Original Article

http://www.jcpjournal.org
pISSN 2288-3649 · eISSN 2288-3657
https://doi.org/10.15430/JCP.24.012

JCP

Risk of Incident Cancer in Veterans with Diabetes Who Use Metformin Versus Sulfonylureas

Maya M. Abdallah[1,*], Beatriz Desanti de Oliveira[2,*], Clark DuMontier[3,4,5], Ariela R. Orkaby[3,4,5], Lisa Nussbaum[5], Michael Gaziano[4,5], Luc Djousse[4,5], David Gagnon[5,6], Kelly Cho[4,5], Sarah R. Preis[6,], Jane A. Driver[3,4,5,**]**

[1]Section of Hematology/Oncology, Department of Medicine, Boston University School of Medicine, Boston, MA, [2]Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, [3]New England Geriatrics Research, Education and Clinical Center (GRECC), VA Boston Healthcare System, [4]Division of Aging, Brigham and Women's Hospital, Harvard Medical School, [5]Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, [6]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

Prior research suggests metformin has anti-cancer effects, yet data are limited. We examined the association between diabetes treatment (metformin versus sulfonylurea) and risk of incident diabetes-related and non- diabetes-related cancers in US veterans. This retrospective cohort study included US veterans, without cancer, aged ≥ 55 years, who were new users of metformin or sulfonylureas for diabetes between 2001 to 2012. Cox proportional hazards models, with propensity score-matched inverse probability of treatment weighting (IPTW) were constructed. A total of 88,713 veterans (mean age 68.6 ± 7.8 years; 97.7% male; 84.1% White, 12.6% Black, 3.3% other race) were followed for 4.2 ± 3.0 years. Among metformin users (n = 60,476), there were 858 incident diabetes-related cancers (crude incidence rate [IR; per 1,000 person-years] = 3.4) and 3,533 non-diabetes-related cancers (IR = 14.1). Among sulfonylurea users (n = 28,237), there were 675 incident diabetes-related cancers (IR = 5.5) and 2,316 non-diabetes-related cancers (IR = 18.9). After IPTW adjustment, metformin use was associated with a lower risk of incident diabetes-related cancer (hazard ratio [HR] = 0.66, 95% CI 0.58-0.75) compared to sulfonylurea use. There was no association between treatment group (metformin versus sulfonylurea) and non-diabetes-related cancer (HR = 0.96, 95% CI 0.89-1.02). Of diabetes-related cancers, metformin users had lower incidence of liver (HR = 0.39, 95% CI 0.28-0.53), colorectal (HR = 0.75, 95% CI 0.62-0.92), and esophageal cancers (HR = 0.54, 95% CI 0.36-0.81). Among US veterans, metformin users had lower incidence of diabetes-related cancer, particularly liver, colorectal, and esophageal cancers, as compared to sulfonylurea users. Use of metformin was not associated with non-diabetes-related cancer. Further studies are needed to understand how metformin use impacts cancer incidence in different patient populations.

Key Words Metformin, Diabetes mellitus, Neoplasms prevention

INTRODUCTION

Patients with diabetes mellitus type 2 have an increased risk of several malignancies including pancreatic, hepatic, colorectal, endometrial, ovarian, breast, and bladder cancer [1-4]. Multiple mechanisms have been hypothesized to explain this association, including a combination of shared risk factors (such as age, obesity, physical inactivity, diet, and alcohol) as well as direct causal effects of metabolic derangement on tumor cell growth [5,6]. There has been growing interest in exploring diabetes medications as prevention or treatment for cancer. Metformin inhibits hepatic gluconeogenesis and reduces insulin resistance in peripheral tissues. It acts primarily by activating AMP-activated protein kinase (AMPK) and modulates numerous downstream pathways associated with cancer risk, including inhibition of mTOR signaling, reduction of protein synthesis, and upregulation of antioxidant genes [7-9].

Early observational studies demonstrated a decreased risk of cancer incidence and/or mortality in metformin users [10-

Received August 16, 2024, Revised December 5, 2024, Accepted December 8, 2024, Published on December 30, 2024
Correspondence to Maya M. Abdallah, E-mail: maya.abdallah@bmc.org, https://orcid.org/0000-0003-1549-6419
*These authors contributed equally to this work as co-first authors.
**These authors contributed equally to this work as co-senior authors.

13]. However, results remain inconclusive due in part to limitations of study design and size [14]. Studies included biases such as time-window bias and immortal time bias [14,15]. Time-related biases, including immortal time bias, can be avoided using incident new-user cohort designs.

Our objective was to examine the association between diabetes treatment (metformin versus sulfonylureas) and incident cancer in a cohort of US veterans. We hypothesized that regular users of metformin would have lower rates of incident cancer than regular users of sulfonylureas because metformin activates anti-cancer pathways, while sulfonylureas primarily increase insulin secretion.

MATERIALS AND METHODS

Study population and selection criteria

To assess risk of incident cancer in regular users of metformin, we designed a large retrospective cohort study using a national representative sample of US veterans initiated on metformin between 2001 and 2012. To overcome time-related biases, as proposed by Yu and Suissa [14], we included new-user design and propensity score (PS) weighting to examine the association between metformin use and the risk of incident cancers. The new user design was used to 1) ensure that all participants had the same probability of receiving a single oral hypoglycemic medication and 2) decrease survivor and prevalent user biases [16,17]. Using the National Veteran Administration's (VA) clinical and administrative databases, we identified US veterans aged 55 years or older who were first prescribed metformin or a sulfonylurea between 2001 and 2012 (Fig. 1). To avoid the influence of other novel oral anti-diabetes medications, we restricted entry into the cohort to 2001 to 2012. We based this on the American Diabetes Association and the European Association for the Study of Diabetes 2012 update, as subsequent updates including 2015 [18], 2018 [19], and 2019 [19], included multiple novel oral medications.

Inclusion criteria included being in the VA system for at least one year and having had at least one visit with a VA provider in the year prior to the participant's first diabetes medication prescription. Since poor renal function is a major contraindication for metformin, we excluded patients with 1) an estimated glomerular filtration rate (eGFR) < 30 mL/minute as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation, 2) International Classification of Diseases (ICD)-9 codes for end stage renal disease or dialysis, and 3) missing information on renal function (either laboratory or ICD-9 code). Other exclusion criteria included any prior cancer history (by ICD-9 code, except non-melanoma skin cancer) or missing data on body mass index (BMI), race, and/or hemoglobin A1c (HbA1c).

Exposure

We assessed drug exposure by extraction of medication lists from pharmacy databases. We excluded medications administered as part of research trials. Regular medication use was defined as filling ≥ 2 outpatient prescriptions per year. After initial prescriptions, a 2-year washout period was observed during which eligible patients continued regular use of the initially prescribed diabetes drug, free of cancer, and had no exposure to other diabetes -medications. Follow-up began at the end of the washout period and ended at first cancer di-

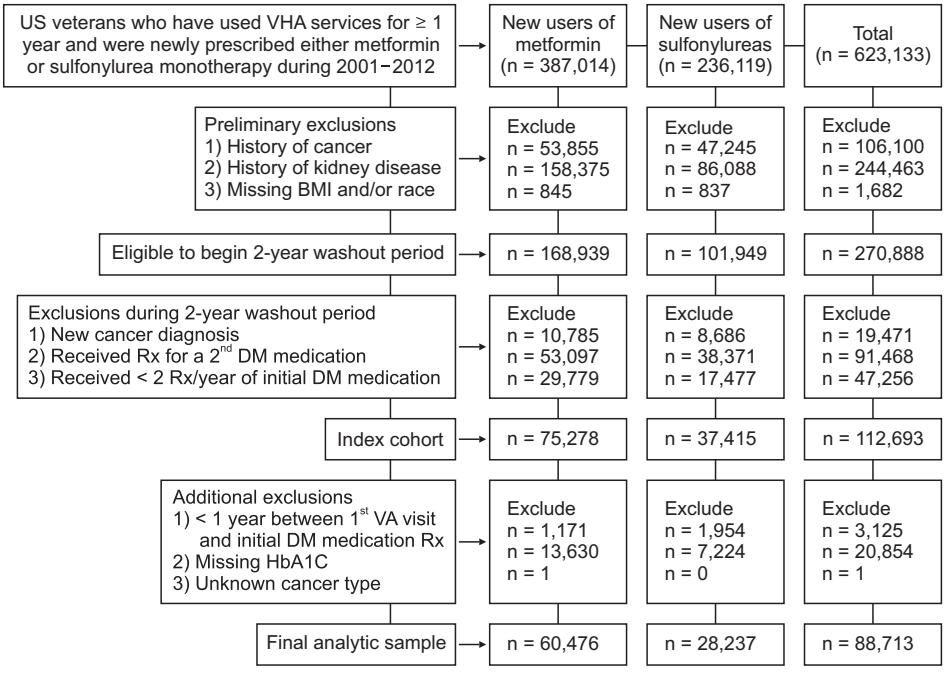

Figure 1. Study sample flow chart. VHA, Veterans Health Administration; BMI, body mass index; DM, diabetes mellitus; Rx, prescription; VA, National Veteran Administration, HbA1C, hemoglobin A1c.

agnosis, death, oral diabetes medication change (metformin users started on/switched to sulfonylurea and vice versa), or the end of follow-up (July 10, 2016), whichever came first.

Outcome

The primary outcome was diagnosis of any type of cancer excluding non-melanoma skin cancer. A cancer outcome was defined as having two or more ICD-9 diagnosis codes for the same cancer, registered at least one week apart, within a 6-month period. We divided the outcome into diabetes-related (pancreas, liver, esophagus, colon, rectum, renal, stomach, breast and endometrium) and non-diabetes-related cancers (Table S1 for a list of diabetes- and non-diabetes-related cancers and ICD-9 codes) [6].

Covariates

All covariates were measured at or before baseline, except for BMI, HbA1c, and renal function for which multiple values were reviewed as follows: For BMI, we accepted weight within 1.5 years and height within 5 years of the date of first prescription for metformin or a sulfonylurea. For HbA1c, we selected values closest to patients' baselines over the two years before and up to one week after index prescription. The same window was allowed for creatinine values used to calculate GFR. Kidney function was classified as normal (GFR ≥ 60 mL/minute), decreased (45 ≤ GFR < 60 mL/minute), or low (30 ≤ GFR < 45 mL/minute). Hypertension was defined by ICD-9 code or antihypertensive drug use. Smoking status (ever/never) was identified in VA electronic health records using electronic medical record data extraction methods and was available for all veterans [20].

Statistical analysis

Given that patients in the metformin and sulfonylurea groups had different baseline characteristics, we employed inverse probability of treatment weighting (IPTW) to achieve comparable groups with regard to potential confounding variables [21,22]. IPTW uses weights based on a PS, defined as the conditional probability of being treated given the subject's covariates [22,23]. We used the following domains of variables in the PS: 1) demographics (race, sex, and geographic region), 2) renal function, 3) comorbidities (obstructive pulmonary disease, cirrhosis, coronary artery disease, cerebrovascular disease, heart failure, hypertension, major mental illness, and statin use), 4) proxies of functional status (arthritis and vision comorbidity, defined as macular degeneration, vision loss, or glaucoma), 5) overall medical complexity (number of drug classes and of VA outpatient visits in the year prior to first diabetes drug prescription), and 6) history of smoking or alcohol abuse. Finally, we included interaction terms for year of first prescription by kidney function, geographic region, and HbA1c in order to account for changes in prescribing practice over time, reflective of the American Diabetes Association 2006 guideline update that recommended metformin be used as initial therapy [24]. Geographic regions, defined as Northeast, South, Midwest and West to reflect divisions used by the United States Census Bureau and by the VA, were included in the analysis to account for the different rates at which providers across the country changed prescribing patterns to adhere to updated guideline recommendations. Additionally, PS were calculated separately for the time period (2001-2004, 2005-2008, 2009-2012) of when the patient received their first prescription. PS trimming was implemented, as previously described [17].

Hazard ratio (HR) and 95% CI were calculated using Cox proportional hazards models using age as the time scale. The proportional hazards assumption was verified by performing a piecewise analysis by age category (< 65, 65-74, ≥ 75 years) in the IPTW-adjusted model. No violations were observed. For our primary analysis we considered the outcomes of any cancer, diabetes-related cancer, and non-diabetes-related cancer. Secondarily, we examined the individual cancers which comprise the diabetes-related and non-diabetes-related cancer subtypes (Table S1). As a sensitivity analysis, we performed an intention-to-treat (ITT) analysis using our primary outcomes measures (any cancer, diabetes-related cancer, and non-diabetes-related cancer). This analysis included all new users of metformin and sulfonylurea, regardless of whether they completed the 2-year lead in period, added an additional diabetes treatment regimen, or discontinued their intial diabetes medication (Figure S1). A *P*-value of < 0.05 was considered statistically significant. All analyses were performed in SAS Enterprise Guide version 8.3 (SAS Institute, Inc). The Institutional Review Board at the Boston VA approved this study (VA Boston Healthcare System IRB #00000629).

RESULTS

The study sample included 88,713 participants; mean age 68.6 ± 7.8 years; 97.7% male; 84.1% White, 12.6% Black, and 3.3% other race (Table 1). After IPTW, baseline characteristics were balanced between groups (Table S2, Figure S2). There were 60,476 new users of metformin and 28,237 new users of sulfonylureas in the study sample (Fig. 1). Over a mean follow-up of 4.2 ± 3.0 years, there were 1,533 diabetes-related cancer cases (crude incidence rate = 4.1 per 1,000 person-years [p-yr]), 5,849 non-diabetes-related cancer cases (15.7 per 1,000 p-yr), and 13,398 deaths (35.9 per 1,000 p-yr).

Table 2 shows the results for the association between metformin use and diabetes-related and non-diabetes-related cancers. After IPTW adjustment, metformin use was associated with a lower incidence of all cancer types (HR 0.88, 95% CI 0.83-0.94) and with a lower incidence of diabetes-related cancer (HR 0.66, 95% CI 0.58-0.75), as compared to sulfonylurea use. There was no association between metformin use and the incidence of non-diabetes related cancers (HR 0.96,

Table 1. Study sample characteristics

Demographics	Metformin (n = 60,476)	Sulfonylurea (n = 28,237)	Total (n = 88,713)
Age (yr)	67.3 ± 7.1	71.4 ± 8.7	68.6 ± 7.8
Age category (yr)			
55-59	15,220 (25.2)	5,064 (17.9)	20,284 (22.9)
60-64	20,073 (33.2)	5,251 (18.6)	25,324 (28.5)
65-69	11,066 (18.3)	4,756 (16.8)	15,822 (17.8)
70-74	7,078 (11.7)	4,855 (17.2)	11,933 (13.5)
75-79	4,556 (7.5)	4,607 (16.3)	9,163 (10.3)
≥ 80	2,483 (4.1)	3,704 (13.1)	6,187 (7.0)
Male sex	58,844 (97.3)	27,844 (98.6)	86,688 (97.7)
Years of follow-up	4.2 ± 2.9	4.3 ± 3.3	4.2 ± 3.0
Race			
White	50,657 (83.8)	23,915 (84.7)	74,572 (84.1)
Black	7,727 (12.8)	3,476 (12.3)	11,203 (12.6)
Other	2,092 (3.5)	846 (3.0)	2,938 (3.3)
Year of treatment initiation			
2001-2004	13,677 (22.6)	14,933 (52.9)	28,610 (32.2)
2005-2008	22,628 (37.4)	9,114 (32.3)	31,742 (35.8)
2009-2012	24,171 (40.0)	4,190 (14.8)	28,361 (32.0)
Geographic region			
Northeast	13,225 (21.9)	5,062 (17.9)	18,287 (20.6)
Southeast	7,570 (12.5)	5,265 (18.6)	12,835 (14.5)
Central	25,020 (41.4)	11,419 (40.4)	36,439 (41.1)
West	14,661 (24.2)	6,491 (23.0)	21,152 (23.8)
Body mass index category (kg/m^2)			
Underweight (< 20.0)	147 (0.2)	143 (0.5)	290 (0.3)
Normal weight (20.0-24.9)	3,589 (5.9)	2,817 (10.0)	6,406 (7.2)
Overweight (25.0-29.9)	18,448 (30.5)	10,692 (37.9)	29,140 (32.9)
Obese (≥ 30)	38,292 (63.3)	14,585 (51.7)	52,877 (59.6)
Glomerular filtration rate			
30.0-44.9	273 (0.5)	3,760 (13.3)	4,033 (4.6)
45.0-59.9	6,022 (10.0)	7,583 (26.9)	13,605 (15.3)
≥ 60	54,181 (89.6)	16,894 (59.8)	71,075 (80.1)
A1c			
< 7.0	33,594 (55.6)	12,930 (45.8)	46,524 (52.4)
7.0-8.0	18,861 (31.2)	9,676 (34.3)	28,537 (32.2)
> 8.0	8,021 (13.3)	5,631 (19.9)	13,652 (15.4)
Comorbidities			
Major psychiatric disease	6,317 (10.5)	2,272 (8.0)	8,589 (9.7)
Arthritis	16,251 (26.9)	7,654 (27.1)	23,905 (27.0)
Coronary artery disease	21,007 (34.7)	13,347 (47.3)	34,354 (38.7)
Heart failure	3,432 (5.7)	3,341 (11.8)	6,773 (7.6)
Hypertension	51,547 (85.2)	24,776 (87.7)	76,323 (86.0)
Eye disease	10,899 (18.0)	5,965 (21.1)	16,864 (19.0)
Smoking	42,952 (71.0)	18,544 (65.7)	61,496 (69.3)
Alcohol abuse	6,240 (10.3)	2,092 (7.4)	8,332 (9.4)
Statin use	36,284 (60.0)	15,430 (54.6)	51,714 (58.3)
Cardiovascular disease	7,564 (12.5)	5,497 (19.5)	13,061 (14.7)
Chronic obstructive pulmonary disease	11,624 (19.2)	6,750 (23.9)	18,374 (20.7)
Cirrhosis	1,616 (2.7)	719 (2.5)	2,335 (2.6)
Number of visits	6 [3, 11]	6 [3, 11]	6 [3, 11]
Number of prescriptions	6.8 ± 3.8	7.2 ± 3.8	6.9 ± 3.8

Values in the table represent n (%), mean ± SD, or median [25th, 75th percentile].

Table 2. HR for the association between treatment (metformin vs. sulfonylureas) and diabetes-related cancers and non-diabetes-related cancers

Outcome	Metformin users (n = 60,476)		Sulfonylurea users (n = 28,237)		Unadjusted model		IPTW adjusted model	
	No. events/ total n	Rate (per 1,000 p-yr)	No. events/ total n	Rate (per 1,000 p-yr)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Any cancer	4,391	17.5	2,991	24.5	0.76 (0.73-0.80)	< 0.001	0.88 (0.83-0.94)	< 0.001
Diabetes related cancer	858	3.4	675	5.5	0.65 (0.59-0.73)	< 0.001	0.66 (0.58-0.75)	< 0.001
Non-diabetes related cancer	3,533	14.1	2,316	18.9	0.80 (0.75-0.84)	< 0.001	0.96 (0.89-1.02)	0.200

HR, hazards ratio; No., number; p-yr, person-years; IPTW, inverse probability of treatment weighting.

Table 3. HR for the association between treatment (metformin vs. sulfonylureas) and diabetes-related cancer subtypes

Outcome	Metformin users (n = 60,311)		Sulfonylurea users (n = 28,078)		Unadjusted model		IPTW adjusted model	
	No. events	Rate (per 1,000 p-yr)	No. events	Rate (per 1,000 p-yr)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Colorectal	303	1.21	258	2.12	0.68 (0.57-0.80)	< 0.001	0.75 (0.62-0.92)	0.005
Renal	184	0.73	105	0.86	0.80 (0.63-1.03)	0.081	0.95 (0.70-1.28)	0.722
Liver	114	0.45	114	0.94	0.47 (0.36-0.61)	< 0.001	0.39 (0.28-0.53)	< 0.001
Esophageal	86	0.34	67	0.55	0.59 (0.42-0.82)	0.002	0.54 (0.36-0.81)	0.003
Pancreas	74	0.29	61	0.50	0.64 (0.45-0.91)	0.014	0.71 (0.45-1.12)	0.139
Stomach	50	0.20	38	0.31	0.73 (0.47-1.14)	0.167	0.77 (0.47-1.28)	0.319
Breast	32	0.13	13	0.11	1.14 (0.59-2.23)	0.695	0.63 (0.25-1.62)	0.340
Endometrial[a]	4	0.59	2	1.24	-[b]	NA	-[b]	NA

Any participant with cancer where the primary cancer type could not be identified (≥ 2 cancer types at the time of initial diagnosis [n = 90] or a diagnosis of metastatic-unknown primary type [n = 234]) was excluded from the analysis of the individual cancer subtypes. HR, hazards ratio; No., number; p-yr, person-years; IPTW, inverse probability of treatment weighting; NA, not available. [a]Female participants only (n = 1,630 metformin, n = 391 sulfonylurea), [b]insufficient sample size.

95% CI 0.89-1.02).

The frequencies of the individual cancer subtypes that compose the diabetes-related and non-diabetes related cancer groups are shown in Table S3. Colorectal cancer was the most common type of diabetes-related cancer (35% among metformin users, 38% among sulfonylurea users). The most common type of non-diabetes related cancer was prostate cancer (39% for metformin, 32% for sulfonylurea). Table 3 shows HRs for the individual subtypes of diabetes-related cancer. As compared to sulfonylurea, metformin use was associated with a lower incidence of colorectal (HR 0.75, 95% CI 0.62-0.92), liver (HR 0.39, 95% CI 0.28-0.53), and esophageal (HR 0.54, 95% CI 0.36-0.81) cancers. There was no association between the treatment group and the remaining diabetes-related cancer subtypes (renal, pancreas, stomach, and breast). The HRs for the individual subtypes of non-diabetes-related cancer are shown in Table S4. After IPTW adjustment, metformin use (versus sulfonylurea use) was associated with a lower incidence of male genital tract (not otherwise specified) cancers (HR 0.31, 95% CI 0.11-0.83), but not with any of the other non-diabetes-related subtypes.

Our sensitivity analysis, which used an ITT approach, included 168,939 new users of metformin and 101,949 new users of sulfonylureas (Figure S1). The HRs were attenuated compared to the HRs from the main analysis. In the ITT analysis, metformin use was associated with a HR of 0.97 (95% CI 0.94-1.00, $P = 0.038$) for any cancer, 0.87 (95% CI 0.81-0.92, $P < 0.001$) for diabetes-related cancer, and 1.00 (95% CI 0.97-1.03, $P = 0.99$) for non-diabetes-related cancer (Table S5).

DISCUSSION

In this large retrospective cohort study of US veterans aged 55 years and older with diabetes, using multiple methods to account for potential bias and confounding, we found that metformin users had lower incidence of all cancers compared to sulfonylurea users. This was primarily driven by the lower incidence of diabetes-related cancers in the metformin group. There was no association between metformin use (versus sulfonylureas) and incidence of non-diabetes-related cancers. These findings support the hypothesis that metformin may activate anti-cancer pathways more so than sulfonylureas.

The lower incidence of cancer observed among regular users of metformin in our cohort is similar to that seen in the many published observational studies, with meta-analyses of these studies reporting up to 31% to 34% reduction in risk of incident cancer [25,26]. As previously noted, many early

observational studies were limited by time-related biases [14,27]. Our utilization of a new-user design ensures avoidance of time-related biases. Our study is most similar in design to the large retrospective cohort study in the UK Clinical Practice Research Datalink that used a new-user design and an "intent to treat" analysis to assess cancer incidence in patients with diabetes initiated on metformin compared with other oral anti-diabetes medications [28]. They found a similar incidence of cancer in metformin initiators (51,484 individuals) and sulfonylurea initiators (18,264 participants). Our results may differ due to the implementation of the IPTW propensity approach, which matches individuals at a similar stage in the natural history of their disease, allowing for adjustment of pre-treatment variables. Furthermore, by using PS [29] and IPTW methods [21], we controlled for the confounding by indication that is inherent in a non-randomized trial of drug effects. These statistical analyses may account for the difference in results in our study (whereby metformin use was associated with lower incidence of malignancy), compared to the findings of the UK Clinical Practice Research Datalink study [28].

In our cohort, use of metformin was associated with lower incidence of all cancers with the association being strongest in diabetes-related cancers, particularly liver, colorectal and esophageal cancer. A prior systematic review of observational studies demonstrated significant reductions in risk of the same cancer types (liver, colorectal and esophageal) as well as stomach and pancreatic cancer [4]. While the exact mechanisms of the association between diabetes and lower observed incidence of cancer are not fully understood, prior studies suggest underlying risk factors for diabetes and metabolic syndrome may lead to a proinflammatory state which in turn is protumorigenic [30]. Metformin likely decreases inflammation by acting on different cellular processes, including cell cycle arrest and genomic stability [31]. Metformin activates AMPK [7] which leads to the inhibition of mTOR signaling, the reduction of protein synthesis [8], and possibly to regulating p53-mediated cell-cycle arrest [32]. Metformin has also been reported to scavenge free radicals, to prevent damage to mitochondrial DNA, and to enhance DNA repair thus affording cells greater genomic stability [9]. In addition to the changes effected on the cellular level, metformin improves glycemic control; since elevated glucose, insulin resistance, and diabetes have been implicated in the development of several diabetes-related cancers, (including liver, colorectal and esophageal cancer) [3], metformin's protective benefits may be higher in these cancers. Our data adds to the existent literature and suggests metformin may continue to have a role in improving the overall health of individuals with metabolic syndrome and/or diabetes, even in this era of novel oral diabetes medications.

Our study's strengths include analysis of a large cohort of patients and the implementation of PSs and IPTW methodology. A number of limitations should also be considered in the interpretation of our results. We did not collect data on dose or duration of exposure to metformin or sulfonylureas during follow-up, and thus we cannot assess whether the inverse association between metformin and cancer incidence is affected by these factors. Since our cohort is based on Veterans Health Administration health records, regular measurements of treatment efficacy, such as fasting blood glucose and HbA1c, are not available. Additionally, the nature of our study design precludes us from establishing causality for the association between metformin and lower cancer risk. Finally, the subjects in our cohort were mostly male, limiting the generalizability of our findings.

In summary, we provide observational data leveraging a new-user cohort design and PS matching that support the finding that metformin use is associated with a lower incidence of diabetes-related cancers as compared to sulfonylurea use. Ongoing randomized controlled trials (RCTs), such as the Diabetes Prevention Program Outcomes Study, will provide valuable insight into the metformin-cancer association. By 2025, this program is expected to provide data on cancer outcomes based on 25 years of follow up (ClinicalTrials.gov Identifier: NCT00038727) [33]. Results of RCTs are needed to determine the potential of metformin in the primary prevention of cancer, as well as further studies into the mechanism of metformin's anti-cancer effects.

FUNDING

This study was supported by Veterans' Administration (VA) Merit Review Award Clinical Science R&D I01CX000934-01A1 (Awarded to Jane Driver, MD, MPH). The sponsors had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Clark DuMontier, MD, MPH is supported by a VA Career Development Award, IK2CX002218. Ariela Orkaby, MD, MPH is supported by a VA Career Development Award, IK2-CX001800. Support for VA/CMS data provided by the Department of Veterans Affairs, VA Health Services Research and Development Service, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004).

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.15430/JCP.24.012.

ORCID

Maya M. Abdallah, https://orcid.org/0000-0003-1549-6419

Beatriz Desanti de Oliveira, https://orcid.org/0000-0002-1352-0115
Clark DuMontier, https://orcid.org/0000-0003-2582-7816
Ariela R. Orkaby, https://orcid.org/0000-0002-4297-6306
Lisa Nussbaum, https://orcid.org/0000-0001-6146-1538
Michael Gaziano, https://orcid.org/0000-0002-5384-9767
Luc Djousse, https://orcid.org/0000-0002-9902-3047
David Gagnon, https://orcid.org/0000-0002-6367-3179
Kelly Cho, https://orcid.org/0000-0003-1727-7076
Sarah R. Preis, https://orcid.org/0000-0002-9360-4166
Jane A. Driver, https://orcid.org/0000-0001-9759-4607

REFERENCES

1. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607.
2. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674-85.
3. Deng L, Liu T, Liu CA, Zhang Q, Song MM, Lin SQ, et al. The association of metabolic syndrome score trajectory patterns with risk of all cancer types. Cancer 2024;130:2150-9.
4. Mekuria AN, Ayele Y, Tola A, Mishore KM. Monotherapy with metformin versus sulfonylureas and risk of cancer in type 2 diabetic patients: a systematic review and meta-analysis. J Diabetes Res 2019;2019:7676909.
5. Yuan S, Kar S, Carter P, Vithayathil M, Mason AM, Burgess S, et al. Is type 2 diabetes causally associated with cancer risk? Evidence from a two-sample mendelian randomization study. Diabetes 2020;69:1588-96.
6. Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. Nat Rev Cancer 2020;20:629-44.
7. Emami Riedmaier A, Fisel P, Nies AT, Schaeffeler E, Schwab M. Metformin and cancer: from the old medicine cabinet to pharmacological pitfalls and prospects. Trends Pharmacol Sci 2013;34:126-35.
8. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell 2007;12:9-22.
9. Najafi M, Cheki M, Rezapoor S, Geraily G, Motevaseli E, Carnovale C, et al. Metformin: prevention of genomic instability and cancer: a review. Mutat Res Genet Toxicol Environ Mutagen 2018;827:1-8.
10. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010;33:1304-8.
11. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer 2011;11:20.
12. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 2010;116:1938-46.
13. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. Cancer Causes Control 2009;20:1617-22.
14. Yu OHY, Suissa S. Metformin and cancer: solutions to a real-world evidence failure. Diabetes Care 2023;46:904-12.
15. Zhang HS, Yang Y, Lee S, Park S, Nam CM, Jee SH. Metformin use is not associated with colorectal cancer incidence in type-2 diabetes patients: evidence from methods that avoid immortal time bias. Int J Colorectal Dis 2022;37:1827-34.
16. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20.
17. Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA. Metformin vs sulfonylurea use and risk of dementia in US veterans aged ≥65 years with diabetes. Neurology 2017;89:1877-85.
18. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429-42.
19. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:487-93.
20. Wicentowski R, Sydes MR. Using implicit information to identify smoking status in smoke-blind medical discharge summaries. J Am Med Inform Assoc 2008;15:29-31.
21. Rosenbaum PR. Model-based direct adjustment. J Am Stat Assoc1987;82:387-94.
22. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. Med Care 2007;45(10 Supl 2):S103-7.
23. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81.
24. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
25. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One 2012;7:e33411.
26. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2010;3:1451-61.
27. Johnson ES, Bartman BA, Briesacher BA, Fleming NS, Gerhard T, Kornegay CJ, et al. The incident user design in comparative effectiveness research. Pharmacoepidemiol Drug Saf 2013;22:1-6.
28. Tsilidis KK, Capothanassi D, Allen NE, Rizos EC, Lopez DS,

van Veldhoven K, et al. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. Diabetes Care 2014;37:2522-32.
29. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.
30. Harvey AE, Lashinger LM, Hursting SD. The growing challenge of obesity and cancer: an inflammatory issue. Ann N Y Acad Sci 2011;1229:45-52.
31. Lord SR, Harris AL. Is it still worth pursuing the repurposing of metformin as a cancer therapeutic? Br J Cancer 2023;128:958-66.
32. Jones RG, Plas DR, Kubek S, Buzzai M, Mu J, Xu Y, et al. AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. Mol Cell 2005;18:283-93.
33. Diabetes prevention program outcomes study (DPPOS). https://classic.clinicaltrials.gov/ct2/show/NCT00038727 (Accessed May 16, 2024).