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Survival benefits in colorectal adenocarcinoma with the use of metformin among a black diabetic inner city population

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Abstract

We assessed the association of metformin use with survival in colorectal cancer in a population consists mostly of African-American and Afro-Caribbean patients. We identified 585 colorectal cancer patients, 167 (28.6%) and 418 (71.5%) were as diabetic (DM) and nondiabetic, respectively. The diagnosis of diabetes did not impact cancer survival or extent of disease. Overall, DMs with metformin use (D+M+) have better overall survival than both DMs without metformin use (D+M~) and nondiabetics (D~M~), with a mean survival of 109.9 months compared with 95.7 and 106.1 months, respectively (log-rank $p < 0.05$). The use of metformin shows significant reduction of risk of mortality compared with nonusers (hazard ratio: 0.34; 95% CI: 0.15–0.81; $p = 0.01$). Use of insulin and status of diabetes did not have a significant impact on overall cancer survival.

Keywords

African-American; Afro-Caribbean; colorectal cancer; diabetes; metformin; survival

Colorectal cancer (CRC) is the third leading cause of cancer-specific mortality in the USA for men and women and is accountable for 694,000 deaths estimated to have occurred in 2012 [1]. The estimated incidence of CRC cases in the USA is nearly 140,000 as per the American Cancer Society. Many risk factors, such as age, black race, metabolic syndrome, smoking and low-fiber diet, are associated with decreased overall survival (OS) [2–4]. The risk of developing CRC has been demonstrated to be increased in diabetes, but may be influenced by medications such as metformin, the first-line treatment for Type 2 diabetes mellitus [5–8]. Recent studies have shown that this drug is associated with a decrease in occurrence and overall cancer mortality in pre-surgical diabetics (DMs) [9]. Although the

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

association between the two diseases is well studied, data regarding the impact of metformin on CRC outcomes in African descendant, a population that has the highest CRC incidence rate out of all ethnicities, is underrepresented and can be examined in our institution, a safety net hospital that serves predominantly African–American and Afro–Caribbean.

Methods

Data collection/chart review

This is a single institution retrospective chart review of all patients with colon or rectal adenocarcinoma diagnosed from January 2002 to November 2014. The study has been submitted to the institutional review board (State University of New York Downstate College of Medicine) for review and approval. Patients over 18 years of age with colon or rectal cancer were identified via tumor registry at the institution using the ICD-0–3 code C180, C182–C189, C199 and C209. Then, patient data were collected through reviewing patient health information using electronic health record. For the chart review, we obtained information regarding demographics information such as age at diagnosis, race/ethnicity and sex, tumor node metastasis classifications, American Joint Committee on Cancer (AJCC) disease stage, pathological diagnosis, DM status, BMI, metformin and insulin use at the time of diagnosis and survival after cancer diagnosis. This information was extracted through reviewing patient's electronic health record. The records include notes written by physicians, nursing notes, laboratory values, pharmacy records, etc. Findings other than adenocarcinoma on pathology were excluded from the study. Patients with metastatic disease from a primary source other than colon or rectum were also excluded.

Patients were first stratified into two groups: DMs and nondiabetics (non-DM). Then, these two groups were further stratified into three groups by diabetes status and metformin use at the time of diagnosis: DMs who are using metformin (D+M+), DMs who were not on metformin (D+M~) and patients without diabetes (D~M~).

Statistical method

Patient characteristics were reported as means and plus or minus standard deviation for continuous variables and as relative frequencies for categorical variables. The survival outcomes, OS were analyzed using Kaplan–Meier estimator, including the log-ranked test and the Cox regression model. The survival outcomes were analyzed using standard Kaplan–Meier methods. The log-rank test was used to compare survival among the different groups (i.e., DM vs non-DM). Cox regression models were used to obtain hazard ratios (HRs) for comparing risks of OS.

All statistical analysis was conducted using MedCalc for Windows, version 16.2.0 (MedCalc Software, Ostend, Belgium).

Results

We identified 585 patients diagnosed with CRC with the inclusion criteria and the exclusion criteria (Table 1). A total of 509 (87%) black and 58 (9.9%) non-Hispanic white patients were identified. A total of 167 (28.6%) and 418 (71.5%) were identified as DM and non-

DM, respectively. DM was significantly older than non-DM, 65.1 versus 60.5 years ($p < 0.001$). The DM group also had higher BMI when compared with non-DM groups. DM group comprised 42.5% males compared with 52.9% of the non-DM group. There are more white patients in the non-DM group than in the DM group (12.0 vs 4.8%; $p = 0.03$). There is no difference in the AJCC staging of disease and locations of the tumor between the two groups ($p > 0.05$). The Kaplan–Meier plot showed no significant survival difference between DM and non-DM group, 111.6 vs 106.1 months, respectively (log-rank $p = 0.56$) (Figure 1).

Out of 167 who had diabetes, 74 patients had metformin on their medication list at the time of diagnosis (Table 1). DMs who use metformin (D+M+) and DMs without metformin use (D+M~) have an average age of 63.4 versus 66.5 years ($p = 0.10$). There is no difference in the distribution of race, gender, AJCC staging of disease and tumor location between the two groups ($p > 0.05$). D+M+ group was found to have a longer mean OS than D+M~ group, 109.9 versus 95.7 months (log-rank $p < 0.01$). When comparing all three groups (D~M~, D+M~ and D+M+), D+M+ groups show to have statistically significant improved survival outcome than the other two groups (log-rank $p < 0.05$) (Figure 2).

Multivariate analyses were used to identify factors independently associated with overall mortality. DM disease does not make a difference in survival in our patient population (HR: 1.32; 95% CI: 0.73–2.39; $p = 0.35$). Metformin use was a beneficial prognostic factor associated with decrease in overall mortality (HR: 0.34; 95% CI: 0.15–0.81; $p = 0.01$) (Table 2). Metastatic disease has a significantly increased hazard (HR: 10.51; 95% CI: 6.96–15.89; $p < 0.0001$). Insulin use, on the other hand, does not have a significant impact on survival (HR: 0.85; 95% CI: 0.41–1.76; $p = 0.85$). In the subgroup of patients who had metastatic disease, there was no significant survival difference between the three groups with the overall median survival of 1.72 years (Figure 3). Excluding those with metastatic disease, there was no 10-year mortality in the D+M+ group, but D+M~ and D~M~ had 10-year mortality rates of 16.67 and 9.56%, respectively (log-rank $p < 0.01$) (Figure 4).

Discussion

CRC is the third leading cause of cancer-specific mortality in the USA for men and women and is accountable for 694,000 deaths estimated to have occurred in 2012 [1]. The estimated incidence of CRC cases in the USA is almost 140,000 according to the American Cancer Society. In 2011 to 2012, the prevalence of diabetes among USA adults was around 12–14%, which has doubled since 1994 [10]. Diabetes has been associated with elevated risk of developing CRC and increased mortality rates in these patients [7–9,11].

In our retrospective study, we demonstrated that pre-existing diabetes does not have an impact on CRC survival in our population. However, when we separated the DM group by the status of metformin use, we observed a significant survival difference among D~M~, D+M~ and D+M+ groups and that metformin use was associated with a 70% decreased in all-cause mortality in our population, altogether highlighting this drug's potential anticancer properties in CRC patients.

We observed no mortality in the D+M+ group when we examined patients diagnosed with nonmetastatic disease. This observation may suggest metformin as a protective factor for nonmetastatic disease patients. We also observed no significant difference in survival in patients with metastatic disease, inconsistent with the current data on metformin and likely due to the small sample size ($n = 14$) in that group.

One commonly accepted mechanism of carcinogenesis in DM patients is chronic hyperinsulinemia in insulin-resistant patients. Exogenous insulin administration has also been linked to neoplastic disease as evidence has shown a significant increase in cancer-related mortality in insulin-treated Type II diabetes mellitus (T2DM) patients [11]. Hyperinsulinemia contributes to carcinogenesis through overactivation of the insulin receptor, IGF-1 receptor and hybrid insulin/IGF-1 receptors that are all expressed in colorectal epithelial and carcinoma cells. Activation of these receptors triggers both the PI3K/Akt and mitogenic-activated protein kinase pathways [12,13]. The protein kinase Akt regulates mRNA translation of the mammalian target of rapamycin complex 1 pathway that functions in cell metabolism and proliferation. Activation of the mitogenic-activated protein kinase pathway leads to ERK-mediated phosphorylation of substrates, such as c-Jun, c-Fos and c-Myc, that govern cell survival and growth [12].

Other mechanisms have also been postulated to explain the relationship between diabetes and cancer. Hyperglycemia is associated with accelerated tumor growth through increased advanced glycation end-product formation, contributing to DNA damage via induction of oxidative stress primarily in lymphocytes needed in cell-mediated immunity [12,14]. Elevated levels of inflammatory cytokines such as IL6 and TNF- α exhibited in diabetes have also been implicated in multiple cancer types [3,12].

Metformin is an oral biguanide commonly used as first-line treatment for T2DM mainly through its inhibition of hepatic gluconeogenesis, a process that is increased by twofold in these patients [15,16]. Its efficacy is comparable to those of insulin and sulfonylurea when used as monotherapy for T2DM with an added benefit of weight loss in obese, insulin-resistant patients [15]. Although the exact mechanism of metformin's reduction in gluconeogenesis is unclear, it has been proposed to be due to disruption of respiratory chain oxidation of complex I substrates that affect cellular respiration and in turn, gluconeogenesis [15]. Its glucose-lowering effect has also been attributed to a lesser extent to its inhibition of glycogenolysis and insulin-sensitizing capacity, which stimulates glucose uptake in skeletal muscle and adipocytes [15,17]. This is explained in part by metformin's reduction in free fatty acid oxidation as the accumulation of byproducts in this process inhibits glycolysis that leads to the reduction of glucose uptake and oxidation via inhibition of the glycolytic enzyme hexokinase [15].

Metformin has been gaining interest for its anticancer properties and has demonstrated *in vitro* growth inhibition of cancer cells in colorectal, breast, renal cell, pancreatic and lung cancers [18–21]. It has been observed that in T2DM patients using sulfonylureas or exogenous insulin, the risk of cancer-related mortality was significantly increased compared with metformin users [11]. Low dose metformin recently has also been demonstrated to

decrease incidence of metachronous adenoma formation after polypectomy in a randomized controlled trial.

There have been several proposed mechanisms explaining metformin's antineoplastic effects. It is currently proposed that metformin reduces circulating insulin and IGF-1 levels, leading to inhibition of the mTORC1 pathway, which regulates cell proliferation [7,12]. Second, metformin's insulin sensitizing effect on peripheral tissues attenuates hyperinsulinemia, which inhibits carcinogenesis through the previously stated mechanism [4,11,15].

Metformin has been proposed to selectively kill cancer stem cells (CSC). The CSC hypothesis suggests that cancers are driven by a subset of cells that are chemoresistant and have the capacity to repopulate a tumor, thus leading to relapse of disease. Drugs that specifically target these cells can potentially serve as alternative treatments and work has shown that metformin specifically targets CSCs through mTOR inhibition that subsequently leads to suppression of the S6K1 and 4EBP1, two effectors needed for proliferation of CSCs [22]. Metformin has been demonstrated to selectively inhibit growth of a subpopulation of breast cancer cells that both express the stem cell marker CD44 and have the ability to form new breast cancer tumor [23]. Metformin's targeting of CSCs suggests that possible treatment in conjunction with current chemotherapeutic agents may have therapeutic benefit. One study has shown that combinatorial treatment of metformin and the chemotherapeutic doxorubicin leads to death of both CSCs and nonstem cancer cells in culture and prolonged relapse rate in a mouse xenograft model of breast cancer cells [23]. Similar promising findings have been seen with other chemotherapeutic agents such as paclitaxel and cisplatin [24,25]. Moreover, CSCs in CRC are CD133 high/CD44 high expressing and exhibit radiation resistance, further investigation is needed to examine the effect of metformin use in patients treated with neoadjuvant or adjuvant chemotherapy on both mortality and relapse rate [26].

Metformin's selective targeting of CSCs also suggests that it can potentially be used in preventing metastasis. Metformin inhibits epithelial to mesenchymal transition that involves epithelial cancer cells acquiring mesenchymal properties and gives them capacity for both prolonged survival and metastasis through breakdown of cell-cell junctions and changes to the cytoskeleton [17]. It has been proposed that metformin interferes with epithelial to mesenchymal transition via inhibition of the mTOR-S6K pathway, which when activated leads to expression of p70S6K and in turn, underexpression of E-cadherin needed for cell adhesion [27]. Many reports have highlighted metformin's antimetastatic potential, including findings that demonstrate metformin's inhibition of migration and invasion of fibrosarcoma cells as well as decreased metastasis in a mouse xenograft model of ovarian cancer [28,29].

The black population generally has the highest CRC incidence rate of all ethnic groups and is 20% more likely to have CRC than the white population [30]. Black patients also tend to be diagnosed at a later stage compared with whites and predominantly suffer from right-sided tumors. Moreover, racial disparities exist in CRC screening, which may be due to many reasons such as low-socioeconomic status, education and cultural factors.

Additionally, the prevalence of T2DM among non-Hispanic black youth is about five-times that of non-Hispanic white youth [31]. Altogether, it is prudent to understand CRC trends in mortality, metastasis and relapse as well as metformin's impact on these factors in our safety net hospital that serves predominantly African-Americans and Afro-Caribbeans, as this population is at higher risk for development of CRC and its complications and has also not been well studied.

Finally, our data are consistent with the recently published report indicating that metformin is associated with increased survival among DMs with pancreatic ductal adenocarcinoma [32]. Our result is also consistent with recent meta-analysis of six studies of metformin use in colorectal patients with diabetes by Mei *et al.*, which shows metformin to have an improved survival outcome in these patients [33]. Given the pleotropic effects of this medication above and beyond its glucose lowering effects such as its favorable effects on cardiovascular disease including myocardial infarction, stroke and atrial fibrillation as well as overall mortality, metformin has emerged as the first-line therapy for Type 2 diabetes [34,35]. Furthermore, accumulating evidence indicates that metformin has nephroprotective effects in patients with DM nephropathy, likely mediated via activation of AMP-activated kinase pathway [36]. Collectively these data have been reflected in the recent US FDA recommendations for metformin use in patients with chronic kidney disease (CKD) including those with an eGFR between 30 and 45 ml/min/1.73 m² [34,35]. This ease on the restriction of metformin use has the potential of increasing the use of metformin that currently includes nearly 15 million patients with diabetes, thus providing more opportunities for cancer prevention, decrease cardiovascular disease and potential amelioration of CKD among DMs, a population that vulnerable to both CKD as well as malignancy [37].

Limitations

The retrospective design of this study poses some inherent limitations. The data were extracted over a 12-year period with incomplete medical records. There is significant amount of missing data on important variables such as duration of metformin use, hemoglobin A1C, neoadjuvant and adjuvant treatment modalities including chemotherapy and radiation therapies and the duration of these treatments. Analysis with these variables were not able to be performed.

Conclusion

In an urban safety net hospital, black patients with type 2 diabetes mellitus who were prescribed metformin had a lower risk of all-cause mortality than those who were not prescribed metformin in the setting of local and regional colorectal adenocarcinoma, with decreased mortality by as much as 59% and with a HR of 0.41 (95% CI: 0.19–0.87). Metformin exhibited mortality benefit in patients with nonmetastatic disease but not in metastatic disease, which is likely to be due to the small sample size. This data may serve as a pilot for a larger prospective study to further evaluate metformin's anticancer properties both alone and in conjunction with available chemotherapeutics for CRC in our patient population. Furthermore, expansion of this study to incorporate a more diverse patient

population would be helpful to attain a better assessment of metformin's survival benefits in CRC patients.

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Practise points

- Use of metformin demonstrates a potential benefit in nonmetastatic colorectal adenocarcinoma patients who has diabetes mellitus
- Larger prospective study is needed to further evaluate metformin's anticancer properties.

Figure 1.

Kaplan–Meier survival plots comparing survival probability over time between diabetic and nondiabetic groups. There was no difference in survival between the two groups.

Figure 2.

Kaplan–Meier survival plots comparing survival probability over time among metformin-using diabetics (D+M+), nonmetformin using diabetics (D+M~) and nondiabetics (D~M~). The D+M+ has better overall survival outcome than both D+M~ and D~M~ groups (log-rank $p < 0.05$).

Figure 3. Kaplan–Meier survival plots comparing survival probability over time among the patients with American Joint Committee on Cancer Stage IV disease within the groups. There was no survival difference observed among the groups.

Figure 4.

Kaplan–Meier survival plots comparing survival probability over time among the DM/metformin use groups with American Joint Committee on Cancer Stage I–III disease. There were no adverse events observed in the D+M+ group.

Table 1

Patient characteristics.

	Nondiabetics (n = 418) n (%)	Diabetes (n = 167) n (%)	p-value*	Diabetics without metformin (n = 93)	Diabetics with metformin (n = 74)	p-value*
Age, mean (SD)	60.5 (12.7)	65.1 (12.1)	<0.001*	66.5 (12.7)	63.4 (11.2)	0.10
Sex:						
Male	221 (52.9%)	71 (42.5%)	0.02*	39 (41.9%)	32 (43.2%)	0.87
– Race:						
– White	50 (12.0%)	8 (4.8%)	0.03*	5 (5.4%)	3 (4.1%)	0.72
– Black	355 (84.9%)	154 (92.2%)		86 (92.5%)	68 (91.9%)	
– Other	13 (3.1%)	5 (3.0%)		2 (2.2%)	3 (4.1%)	
BMI (kg/m ²):						
– <18.5	15 (3.6%)	4 (2.4%)	<0.01*	4 (4.3%)	0 (0.0%)	0.01*
– 18.5–24.9	153 (36.6%)	52 (31.1%)		36 (38.7%)	16 (21.6%)	
– 25.0–29.9	116 (27.8%)	49 (29.3%)		21 (22.6%)	28 (37.8%)	
– >30.0	79 (18.9%)	51 (30.5%)		24 (25.8%)	27 (36.5%)	
– N/A	55 (13.2%)	11 (6.6%)		8 (8.6%)	3 (4.1%)	
AJCC:						
– Stage I	93 (22.2%)	56 (33.5%)	0.08	27 (29.0%)	29 (39.2%)	0.38
– Stage II	92 (22.0%)	36 (21.6%)		18 (19.4%)	18 (24.3%)	
– Stage III	87 (20.8%)	30 (18.0%)		19 (20.4%)	11 (14.9%)	
– Stage IV	125 (29.9%)	41 (24.6%)		27 (29.0%)	14 (18.9%)	
– N/A	19 (4.5%)	4 (2.4%)		2 (2.2%)	2 (2.7%)	
CEA:	154 (50.8%)	63 (56.2%)	0.33	30 (50.8%)	33 (62.3%)	0.30
– <5 ng/ml	149 (49.2%)	49 (43.7%)		29 (49.2%)	20 (37.7%)	
– 5 ng/ml						
Location of tumor:						
– Proximal colon	144 (34.4%)	71 (42.5%)	0.22	40 (43.0%)	31 (41.9%)	0.16
– Distal colon	128 (30.6%)	51 (30.5%)		31 (33.3%)	20 (27.0%)	
– Rectum	116 (27.8%)	36 (21.6%)		15 (16.1%)	21 (28.4%)	

	Nondiabetes (n = 418) n (%)	Diabetes (n = 167) n (%)	p-value*	Diabetics without metformin (n = 93)	Diabetics with metformin (n = 74)	p-value*
– Unspecified	30 (7.2%)	9 (5.4%)		7 (7.5%)	2 (2.7%)	
Mean survival (months)	106.1	111.6	0.56	95.7	109.9	<0.01

AJCC: American Joint Committee on Cancer; CEA: Carcinoembryonic antigen; N/A: Not available; SD: Standard deviation.

Table 2

All-cause mortality analyzed by multivariate Cox hazard regression.

	HR	CI	p-value*
Age	1.02	1.002–1.04	0.047
Race:			
– White	1		
– Black	1.58	0.79–3.16	0.36
– Other	0.91	0.19–4.25	0.90
Diabetes:			
– Nondiabetes	1		
– Diabetes	1.22	0.68–2.18	0.51
Insulin use:			
– No	1		
– Yes	1.19	0.59–2.50	0.64
Metformin use:			
– No metformin	1		
– Metformin	0.30	0.16–0.91	0.0301*
Metastatic disease	10.51	6.96–15.89	<0.0001*

DM: Diabetes; HR: Hazard ratio.