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Metformin and survival: Is there benefit in a cohort limited to diabetic women with endometrial, breast, or ovarian cancer?

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HIGHLIGHTS

- Metformin has been shown to increase cancer survival, potentially through known metabolic and hormonal effects.
- Ovarian, endometrial and breast cancer are all hormonally mediated.
- Metformin demonstrated survival benefit in these cancers after accounting for diabetes progression.
- Survival benefit was consistent across all three cancer types and when assessed individually.

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ABSTRACT

Objective. Evaluate the association between metformin and survival in women with Type 2 diabetes (T2DM) and breast, endometrial and ovarian cancer— 3 hormonally mediated cancers.

Methods. We evaluated outcomes in a cohort of 6225 women with T2DM with a new diagnosis of ovarian, breast or endometrial cancer from 2010 to 2019. We classified glycemic medications at time of first cancer diagnosis into 3 tiers in accordance with ADA guidelines.

Approaches compared: (i) metformin (tier 1) vs. no glycemic medication, (ii) metformin vs tier 2 medications (sulfonylureas, thiazolidinediones, SGLT2-inhibitors, DPP4-inhibitors, alpha glucosidase-inhibitors, GLP-1 agonists), (iii) metformin vs tier 3 medications (insulins, amylinomimetics), and (iv) tier 2 vs tier 3 medications. Analyses included Cox proportional-hazards models, Kaplan-Meier curves, and conditional logistic regression in a risk set-sampled nested case-control matched on T2DM duration— all modeling survival. Models were adjusted for demographics, cancer type, A1C, T2DM duration, and number of office visits and hospitalizations.

Results. Metformin was the most used medication ($n = 3232$) and consistently demonstrated survival benefit compared with tier 2 and 3 medications, across all methods. Tier 3-users demonstrated highest risk of death when compared to metformin rather than tier 2 [adjHR = 1.83 (95% CI: 1.58, 2.13) vs. adjHR = 1.32 (95% CI: 1.11, 1.57)], despite similar baseline profiles between tier 1 and 2 users.

Conclusions. Metformin users experienced increased survival even after accounting for surrogates of diabetes progression. Benefit extended beyond that seen in tier 2-users. Our findings, consistent with prior studies, indicate metformin use improves survival in women with T2DM and hormonally mediated women's cancers.

1. Introduction

Type 2 diabetes mellitus (T2DM) has been associated with an increased risk of breast, ovarian and endometrial cancers [1–4] and women with T2DM who develop these cancers are reported to have higher mortality [5–9]. While both T2DM and cancer share many risk

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factors, such as obesity, smoking, and age, it is unclear whether these risk factors predispose women to both diseases or whether metabolic dysregulation associated with T2DM, such as hyperglycemia, hyperinsulinemia, oxidative stress, chronic inflammation, and sex hormone dysregulation is the underlying link [1].

Metformin, a biguanide, is first line pharmacologic therapy for individuals with T2DM because of its glycemic efficacy, lack of weight gain and hypoglycemia, overall tolerability, and low cost. Because diabetes is the most common indication for metformin use, studying its effects on cancer outcomes in individuals with diabetes, a readily available retrospective population, has been an area of substantial interest. To date, however, the association between metformin use and cancer survival remains unclear. Some studies have demonstrated inverse associations, some no associations, and still others showed positive associations [10–18]. Differences in study design, biases, and lack of data on potential confounders likely explain these disparate findings [12]. Importantly, meta-analyses have demonstrated survival benefit for diabetic patients with breast, ovarian, and endometrial cancer [19].

Though the exact anti-cancer effect of metformin is unclear, the prominent hypothesized mechanisms are ideally suited to the tumor biology of these select tumors given one of the common biological links between diabetes and cancer is the dysregulation of sex hormones and all three of the cancers are known to be hormonally linked. More specifically high blood glucose and insulin is associated with low levels of circulating sex hormone binding globulin, which is associated with diabetes risk, but also leads to free estrogen synthesis, which is known to drive these cancers [20–23]. Some data suggests that metformin may act indirectly by effecting sex hormone [24,25]. And while hormonal stimulation is not the only driver for these cancers it may be one of the reasons why metformin has potential anti-cancer effects in this subset of disease. Additional mechanisms of action for metformin that have been posed for metformin suggests that effective therapies have the potential to impact the cellular dysregulation that occurs with cancer on multiple fronts. In addition to the linkage with sex hormones, at a molecular level some have suggested that metformin modulates AMPK signaling, AKT activity, and the induction of apoptosis [26,27]. In parallel with this, metabolic actions have been proposed related to gluconeogenesis, mitochondrial function, cellular metabolism and how the metabolic impact can reduce immune exhaustion and enhance PD-1 blockade [28–30]. At the cellular level, metformin has also been reported to inhibit epithelial mesenchymal transition, IGF signaling, and selectively suppress cancer stem-like cell (CSC) growth [31–35]. Metformin is reported to reverse chemotherapy resistance, reduce cancer cell migration and metastasis and prevent epithelial mesenchymal transition [27,29,35–38].

We chose to study these three female-cancers collectively as they are uniquely hormonally associated for which metformin is known to decrease estrogens levels [25]. We also looked at each cancer individually, understanding that there are likely additional factors at play. Notwithstanding this, evaluating the association between metformin use and cancer survival in the context of treatment for T2DM presents unique challenges. Diabetes varies in severity and control over time— two factors that directly impact morbidity and mortality from the disease. Thus, when assessing the relationship between metformin use and cancer survival, it is critical to dissect the associations with each factor to avoid potential confounding by diabetes progression.

Using an observational retrospective cohort, we aimed to evaluate the association between metformin use and survival in women with T2DM with newly diagnosed ovarian, endometrial or breast cancer, while controlling for confounding introduced with diabetes severity and control over time.

2. Materials and methods

2.1. Data source and population

Our retrospective cohort was comprised of women with a new diagnosis of ovarian, breast or endometrial cancer from January 1, 2010 through June 1, 2019 at an outpatient University of Pittsburgh Medical Center (UPMC) facility. UPMC is the largest health system network in Pennsylvania, providing care for an estimated 150,000 oncology patients each year. Patients entered the cohort at their first visit with a cancer diagnosis, referred to as their index visit throughout. Within the cohort of women with ovarian, breast or endometrial cancer, we then identified those women with a concurrent diagnosis of T2DM at their first visit for a cancer diagnosis documented using ICD codes. Follow-up was allowed through September 1, 2019. This study was approved by the University of Pittsburgh's Institutional Review Board.

2.2. Clinical data

All discrete data entered into the electronic medical record are stored in UPMC's Clinical Data Warehouse and were available for this study. To estimate a similar stage of diabetic disease, we calculated the duration of diabetes for each patient as time from first T2DM diagnosis to the first cancer diagnosis. For example, a patient diagnosed with T2DM on 1/1/2015 and diagnosed with ovarian cancer on 1/1/2016, had a duration of T2DM of 365 days. For women with first T2DM and cancer diagnoses on the same day, duration is 0.

2.3. Medication exposure

Medication exposure is self-reported and documented in the electronic health record by the healthcare provider at the time of a woman's index visit. Glycemic medication was classified into three tiers consistent with the American Diabetes Association guidelines [39]. Tier 1, first-line therapy and our exposure of interest, includes only metformin. Tier 2 is comprised of all second-line medications: sulfonylureas, thiazolidinediones, SGLT2-inhibitors, DPP4-inhibitors, alpha glucosidase-inhibitors, and GLP-1 agonists. Injectable medication, including both insulin and amylinomimetics, are considered last line and comprise tier 3.

Metformin is expected to influence cancer survival regardless of polytherapy. Therefore, treatments were grouped in a hierarchal and exclusive manner. Specifically, patients on metformin were classified as 'metformin exposed' regardless of concomitant treatment. Patients receiving at least one tier 2 medication and not metformin were classified as tier 2. Patients receiving insulin alone were classified as tier 3. As an example, if metformin and insulin are documented in the chart, the patient was classified as tier 1; documentation of a sulfonylurea and insulin was considered tier 2; a patient on insulin alone was tier 3. Women receiving none of these medications were analyzed in the 'no medication group'.

2.4. Endpoint

The outcome of interest was death from any cause between time of cancer diagnosis (index visit) and September 1, 2019.

2.5. Statistical analysis

All analyses were conducted in the population of women with T2DM. Descriptive comparisons were made by glycemic medication type, using chi-2 for categorical data and ANOVA/Kruskal-Wallis for continuous as appropriate.

Primary analyses were conducted using Cox Proportional Hazards models evaluating survival time. Four comparisons were performed:

(i) metformin vs. no glycemic medication, (ii) metformin vs tier 2, (iii) metformin vs tier 3, and (iv) tier 2 vs tier 3. Each of these models is presented as unadjusted and adjusted; using direct acyclic graphs to determine potential confounding factors [40]. Confounding factors included age, cancer type (breast, endometrial, ovarian), UPMC Heath Plan subscriber (yes/no), race (white, black, other), number of office visits for cancer diagnosis, number of hospitalizations after cancer diagnosis, body mass index (kg/m^2) at first visit and HbA1C value within 180 days of first cancer visits.

Values of HbA1C and body mass index, the only two potential confounders with missing data, were jointly imputed as continuous variables using chained equations across 40 simulated datasets [41]. Estimates presented are results from a pooled analysis synthesizing the point estimates and standard errors across all 40 datasets.

Survival differences were visualized using Kaplan Meier curves. Equality of curves were tested using log-rank tests.

All analyses were done using Stata version 15 and a p-value of <0.05 was considered statistically significant.

2.6. Sensitivity analyses

Because survival benefits of metformin may be attributable to earlier diabetes progression, we created a nested case-control using risk-set sampling without replacement matched on T2DM duration [12]. We generated this nested cohort by sampling 1 control (non-death) for each death matching on duration of diabetes. Sampling was run across 100 Monte Carlo simulations to decrease sampling bias. Within the nested cohort we ran conditional logistic regressions for the same comparisons (1–4 listed above). Unadjusted and adjusted results are presented. Finally, regressions were repeated within each cancer type.

As supplemental analyses, we compared baseline demographics by T2DM status and glycemic medication in the full population, not limited to diabetics (Supplemental Material). We modeled death by T2DM status and by metformin use, independent of diabetes, using logistic regressions. These analyses were run both unadjusted and adjusted significant for baseline covariates in univariate comparisons, then adjusted for T2DM alone. Sensitivity analyses evaluated maintenance of treatment regimen over the study period. All analyses were rerun excluding women who did not maintain treatment exposure over the study period.

3. Results

Of 46,563 women with a new diagnosis of breast ($n = 34{,}683$), endometrial ($n = 8003$), or ovarian ($n = 4219$) cancer, 6225 (13%) also had a diagnosis of T2DM at index visit and were therefore available for primary analyses.

In the T2DM population, the most common glycemic medication used was metformin ($n = 3232$) (Fig. 1). Crude rates of death were highest in women treated with only tier 3 medications: 18%, 23%, 33%, and 37% for metformin, no medication use, tier 2, and only tier 3 respectively. When comparing women with T2DM receiving treatment, women on metformin were younger, more likely to be a member of UPMC Health Plan, have more office visits over the study period, and less likely to have comorbidities, and hospitalizations after diagnosis (Table 1). Women on metformin or tier 2 agents had similar body mass index, A1Cs and duration of diabetes. When comparing women with T2DM with no glycemic treatment at time of cancer diagnosis to the treated, they had lower BMIs, lower HbA1Cs, and more office visits over the study period.

Of the confounders chosen a priori the only covariates with missing data were HbA1C within 180 days of visit ($n = 2216$; 36%) and BMI ($n = 596$; 10%). To impute these variables using chained equations, the following auxiliary variables were chosen and included in the imputation models: race, age, number of office visits, hospitalizations post-diagnoses, cancer diagnosis occurring at a primary care physician, obesity/morbid obesity/CKD at index visit, days with diabetes at index visit, closest glucose measurement within 180 days of diagnosis, UPMC Health Plan member, and death.

Kaplan Meier curves displayed metformin benefit with users exhibiting significantly increased survival (Fig. 2); more markedly so than tier 2 medications compared with tier 3. Women taking tier 2 or 3 medications had a statistically significant increased risk of death compared with metformin users (Table 2). This association persisted

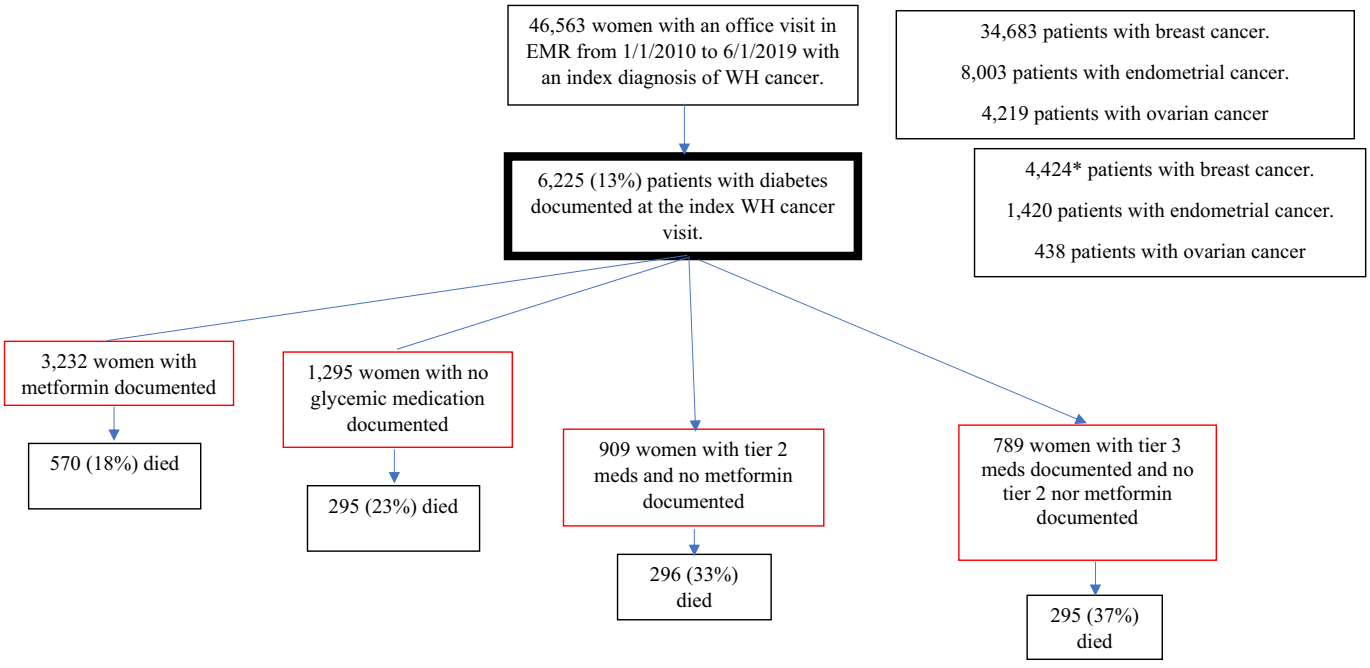

Fig. 1. Population of patients with a diagnosis of women's health cancer in an outpatient UPMC facility from 01 to 01-2010 to 06-01-2019.
EMR = electronic medical record; WH = women's health.
*29 Women have breast cancer and endometrial; 15 have breast and ovarian; 13 have ovarian and endometrial.

Table 1
Characteristics of women with diabetes at the time of their first visit with a cancer diagnosis at a UPMC facility from 1 to 1-2010 to 6-1-2019. Comparison of patients by tier of diabetic medication treatment ($n = 6225$).

Factor	No Medication	Metformin	Tier 2[a]	Tier 3[b]	*p*-value[c]
N	1295	3232	909	789	
UPMC Health Plan	312 (24.1%)	880 (27.2%)	206 (22.7%)	187 (23.7%)	0.009
Age in years, mean (SD)	71.3 (11.5)	68.0 (10.4)	73.4 (11.1)	68.8 (12.3)	<0.001
Race					0.039
White	1149 (88.7%)	2903 (89.8%)	822 (90.4%)	681 (86.3%)	
Black	132 (10.2%)	277 (8.6%)	75 (8.3%)	94 (11.9%)	
Other	14 (1.1%)	52 (1.6%)	12 (1.3%)	14 (1.8%)	
Body Mass Index (kg/m^2), median (IQR)	31.3 (26.8, 36.7)	33.3 (28.7, 38.8)	33.7 (29.2, 39.0)	34.3 (28.0, 39.8)	<0.001
Cancer type					0.10
Breast	946 (73.1%)	2247 (69.5%)	637 (70.1%)	550 (69.7%)	
Endometrial	251 (19.4%)	755 (23.4%)	202 (22.2%)	170 (21.5%)	
Ovarian	87 (6.7%)	201 (6.2%)	65 (7.2%)	57 (7.2%)	
>1 Women's' health cancer	11 (0.8%)	29 (0.9%)	5 (0.6%)	12 (1.5%)	
Comorbidities[d]					
Morbid obesity	280 (21.6%)	870 (26.9%)	238 (26.2%)	240 (30.4%)	<0.001
Atrial fibrillation	122 (9.4%)	226 (7.0%)	120 (13.2%)	84 (10.6%)	<0.001
Chronic obstructive pulmonary disease	173 (13.4%)	356 (11.0%)	132 (14.5%)	124 (15.7%)	<0.001
Congestive heart failure	111 (8.6%)	194 (6.0%)	123 (13.5%)	135 (17.1%)	<0.001
Osteoporosis	223 (17.2%)	343 (10.6%)	112 (12.3%)	84 (10.6%)	<0.001
Hypertension	994 (76.8%)	2541 (78.6%)	752 (82.7%)	606 (76.8%)	0.004
Depression	254 (19.6%)	593 (18.3%)	173 (19.0%)	167 (21.2%)	0.31
Rheumatoid arthritis	42 (3.2%)	71 (2.2%)	30 (3.3%)	28 (3.5%)	0.050
Lupus	9 (0.7%)	21 (0.6%)	5 (0.6%)	6 (0.8%)	0.96
Stroke	122 (9.4%)	259 (8.0%)	98 (10.8%)	91 (11.5%)	0.004
Deep vein thrombosis	43 (3.3%)	54 (1.7%)	33 (3.6%)	30 (3.8%)	<0.001
Pulmonary embolism	37 (2.9%)	53 (1.6%)	18 (2.0%)	28 (3.5%)	0.003
Hypothyroidism	374 (28.9%)	814 (25.2%)	256 (28.2%)	223 (28.3%)	0.031
Chronic kidney disease (CKD)	122 (9.4%)	141 (4.4%)	141 (15.5%)	120 (15.2%)	<0.001
Closest HbA1C[d], median (IQR)	6.2 (5.9, 6.7)	6.9 (6.3, 7.7)	6.8 (6.3, 7.8)	7.6 (6.7, 8.9)	<0.001
Days with diabetes	337 (0, 1182)	288.5 (0, 1256.5)	203 (0, 1091)	344 (0, 1400)	0.045
Year of first cancer visit 2010	157 (12.1%)	255 (7.9%)	92 (10.1%)	66 (8.4%)	0.010
2011	65 (5.0%)	149 (4.6%)	49 (5.4%)	38 (4.8%)	
2012	179 (13.8%)	474 (14.7%)	132 (14.5%)	105 (13.3%)	
2013	186 (14.4%)	460 (14.2%)	146 (16.1%)	123 (15.6%)	
2014	193 (14.9%)	472 (14.6%)	137 (15.1%)	129 (16.3%)	
2015	114 (8.8%)	353 (10.9%)	79 (8.7%)	73 (9.3%)	
2016	110 (8.5%)	294 (9.1%)	72 (7.9%)	89 (11.3%)	
2017	105 (8.1%)	278 (8.6%)	65 (7.2%)	73 (9.3%)	
2018	133 (10.3%)	338 (10.5%)	96 (10.6%)	64 (8.1%)	
2019	53 (4.1%)	159 (4.9%)	41 (4.5%)	29 (3.7%)	
Dead	295 (22.8%)	570 (17.6%)	296 (32.6%)	295 (37.4%)	<0.001
Office visits over study period, median (IQR)	16 (6, 32)	14 (6, 30)	12 (4, 27)	13 (4, 28)	<0.001
Hospitalizations after cancer diagnosis, median (IQR)	1 (0, 4)	1 (0,3)	1 (0, 5)	2 (0, 6)	<0.001
Surgeries after cancer diagnosis, median (IQR)	1 (0,2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	<0.001

UPMC = University of Pittsburgh Medical Center; SD = standard deviation; BMI = body mass index; IQR = interquartile range;
[a] Sulfonylureas, thiazolidinediones, SGLT2-inhibitors, DPP4-inhibitors, alpha glucosidase-inhibitors, and GLP-1 agonists.
[b] Insulin and amylinomimetics.
[c] Chi-2 testing for categorical; ANOVA and Kruskal Wallis for continuous.
[d] Within 180 days of their first visit with a cancer diagnosis.

whether adjusted or unadjusted. Increased risk of death was 1.35 (95% CI: 1.17, 1.57) for tier 2, and 1.83 (95% CI: 1.58, 2.13) for tier 3 compared with metformin. Tier 3 demonstrated highest risk of death when compared to metformin rather than tier 2 [adjHR = 1.83 (95% CI: 1.58, 2.13) vs. adjHR = 1.32 (95% CI: 1.11, 1.57)]. There was a trend of increased risk of death in women using no medication compared with metformin, though this did not remain significant after adjustment.

In sensitivity analyses, the benefit of metformin use persisted after accounting for duration of diabetes (Table 3). Compared with patients taking metformin, tier 2 medication users with a similar duration of diabetes experienced almost twice the mortality, though no longer statistically significant in the smaller cohort [adjHR = 1.75 (0.99, 3.26)].

In the full population, non-diabetics had an overall healthier profile (Supplemental Material; STable 1). They were younger, had lower body mass indexes and had less comorbid conditions. Preliminary results showed that, as expected, T2DM itself carried an increased risk of death. Metformin use demonstrated no overall benefit in the full population [adjOR = 1.02 (0.93, 1.12)]; however, there was a statistically significant survival benefit after accounting for a patient's diabetic status [Supplemental Material; STable 2; adjOR = 0.65 (0.59, 0.72)]. Results were consistent across cancer types, demonstrating a benefit in ovarian, endometrial and breast cancer, though statistical significance was not always reached with smaller population subsets (Supplemental Material; STable 3). Most patients remained on the same medication throughout the study period. A total of 438 metformin users (14%) were no longer taking this medication at the time of their last visit (Supplemental Material; STable 4). Conclusions did not change after removing all 857 women who did not maintain treatment exposure over the study period (STable 5).

4. Conclusions

Using a large cohort of women with Type 2 diabetes identified through existing electronic health record data, patients being treated with metformin had improved ovarian, endometrial, and breast cancer survival. This benefit was observed across three types of cancer presenting at varying stages and persisted after accounting for surrogates of diabetes progression such as HbA1C, body mass index and duration of diabetes. Our results add to the existing literature supporting metformin's impact on patient survival in ovarian, breast, and endometrial cancers

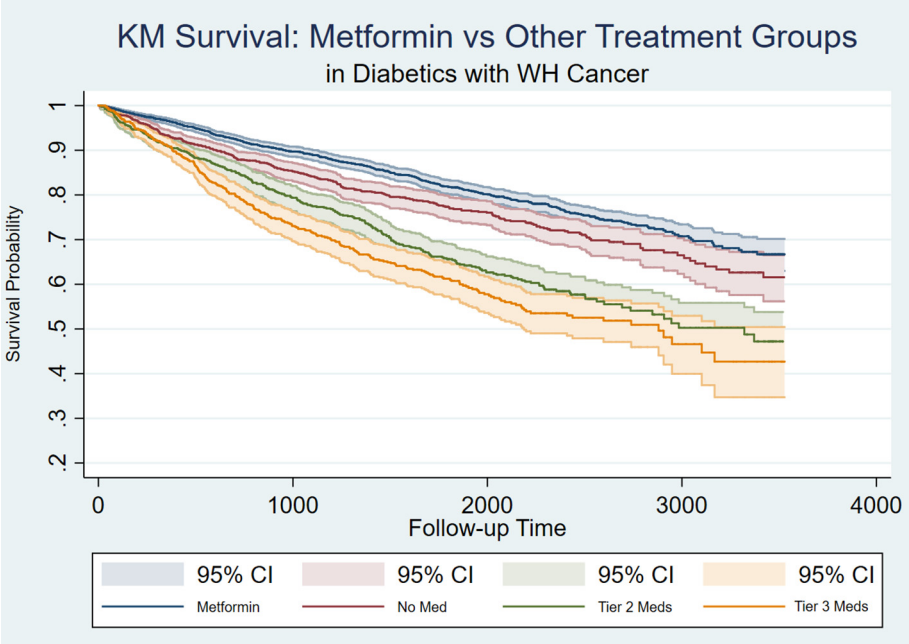

Fig. 2. Kaplan Meir curves comparing survival by treatment in diabetic women.
Log rank: <0.0000.

[15,42–46]. Further, they support mechanistic research and clinical trials in these cancer types to further understand the mechanism and ultimately target this medication's use.

Suggesting metformin could be directly impacting cancer, we found that women on metformin and tier 2 medications, such as sulfonylureas, had similar baseline T2DM characteristics yet tier 2 users had a significantly higher risk of death. Furthermore, survival benefit persisted after addressing the competing risk of death from diabetes by matching on duration of disease and adjusting for glycemic control to approximate diabetes progression.

Our conclusions are consistent with several studies' previous findings evaluating the use of metformin and survival in these hormonally mediated cancers, though there are studies with conflicting results. Biases resulting from competing risks of T2DM and unmeasured confounding variables contribute to the discrepancy in findings across many of the retrospective cohorts [12]. We attempted to address this by accounting for surrogates of diabetes progression. Importantly, recent clinical trials and meta-analyses have shown that metformin can increase the response to chemotherapy and be useful as adjuvant therapy in some cancers, including endometrial and breast [15,47,48], and basic science has shown promising results on the effects of metformin on tumor cell proliferation and other indirect pathways [49–53]. To our knowledge there are also no other existing trials evaluating these three female-cancers collectively nor any that demonstrate benefit when comparing across different tiers of diabetic treatments.

Though our findings are robust and demonstrated benefit in a large population, they must be interpreted within the constraints of our limitations. Inherent in using a large clinical data warehouse, information is only available as clinics go onto the electronic medical record. Both cancer and T2DM diagnosis are very likely skewed as clinics adopt the electronic medical record. We do not anticipate that the resulting misclassification of time varies by medication treatment nor survival, making impact negligible. Our clinical data warehouse also does not store reliable staging, histological and hormonal receptor status, nor chemotherapy. These big data limitations result in a diverse population potentially diluting a relationship that is limited to specific cancer subtype or stage. Nevertheless, metformin at first visit demonstrated a survival benefit, making the threat of diluted results less concerning. We also did not have access to cause of death which would have allowed us to conduct a competing risk analysis. Using a large clinical data warehouse also has intrinsic strengths— it provides a large sample size and allows us to deploy a broad intervention across our

Table 2
Results comparing mortality in diabetic patients with cancer documented in an outpatient visit by glycemic medication use.

Exposure	Population at Risk	Died	Unadjusted Risk per 100 women	Cox Proportional Hazards [b, c]	
				Unadjusted HR	Adjusted [a] HR
Metformin	3232	570	18	Referent	Referent
No glycemic med	1295	295	23	1.30 (1.13, 1.50)	1.10 (0.94, 1.27)
Metformin	3232	570	18	Referent	Referent
Tier 2	909	296	33	2.06 (1.79, 2.37)	1.35 (1.17, 1.57)
Metformin	3232	570	18	Referent	Referent
Tier 3	789	295	37	2.48 (2.15, 2.86)	1.83 (1.58, 2.13)
Tier 2	909	296	33	Referent	Referent
Tier 3	789	295	37	1.20 (1.02, 1.41)	1.32 (1.11, 1.57)

HR = Hazards Ratio.
[a] Adjusted for age, cancer type, Health Plan membership, race, number of office visits and hospital visits post-cancer diagnosis, days with diabetes, body mass index at first visit (imputed), and closest A1C (imputed) recorded within 180 days of first visit.
[b] 17 patients died but do not have a date of death allowing us to calculate survival time.
[c] Run in 40 imputed datasets.

Table 3
Results of a risk set sampling in a nested case-control study comparing risk of death among women with diabetes with breast, endometrial or ovarian cancers by glycemic treatment.

Exposure	Risk-Set Sampled Case Control[a, b]	
	Unadjusted RR	Adjusted[c] RR
Metformin	Referent	Referent
No glycemic med	1.29 (0.97, 1.69)	1.10 (0.79, 1.56)
Metformin	Referent	Referent
Tier 2	2.14 (1.57, 3.04)	1.75 (0.99, 3.26)
Metformin	Referent	Referent
Tier 3	2.53 (1.93, 3.95)	1.79 (0.99, 3.35)
Tier 2	Referent	Referent
Tier 3	1.21 (0.68, 1.83)	1.36 (0.69, 2.91)

RR = Risk Ratio.
[a] Matched 1:1 on duration of diabetes at time of cancer diagnosis from first diagnosis documented in electronic health record.
[b] Ran in 100 Monte Carlo simulations to account for sampling bias.
[c] Adjusted for age, Health Plan membership, race, number of office visits and hospital visits post-cancer diagnosis, cancer type, and BMI at first visit.

system if benefit is suspected. Analyzing endometrial, ovarian and breast cancer together has its weaknesses; however, as analyses stratified by cancer type demonstrated consistent direction of associations with metformin, this diverse population also provides a strength in population size and potentially similar pathways of associations.

Epidemiologically, the major obstacles when studying this relationship are time-varying exposures and confounding [12,54]. Using risk set sampling, we decrease the likelihood of immortal time which can lead to an overestimation of the benefit of metformin [55]. However, we assumed that self-reported medication use captured at the index visit was sufficient and were not able to account for changes in a patient's treatment plan. Though a limitation, this pragmatic approach evaluates the first opportunity an oncologist can intervene by adding metformin to the patient's medication regimen. The benefit may only be strengthened when used as a more targeted treatment strategy. Furthermore, there was little changing between treatments when looking from first to last visit and sensitivity analysis showed only further benefit when excluding those who changed treatment. As with all retrospective studies, there is also a possibility of residual unmeasured confounding. We must assume that adjusting for HbA1C and body mass index, and matching on diabetes duration in the sensitivity analysis, is sufficient to control for the role of diabetes progression.

In a cohort of women with T2DM with newly diagnosed ovarian, endometrial or breast cancer metformin use was associated with improved survival. Considering our findings in concert with extant literature, further study of the mechanism of metformin's benefit is warranted. Understanding the mechanism would allow providers to target its use, both by cancer type and stage, potentially expanding to non-diabetics. Finally, conducting a randomized controlled trial of metformin therapy in women with these cancer types is justified.

CRediT authorship contribution statement

Lara S. Lemon: Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Brian Orr:** Conceptualization, Methodology, Validation, Resources, Writing – original draft. **Francesmary Modugno:** Methodology, Writing – review & editing, Supervision. **Ronald J. Buckanovich:** Resources, Writing – review & editing. **Lan Coffman:** Writing – review & editing. **Robert P. Edwards:** Conceptualization, Resources, Writing – review & editing, Supervision. **Sarah Taylor:** Conceptualization, Methodology, Validation, Resources, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.01.022.

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