and inflammation (32). Insulin resistance and resultant endogenous hyperinsulinemia may promote gene transcription and cell growth and the inhibition of apoptosis through activation of the PI3K-Akt-mTOR pathway (32,33). Hyperglycemia may promote cell proliferation through the generation of reactive oxygen species and subsequent activation of the extracellular-signal-regulated kinases–mitogen-activated protein kinases pathway (32). Diabetes and body mass index were marginally interactive with both PFS and OS. Among individuals with diabetes, lower body mass index is associated with a higher risk of cancer-specific and all-cause mortality (34). The biological rationale proposed for this association is that diabetes in normal weight has an increased genetic influence and more severe disease (35,36). Further translational research is necessary to elucidate these hypothesized physiologic mechanisms toward the goal of identifying additional therapeutic targets.

If the association between diabetes and clinical outcome is not causal, there are several plausible alternative explanations. Patients with diabetes often have additional comorbid health conditions, such as cardiovascular and pulmonary disease, which are independently prognostic of clinical outcome. However, in exploratory analyses, adjustment for these comorbid health conditions among patients who enrolled in the lifestyle substudy modestly attenuated our effect estimates for OS. We demonstrated that physicians less frequently use the oxaliplatin-containing FOLFOX regimen in patients with diabetes. Although the FOLFOX regimen and irinotecan-containing FOLFIRI regimen have similar efficacy in the first-line setting for advanced or metastatic CRC (12), patients with diabetes may never receive treatment with oxaliplatin in later lines of therapy. Our subgroup analyses did not identify an interaction effect between diabetes and physician-selected chemotherapy (P = .71) or randomized biologic therapy (P = .54). Further, there was no effect modification by cytotoxic chemotherapy regimen on outcomes; thus, patients who started on FOLFOX had similar OS and PFS compared to those started on FOLFIRI. Last, it is possible that with the diagnosis of metastatic CRC, less attention is devoted to glycemic management and control of other relevant cardiovascular risk factors, which may increase overall morality without directly influencing cancer growth or metastatic potential. However, we did observe a statistically significant effect of diabetes on PFS, suggesting that diabetes may have a direct effect on tumor growth and progression.

In conclusion, our data support the hypothesis that diabetes is associated with an increased risk of mortality and tumor progression in patients with metastatic CRC. These results underscore the need for further research to understand the physiologic mechanisms that underpin this relationship. Patients with diabetes tolerate first-line treatment with chemotherapy and monoclonal antibodies similarly to patients without diabetes.

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