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Metformin Use and Pancreatic Cancer Survival among Non-Hispanic White and African American U.S. Veterans with Diabetes Mellitus

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ABSTRACT

Background: The effect of metformin use on survival among patients with pancreatic ductal adenocarcinoma (PDAC) is controversial. Furthermore, there are no data on African American patients. To address these, we analyzed data from the United States Veterans Health Administration (VHA).

Methods: A population-based retrospective cohort study evaluating overall survival among 3,811 patients with PDAC with preexisting diabetes mellitus, diagnosed with PDAC within the VHA between 1998 and 2013. We calculated HRs and 95% confidence intervals (CI) using multivariable adjusted time-varying Cox proportional hazards regression to control for immortal time bias and confounders.

Results: Metformin use was not associated with overall survival in the complete analyses (HR = 1.05; 95% CI, 0.92–1.14; $P = 0.28$). However, among patients who were metformin naïve at the time of PDAC diagnosis ($N = 1{,}158$), metformin use was associated with improved overall survival in non-Hispanic white patients (HR = 0.78; 95% CI, 0.61–0.99; $P = 0.04$), but not African American patients (HR = 1.20; 95% CI, 0.75–1.93; $P = 0.45$). The survival benefit among non-Hispanic whites was limited to patients with metastatic disease (HR = 0.67; 95% CI, 0.44–1.01; $P = 0.06$). Among African American patients with metastatic disease, HR was 1.30 (95% CI, 0.77–2.53; $P = 0.28$). There was a suggestion of heterogeneity by race in patients with metastatic disease ($P_{heterogeneity} = 0.05$).

Conclusions: We observed no associations between metformin use and survival in patients with PDAC, but there appears to be a survival benefit among non-Hispanic white patients who were metformin naïve at the time of PDAC diagnosis.

Impact: If confirmed in other studies, our findings suggest that metformin as an adjunctive treatment for PDAC may not improve survival among African American patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a fatal malignancy with a case fatality ratio of 0.98 (1). PDAC is currently the third leading cause of cancer-related death in the United States and is projected to become the second leading cause of cancer-related death by 2020 (2–4). The only potentially curative therapy is surgery; however, less than 20% of patients are candidates for surgery because most patients present with locally advanced or metastatic disease (5). Currently available systemic treatments provide modest survival benefit and the 5-year survival is still only 8% (6, 7). Thus, there is a compelling need to identify factors that will improve survival.

Prior observational studies have described associations between metformin use and reductions in cancer-related mortality, including PDAC (8–12). Metformin could impact pancreatic cancer survival through direct and indirect biological mechanisms. Metformin directly inhibits mitochondrial ATP synthesis, leading to pancreatic cancer cell death (13). In combination with gemcitabine, metformin enhances the induction of pancreatic cancer cell apoptosis (14). The indirect effects could be through reduction in insulin signaling. Excess insulin is mitogenic (15), causing upregulation and activation of the Ras/Raf/MAP kinase signaling pathway (16). By activating AMPK, metformin downregulates several signaling pathways essential for cancer progression and reduces mitogenic insulin and insulin-like growth factor I (IGFI) levels (17–19).

A recent meta-analysis of 8 observational studies reported that metformin use was associated with a 12% survival benefit among non-Hispanic white patients and a 36% survival benefit among Asian patients (9), suggesting a role for metformin use as an adjunct to standard therapies in the treatment of PDAC. However, prior observational studies suffer from some notable limitations. First, studies were limited to non-Hispanic white and Asian patients, and have no data on African American patients. Thus, it is impossible to determine whether African American patients with PDAC will benefit from any survival advantage conferred by metformin. PDAC mortality rates are higher among African American patients (9.4/100,000 person-years) compared with non-Hispanic white patients (6.4/100,000 person-years; ref. 20) and genetic factors play a critical role in how well patients respond to metformin for glycemic control (21). Second, the majority of studies did not control for immortal time bias, which can overestimate the survival benefit of a drug.

Our goals in this study were 2-fold: (i) investigate the associations between metformin use and overall survival among patients with

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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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PDAC with existing diabetes mellitus, controlling for immortal time bias; and (ii) provide the first data on the associations between metformin use and PDAC survival among African American patients with diabetes mellitus. To achieve these goals, we analyzed data from a large cohort of U.S. veterans with PDAC who had preexisting diabetes mellitus ($N = 3811$), diagnosed and treated within the Veterans Health Administration (VHA) system.

Materials and Methods

Study population

A population-based retrospective cohort study within the Veterans Affairs system, using data from all 21 VHA regional districts throughout the United States. Multiple VHA datasets were linked using unique patient identifiers. We used the Veterans Affairs Central Cancer Registry (VACCR) to identify patients diagnosed with PDAC between January 1, 1998, and December 31, 2013. VACCR dataset includes confirmation of diagnosis, data on treatments, and stage at diagnosis. An initial data date of January 1, 1998, was utilized since electronic medical record system was initiated throughout the Veterans Health Administration system on that day. Case ascertainment in the VACCR is very accurate. The VACCR has been found to have an ascertainment rate of up to 90% (22, 23).

Primary PDAC cases were identified using the International Classification of Disease for Oncology, Third Edition (ICD-O-3) histology codes: 8000, 8010, 8020, 8021, 8022, 8140, 8141, 8211, 8230, 8500, 8521, 8050, 8260, 8441, 8450, 8453, 8470, 8471, 8472, 8473, 8480, 8481, 8503. We identified patients with preexisting diabetes mellitus as those with at least one ICD-9 code for diabetes mellitus (249.00–250.93, V4585, V5391, V6546) and on treatment for diabetes mellitus (e.g., with metformin, sulfonylurea, insulin, thiazolidinedione). Identification of preexisting diabetes mellitus using ICD codes, and treatment of diabetes in the VA database is very accurate. The positive predictive value (PPV) of using ICD code to accurately identify patients with diabetes within the database is 91% and the negative predictive value (NPV) is 95%. For diabetic medication use, the PPV is 97% and NPV is 93% (24).

We linked the VACCR to individual patients' records to obtain information on patients' clinical and demographic characteristics such as age, gender, smoking status, year of diagnosis, and surgery for pancreatic cancer. Height and weight were obtained from the vital sign data. Body mass index (BMI) was derived as weight (kg)/height (m^2). Tumor stage was classified as (i) local disease amenable to surgical resection; (ii) locally advanced disease with extra-pancreatic extension not amenable to surgical resection, but without distant metastases; (iii) distant metastatic disease; and (iv) unknown. The study was approved by the St Louis VHA Medical Center and Washington University School of Medicine Institutional Review Boards.

Metformin use

Data on metformin use were obtained from the VHA Pharmacy Benefits Management database. Patients were identified as metformin users if they had prescriptions for metformin at any time, before or after PDAC diagnosis. Metformin nonusers comprised patients who were not taking just metformin.

Primary outcome measure

The primary endpoint was overall survival, which was determined from the date of pancreatic cancer diagnosis until the date of death, or last follow-up (December 31, 2014). Date of death was obtained from the Veterans Affairs (VA) vital status file, which is a VA database that combines death dates from the VA Beneficiary Identification and Records Locator Subsystem Death File, the Social Security Administration-Death Master File, the Medicare Vital Status File, and the Medical SAS Inpatient Datasets (25, 26). We assumed that patients who were not identified as dead were alive at the time of the last death recorded within the cohort, December 2014, an assumption that has been validated by previous studies within the VHA showing that >97% of deaths are captured in the VHA status files (25, 26).

Statistical analysis

Baseline characteristics were compared using χ^2 test for categorical variables and Student t test for continuous variables. Survival was estimated using the Kaplan–Meier method, with comparison using the log-rank test. We used Cox proportional hazards regression model, adjusting for race, age, gender, and BMI at 1 year before pancreatic cancer diagnosis, year of diagnosis (2004 and before, 2005 to 2008, 2009, and after), surgery (yes or no), smoking status (never, current, or previous), and stage of disease (resectable, locally advanced, metastatic, or unknown) to investigate the associations of metformin use with survival. The confounders were all measured at baseline. Metformin initiation date varied among patients, so we accounted for variation in metformin use over time, by assessing metformin use as a time-varying covariate.

In the time-varying Cox model, patients who started metformin before or at PDAC diagnosis were coded as metformin users. For patients who started using metformin after PDAC diagnosis, they were coded as nonusers before metformin initiation, then recoded to users on the date when metformin was started. Patients who never received metformin were coded as nonusers. The time-varying Cox model method minimizes immortal time bias because the survival experience of each patient starts at the time of PDAC diagnosis, but the patient is not considered a metformin user until metformin use is initiated (27, 28). By controlling for time of metformin initiation, we eliminate the artificial survival advantage incurred during the period in which metformin has not yet been started after PDAC diagnosis (29). Next, we performed the same time-varying covariate Cox proportional hazards regression model for the patients who were metformin naïve at the time of pancreatic cancer diagnosis.

To detect differences in metformin use on the survival between non-Hispanic white and African American patients, we included product terms between race and metformin use. We then performed the conventional standard Cox proportional hazards regressions modeling. We further performed sensitivity analyses, in which with repeated analyses for patients who were diagnosed with diabetes mellitus $\geq$2 years before PDAC diagnosis. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC). All tests of statistical significance should be two sided.

Results

We identified 3,811 non-Hispanic white and African American patients with PDAC with preexisting diabetes mellitus diagnosed within the VHA between January 1, 1998, and December 31, 2013 (**Table 1**). The study cohort had a mean age of 67.8 years. The majority: $n = 3038$, (79.7%) were non-Hispanic whites and 773 (20.3%) were African Americans. Many patients (73.3%) were metformin users. A higher proportion of the non-Hispanic white patients were metformin users (74.7%), compared with African Americans (67.8%). There were 981, 368, 1,943, and 519 patients with PDAC who had localized, locally advanced, metastatic, and unknown stage disease, respectively. The median duration of diabetes was 53.8 months: 58.6 months for

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Table 1. Baseline characteristics of 3,811 patients with PDAC with preexisting diabetes mellitus within the Veterans Health Administration by metformin use (ever use), overall and stratified by race.

		All participants			Non-Hispanic white patients		African American patients	
		Metformin use			Metformin use		Metformin use	
Characteristics	*n* = 3,811	Yes *n* = 2,792	No *n* = 1,019	*P*	Yes *n* = 2,268	No *n* = 770	Yes *n* = 524	No *n* = 249
Age at PDAC diagnosis, years, mean	67.8	67.4	68.7	0.0006	67.9	69.3	65.1	67
Gender, number (%)								
Male	3,736 (98.0)	2,735 (98)	1,001 (98.2)	0.59	2,221 (97.9)	756 (98.2)	514 (98.1)	245 (98.4)
Female	75 (2.0)	57 (92.0)	18 (1.8)		47 (2.1)	14 (1.8)	10 (1.9)	4 (1.6)
Race, number (%)								
Non-Hispanic white	3,038 (79.7)	2,268 (81.2)	770 (75.6)	0.0001				
African American	773 (20.3)	524 (18.8)	249 (24.4)					
BMI, kg/m^2								
Mean	30.3	30.6	29.2	0.0001	30.7	29.1	30.1	29.6
<18	26 (0.7)	15 (0.5)	11 (1.1)		10 (0.4)	9 (1.2)	5 (0.9)	2 (0.8)
18 $\leq$ BMI < 25	495 (13.0)	337 (12.1)	158 (15.5)		278 (12.3)	121 (15.7)	59 (11.3)	37 (14.9)
25 $\leq$ BMI < 30	1,118 (29.3)	823 (29.5)	295 (29.0)		656 (28.9)	232 (30.1)	167 (31.9)	63 (25.3)
$\geq$30	1,427 (37.4)	1,148 (41.1)	279 (27.4)		955 (42.1)	206 (26.8)	193 (36.8)	73 (29.3)
Unknown	745 (19.6)	4,689 (16.8)	276 (27.1)		369 (16.3)	202 (26.2)	100 (19.1)	74 (29.7)
Smoking status, number (%)				0.01				
Never	689 (18.1)	521 (18.7)	168 (16.5)		413 (18.2)	139 (18.1)	108 (20.6)	29 (11.7)
Current	1,149 (30.2)	867 (31.1)	282 (27.7)		686 (30.3)	202 (26.2)	181 (34.5)	80 (32.2)
Past	1,539 (40.4)	1,107 (39.7)	432 (42.4)		931 (41.1)	336 (43.6)	176 (33.6)	96 (38.6)
Unknown	434 (11.4)	297 (10.6)	137 (13.4)		238 (10.5)	93 (12.1)	59 (12.3)	44 (17.7)
Stage, number (%)				0.0001				
Localized	981 (25.7)	729 (26.1)	252 (24.7)		603 (26.6)	196 (25.5)	126 (24.1)	56 (22.5)
Locally advanced	368 (9.7)	286 (10.2)	82 (8.1)		234 (10.3)	59 (7.7)	52 (9.9)	23 (9.2)
Metastatic	1,943 (51)	1,438 (51.5)	505 (49.6)		1,158 (51.1)	381 (49.5)	280 (53.4)	124 (49.8)
Unknown	519 (13.6)	339 (12.1)	180 (17.7)		273 (12.1)	134 (17.4)	66 (12.6)	46 (18.5)
Mortality status, number (%)								
Alive	200 (5.3)	169 (6.1)	31 (3.0)	0.0002	131 (5.8)	24 (3.1)	38 (7.3)	7 (2.8)
Dead	3,611 (94.7)	2,623 (94)	988 (97.0)		2,137 (94.2)	746 (96.9)	486 (92.8)	242 (97.2)
Median survival, months	4.2	4.5	3.7	0.0003	4.5	3.8	4.6	3.4
Duration of diabetes before PDAC diagnosis (months)	53.8	58.6	40.4	0.0001	50.1	39.4	58.6	40.4
Other diabetic medications								
Alpha glucosidase inhibitors (%)	3.4	3.8	2	0.006	4	1.7	2.9	2.9
DPP4 inhibitors (%)	0.8	0.9	0.6	0.31	0.8	0.7	1.3	0.4
Thiazolidinediones (%)	19	22.3	10	0.0001	23.1	10.9	18.9	7.2
Sulfonylureas (%)	42.3	42.5	41.7	0.67	42.6	42.1	41.8	40.6
Meglitinides (%)	0.4	0.4	0.5	0.68	0.4	0.5	0.2	0.4
Insulin (%)	64.1	60.5	73.7	0.0001	67.9	69.3	65.1	67.0

Note: Numbers (%) are presented for categorical variables. Mean values are presented for continuous variables.

metformin users and 40.4 months for nonusers. Distribution of other patient characteristics by metformin use was similar among both racial groups, except that non-Hispanic white patients who used metformin had higher mean BMI compared with nonusers (30.7 vs. 29.1 kg/m^2, $P < 0.0001$), while mean BMI was similar among African American patients who were metformin users and nonusers (30.1 vs. 29.6 kg/m^2, $P = 0.38$). There was no significant difference in the Charlson comorbidity index between African American patients (4.8) and non-Hispanic White patients (4.6; $P = 0.14$).

The unadjusted median survival across the entire study cohort was 4.2 months (4.5 among metformin users vs. 3.7 among nonusers, $P < 0.001$; **Table 2**). Median survival was similar among non-Hispanic white patients who were metformin users (4.5 months) and African American patients who were metformin users (4.6 months). In multivariable adjusted analyses using the time-varying Cox model, metformin use was not associated with survival: HR = 1.05 [95% confidence interval (CI), 0.92–1.14; $P = 0.28$]. Results were similar among non-Hispanic white patients: HR = 1.05 (95% CI, 0.96–1.14; $P = 0.26$) and African American patients: HR = 1.01 (95% CI, 0.86–1.19; $P = 0.88$). In multivariable adjusted analyses using the conventional Cox model, there was an artificial survival benefit associated with metformin use: HR = 0.89 (95% CI, 0.83–0.98; $P = 0.01$). Findings were similar for non-Hispanic white patients (HR = 0.90; 95% CI, 0.83–0.98; $P = 0.02$) and African American patients, although not statistically significant for African American patients (HR = 0.89; 95% CI, 0.76–1.05: $P = 0.17$). In sensitivity analyses performed on patients who had a diagnosis of diabetes mellitus $\geq$2 years before PDAC diagnosis ($n = 2{,}588$; Supplementary Table S1), we similarly observed no associations between metformin use and PDAC survival in the time-varying Cox model (HR = 0.97; 95% CI, 0.87–1.09; $P = 0.63$), but

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Table 2. Associations of metformin use with risk of all-cause mortality in patients with PDAC with preexisting diabetes mellitus.

			Time-varying Cox model[a]			Conventional Cox model[a]		
Metformin use	**Deaths/total**	**Median survival (95% CI)**	**HR (95% CI)**	***P***	$P_{heterogeneity}$	**HR (95% CI)**	***P***	$P_{heterogeneity}$
Overall					0.61			0.9
Nonuser[b]	988/1,019	3.7 (3.3–4.0)	Ref.			Ref.		
User	2,623/2,792	4.5 (4.2–4.8)	1.05 (0.92–1.14)	0.28		0.89 (0.83–0.98)	0.01	
Non-Hispanic whites								
Nonuser[b]	746/770	3.8 (3.3–4.3)	Ref.			Ref.		
User	2,137/2,268	4.5 (4.1–4.8)	1.05 (0.96–1.14)	0.28		0.90 (0.83–0.98)	0.02	
African Americans								
Nonuser[b]	242/249	3.4 (2.8–4.0)	Ref.			Ref.		
User	486/524	4.6 (3.4–5.4)	1.01 (0.86–1.19)	0.88		0.89 (0.76–1.05)	0.17	

[a]Adjusted for age (continuous), gender (male or female), BMI, year of diagnosis (2004 and prior, 2005–2008, 2009, and after), surgery (yes or no), smoke status (never, current, or previous), and stage (resectable, locally advanced, metastatic, or unknown).
[b]Metformin nonusers comprised individuals who were not taking just metformin. They could be taking other medications for diabetes.

an artificial survival benefit in the conventional Cox model (HR = 0.85; 95% CI, 0.76–0.96; $P = 0.01$).

Next, we investigated metformin use and survival among patients who were metformin naïve at the time of PDAC diagnosis using the time-varying covariate Cox model (**Table 3**). Among the 3,811 patients in the analytic cohort, 1,158 patients had no evidence of metformin use at the time of PDAC diagnosis. Of these, 139 patients (12%) started using metformin after PDAC diagnosis. The multivariable adjusted HR was 0.77 (95% CI, 0.61–0.98; $P = 0.03$). The HR was 0.78 (95% CI, 0.61–0.99; $P = 0.04$) among non-Hispanic white patients and 1.20 (95% CI, 0.75–1.93; $P = 0.45$) among African American patients. Most baseline characteristics were identical between patients who started metformin at/after pancreatic cancer diagnosis and other patients (Supplementary Table S2). However, patients who started metformin at/after pancreatic cancer were younger (64.9 vs. 67.9 years), had diabetes for a shorter period (25.2 vs. 54.8 months) and had longer median survival compared with other patients (19.6 vs. 4 months).

We performed further multivariable adjusted analyses, stratified by stage at diagnosis, using the time varying Cox model (**Table 4**). Metformin use was not associated with survival among patients with localized/locally advanced diseases: HR = 1.02 (95% CI, 0.73–1.44; $P = 0.90$). When stratified by race, the HR was 1.02 (95% CI, 0.73–1.44; $P = 0.91$) for non-Hispanic white patients and 1.51 (95% CI, 0.51–4.49; $P = 0.46$) for African American patients: $P_{heterogeneity} = 0.48$. Metformin use was associated with improved survival in non-Hispanic white patients who had metastatic disease: HR = 0.67 (95% CI, 0.44–1.01; $P = 0.055$) but not among African American patients with metastatic disease: HR = 1.30 (95% CI, 0.77–2.53; $P = 0.28$). There was suggestion of heterogeneity by race: $P_{heterogeneity} = 0.05$. There were no racial differences in stage at presentation as 46.7% of the non-Hispanic white patients compared with 50.4% of African American patients ($P = 0.45$) had metastatic disease (Supplementary Table S2).

Discussion

In this large population-based cohort study of U.S. Veterans with PDAC and preexisting diabetes mellitus, metformin use was not associated with improved overall survival. Metformin use was, however, associated with improved survival in non-Hispanic white patients who were metformin naïve at the time of PDAC diagnosis, largely driven by survival benefit among patients with metastatic disease. No survival benefit was observed for African American patients. This suggests that using metformin an adjunctive treatment for PDAC may not improve survival among African American patients.

To the best of our knowledge, this is the first study to evaluate the associations of metformin use with PDAC survival among African American patients; hence, this study offers an important novel perspective in this field. African American patients present with more advanced stages of disease at the time of diagnosis and are less likely to receive surgery than other racial groups in the United States (30–32). We observed no survival benefit for metformin use among African American patients in all the analyses. It is intriguing and unclear why

Table 3. Associations of metformin use with risk of all-cause mortality in patients with PDAC with preexisting diabetes mellitus among patients who were metformin naïve at the time of PDAC diagnosis, using the time-varying Cox model.

Metformin use	**Deaths/total**	**Median survival (95% CI)**	**HR (95% CI)[a]**	***P***	$P_{heterogeneity}$
Overall					0.13
Nonuser[b]	988/1,019	3.7 (3.3–4.0)	Ref.		
User	107/139	19.6 (12.0–31.0)	0.77 (0.61–0.98)	0.03	
Non-Hispanic whites					
Nonuser[b]	746/770	3.8 (3.3–4.3)	Ref.		
User	85/112	25.7 (14.9–34.4)	0.78 (0.61–0.99)	0.04	
African Americans					
Nonuser[b]	242/249	3.4 (2.8–4.0)	Ref.		
User	22/27	9.2 (3.4–16.6)	1.20 (0.75–1.93)	0.45	

[a]Adjusted for age (continuous), gender (male or female), BMI, year of diagnosis (2004 and prior, 2005–2008, 2009, and after), surgery (yes or no), smoke status (never, current, or previous), and stage (resectable, locally advanced, metastatic, or unknown).
[b]Metformin nonusers comprised individuals who were not taking just metformin. They could be taking other medications for diabetes.

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Table 4. Associations of metformin use with risk of all-cause mortality, stratified by stage at diagnosis in who were metformin naïve at the time of PDAC diagnosis, using the time-varying Cox model.

Metformin use	Deaths/total	Median survival (95% CI)	HR (95% CI)[a]	*P*	$P_{heterogeneity}$
Patients with localized/locally advanced disease					
Overall					0.48
Nonuser[b]	318/334	7.7 (6.2–8.8)	Ref.		
User	45/64	32.4 (23.7–55.5)	1.02 (0.73–1.44)	0.90	
Non-Hispanic whites					
Nonuser[b]	242/255	8.4 (6.8–9.7)	Ref.		
User	40/56	32.4 (23.9–55.5)	1.02 (0.70–1.48)	0.91	
African Americans					
Nonuser[b]	76/79	5.3 (3.9–7.3)	Ref.		
User	5/8	23.0 (1.6–32.1)	1.51 (0.51–4.49)	0.46	
Patients with metastatic disease					
Overall					0.05
Nonuser[b]	500/505	2.3 (1.9–2.6)	Ref.		
User	43/46	6.3 (4.6–8.8)	0.82 (0.59–1.55)	0.25	
Non-Hispanic whites					
Nonuser[b]	377/381	2.3 (1.9–2.7)	Ref.		
User	29/31	6.4 (4.3–8.9)	0.67 (0.44–1.01)	0.06	
African Americans					
Nonuser[b]	123/124	2.3 (1.7–2.6)	Ref.		
User	14/15	5.8 (1.8–9.2)	1.39 (0.77–2.53)	0.28	

[a]Adjusted for age (continuous), gender (male or female), BMI, year of diagnosis (2004 and prior, 2005–2008, 2009, and after), surgery (yes or no), smoke status (never, current, or previous), and stage (resectable, locally advanced, metastatic, or unknown).
[b]Metformin nonusers comprised individuals who were not taking just metformin. They could be taking other medications for diabetes.

starting metformin after PDAC diagnosis was associated with improved survival among non-Hispanic white patients, but not African American patients. Genetic factors and lower medication adherence among African American patients could contribute. A previous study showed that African American veterans with diabetes were less adherent to metformin treatment than non-Hispanic white veterans (33). In addition, genetic variation accounts for 34% of the variance in response to metformin used for glycemic control (21, 34, 35), and could therefore play a role in the differences observed in PDAC survival. It is also important to consider bias as potential explanations when interpreting our findings among patients who were metformin naïve at the time of PDAC diagnosis. Patients with better disease prognosis (i.e., localized disease, better performance status) who survived longer may have been started on metformin after PDAC diagnosis for management of diabetes, while patients with poor prognosis were not. Nevertheless, it does not explain the racial differences observed among patients with metastatic diseases. A similar proportion of non-Hispanic white patients and African American patients who were metformin naïve at the time of PDAC diagnosis had metastatic disease; hence, stage at diagnosis could not have accounted for the differences. Our findings warrant investigation in future studies with a large number of African American patients.

Our main findings are similar to those reported by Chaiteerakji and colleagues (29), who analyzed data from 980 patients with PDAC with diabetes mellitus. In analyses using conventional Cox model (without time-varying covariates), they reported an artificial survival benefit for metformin (HR = 0.88; 95% CI, 0.77–1.01), which is consistent to what we observed in our study (HR = 0.89; 95% CI, 0.83–0.98). In analyses using the time-varying Cox model, metformin use was not associated with survival in both sets of analyses, highlighting the need for appropriate analytic methods in studies evaluating medication/drug use and PDAC survival. Our findings, however, differ from theirs in the subset of patients who were metformin naïve at the time of PDAC diagnosis. We observed that metformin use was associated with improved survival when patients start metformin after PDAC diagnosis, while they did not. This subset of patients is most representative of patients enrolled in clinical trials, and findings could provide insight into the potential utility of metformin as an adjunctive treatment for PDAC (29). Our larger study population (n = 3,811 vs. 980) could have allowed us to detect smaller differences. In addition, we adjusted for race and smoking status in our analyses, while they did not. Smoking is associated with worse survival in patients with PDAC (36).

Findings on metformin and pancreatic cancer survival in observational studies have led to clinical trials testing the efficacy of metformin as an adjunctive to chemotherapy in patients with PDAC (8–10). Results of two small clinical trials, however, showed that the addition of conventional antidiabetic dose of metformin to chemotherapy did not improve PDAC survival (37, 38). Patients enrolled in these two clinical trials had metastatic disease but did not have diabetes mellitus. Patients assigned to metformin had higher median baseline CA19–9 levels 561 (IQR = 112–6,319) than patients assigned to placebo groups 245 (IQR = 21–2,118), suggesting that patients in the metformin arm may have had a higher burden of disease at the time of enrollment (19). Patients assigned to metformin also received fewer cycles of chemotherapy than those in the placebo arm (median 3 vs. 5 cycles), and were more likely to discontinue the metformin intervention because of side effects (19). Thus, although the initial results from the phase II clinical trials are disappointing, ongoing clinical trials on metformin use and pancreatic cancer survival may provide additional insight on the efficacy of metformin as an adjunctive therapy.

Our population-based retrospective cohort study has strengths and limitations. The VHA is the largest integrated health care system in the United States and provides care to a diverse population of patients. This enabled us to perform robust statistical analyses and, for the first time, evaluate the association of metformin use with PDAC survival in

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African American patients. Our outcomes are robust. Health records within the VHA, including survival status are well maintained and accurate, with 97% of death events accurately captured in the database (25). We acknowledge the following limitations. Being an observational study, there are inherent biases that may not be fully accounted for. One of such is misclassification of metformin use, arising from patient nonadherence or prescriptions from outside of the VHA system. We used pharmacy claims as proxy for adherence, which may not be a true reflection of medication use. A second limitation is that our study population is 98% men; hence, it is unknown whether study findings are generalizable to women. Third, although our study population has a sizeable proportion of African American patients ($N = 773$), the number of patients included in the subgroup analyses among patients who were metformin naïve was small: ($n = 87$ for localized/locally advanced disease and $n = 139$ for metastatic disease); hence, limited power could have prevented us from observing statistically significant associations especially in analyses evaluating localized/locally advanced diseases. These findings should, therefore, be interpreted cautiously until validated in a larger study. Fourth, although we adjusted for smoking, we did not have data on the duration and intensity of smoking.

In conclusion, we observed no consistent associations between metformin use and PDAC survival. Nevertheless, an improved survival was noted in non-Hispanic white patients who were metformin naïve at the time of PDAC diagnosis, but not in African American patients. Because of the potential clinical implications, the racial differences observed deserve further investigation in future studies with a large number of African American patients.

Disclosure of Potential Conflicts of Interest

K.M. Sanfilippo reports receiving other commercial research support from AstraZeneca Research Travel Funds - Investigatory Meeting, speakers bureau honoraria from Bristol-Myers Squibb (apixaban), is a consultant/advisory board member for Bayer Advisory Board (radium 223) and Pfizer Advisory Board (cancer-associated thrombosis), and has provided expert testimony for Luther & Associates (expert witness, thrombosis) and Covington & Burling LLP (expert witness, hemorrhage). K.R. Carson is Senior Medical Director at Flatiron Health, Inc. and has provided expert testimony for Monsanto. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.T. Toriola, T.S. Thomas, K.M. Sanfilippo, K.R. Carson
Development of methodology: A.T. Toriola, T.S. Thomas, K.R. Carson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.T. Toriola, K.M. Sanfilippo, K.R. Carson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.T. Toriola, S. Luo, T.S. Thomas, B.F. Drake, S.-H. Chang, K.M. Sanfilippo, K.R. Carson
Writing, review, and/or revision of the manuscript: A.T. Toriola, T.S. Thomas, B.F. Drake, S.-H. Chang, K.M. Sanfilippo, K.R. Carson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.T. Toriola, K.R. Carson
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