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Relationship of Type II Diabetes and Metformin Use to Ovarian Cancer Progression, Survival, and Chemosensitivity

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Abstract

OBJECTIVE—To estimate whether metformin use by ovarian cancer patients with type II diabetes was associated with improved survival.

METHODS—We reviewed the effect of diabetes and diabetes medications on ovarian cancer treatment and outcomes in a single-institution retrospective cohort. Inclusion criteria were International Federation of Gynecology and Obstetrics (FIGO) stage I–IV epithelial ovarian, fallopian or peritoneal cancer. Exclusion criteria were noninvasive pathology or non-epithelial malignancies. The primary exposures analyzed were history of type II diabetes and diabetes medications. The primary outcomes were progression-free and overall ovarian cancer survival.

RESULTS—Of the 341 ovarian cancer patients included in the study, 297 did not have diabetes, 28 were type II diabetic patients who did not take metformin, and 16 were type II diabetic patients who used metformin. The progression-free survival at five years was 51% for diabetic patients who used metformin compared to 23% for the nondiabetic patients and 8% for the diabetic patients who did not use metformin ($P=.03$). The overall survival at 5 years was 63%, 37%, and 23% for the diabetic patients who used metformin, the nondiabetic patients, and the diabetic patients who did not use metformin, respectively ($P=.03$). The patients with diabetes received the same treatment for ovarian cancer as the patients without diabetes. The association of metformin use and increased progression-free survival, but not overall survival, remained significant after controlling for standard clinico-pathologic parameters.

CONCLUSION—In this ovarian cancer cohort, the patients with type II diabetes who used metformin had longer progression-free survival, despite receiving similar treatment for ovarian cancer.

INTRODUCTION

It is estimated that 2 in 5 women born in the United States in the year 2000 will be diagnosed during their lifetime with type II diabetes.¹ Diabetes is associated with an increased incidence of most cancers and decreased cancer survival.² Understanding how diabetes influences cancer treatment and prognosis is of particular importance in cancers that have high mortality rates, such as ovarian cancer, which is the most lethal gynecological

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cancer.³ Although limited, the available data suggests that ovarian cancer patients with type II diabetes have decreased survival.^{4,5}

It is biologically plausible that the hyperinsulinemia and hyperglycemia induced by type II diabetes negatively promotes tumorigenesis. Insulin stimulates the growth of cancer cells by activating insulin like growth factor I (IGF-I) and decreasing insulin like growth factor binding protein.⁶ Hyperglycemia provides a nutrient rich microenvironment for rapidly dividing cancer cells, which have elevated metabolic demands and consume glucose at a higher rate than normal cells.⁷ Consistent with this concept, elevated plasma glucose levels at the time of ovarian cancer cytoreductive surgery are predictive of decreased survival.⁸

Interestingly, metformin, a diabetic treatment which reduces both insulin and glucose levels may have anti-cancer effects.⁹ Epidemiological studies indicate that patients who use metformin have decreased cancer incidence^{10,11} and increased cancer survival.^{11–14} Pre-clinical studies also corroborate the anti-tumorigenic effect of the drug in breast, prostate and colon cancer.^{15–17} In ovarian cancer, two pre-clinical studies have shown that metformin inhibits the proliferation of cancer cell lines in a dose and time dependent manner.^{18,19}

Based on pre-clinical evidence of a strong anti-cancer effect, we hypothesized that the use of metformin may be associated with improved ovarian cancer outcomes. To test this hypothesis, we evaluated whether ovarian cancer patients with type II diabetes who used metformin had increased progression-free and overall survival.

MATERIALS AND METHODS

This is a retrospective single institution cohort study utilizing an established dataset of women treated for ovarian cancer at the University of Chicago from 1992 to 2010. All women with International Federation of Gynecology and Obstetrics (FIGO) stage I–IV epithelial ovarian, fallopian, or peritoneal cancer were included in the study. We identify, and refer to, these three cancers as ovarian cancer because of their common origin in the Mullerian epithelium. Patients were excluded from the study if they had non-invasive pathology, non-epithelial malignancies, or non-ovarian primary cancer that had metastasized to the ovary. They were also excluded if they did not receive their primary cancer treatment at the University of Chicago, but were only treated for recurrences. The study was approved by the Institutional Review Board at the University of Chicago.

As previously reported, the ovarian cancer dataset contains information on clinico-pathologic parameters, treatment, and outcomes.^{20,21} All pathologic diagnoses had been confirmed by a sub-specialty trained gynecologic pathologist. Follow-up data was obtained from medical records at the University of Chicago, the Illinois Cancer Registry, the United States Social Security Index, and by communicating with physicians involved in the patient's care. For this study, an additional chart abstraction was performed to extract data pertaining to diagnoses of diabetes, diabetic medications, body mass index, glycosylated hemoglobin A1C, fasting glucose, and renal function. Fasting blood glucose and glycosylated hemoglobin A1C values were missing for a large portion of the cohort, prohibiting analysis of these variables. The person abstracting the data on diabetes was unaware of the subject's cancer survival status. All records of diabetic patients were re-reviewed by a second blinded investigator (IR). For secondary review of records for non-diabetic patients, the entries in the dataset were consecutively numbered and every tenth medical record was re-reviewed.

The primary exposures of interest for the study were a history of type II diabetes and the type of diabetic medications used. The primary outcome measures included progression-free

and overall survival. Recurrence was defined using previously published clinical criteria²² and included evidence of reappearance of the cancer by clinical exam (e.g. tumor, ascites), new tumor findings on CT scan or ultrasound, or an increase in CA-125 greater than or equal to two times the upper limit of normal (70 units/ml). Progression-free survival was calculated from the date of diagnosis until the date of ovarian cancer recurrence, or death. Patients without recurrence or death were censored at last follow-up. Overall survival was calculated from the date of diagnosis until death from ovarian cancer or the observation was censored as of the date of last follow-up. The 6 patients out of 341 who died from causes other than ovarian cancer were censored at the time of death.

All statistical analyses were performed using R version 2.11.0 (The R Project for Statistical Computing, <http://www.r-project.org/>). For comparison the cohort was stratified into three groups: patients without diabetes, patients with diabetes who did not use metformin, and patients with diabetes who used metformin. F-tests were used for comparing continuous variables and the Fisher's exact tests were used for categorical variables. Kaplan-Meier survival curves were plotted for the three groups and compared with log-rank tests. Of note, in the metformin group, the event rates and the duration of follow-up were not sufficient to estimate the upper limit of the confidence interval (CI) of progression-free and overall survival. These CIs are reported as not estimable. A Cox proportional hazards model was used to estimate hazard ratios for progression-free and overall survival while adjusting for confounders. For model selection, a univariable Cox regression was run with each of the potential confounders and those found to be significant in predicting recurrence or survival were included in the final model. The resulting Cox regression calculated the hazard ratios for diabetic patients who used metformin and diabetic patients who did not use metformin, with patients without diabetes as the reference group. The hazard ratio of diabetics who took metformin relative to diabetics not on metformin was also calculated.

RESULTS

The study included 341 women. The cancer types included epithelial ovarian (n=273), fallopian (n=34), and peritoneal (n=34) cancer. The median duration of follow-up was 63 months (range 1–245 months). For comparison the cohort was stratified into three groups as follows: non-diabetic patients (n=297), diabetic patients who did not use metformin (n=28) and diabetic patients who used metformin (n=16). Among the metformin users, 5 used only metformin, 4 used metformin and insulin, and 7 used metformin plus another oral anti-diabetic agent. The baseline characteristics of the three groups are reported in Table 1. The patients with diabetes were more likely to have higher BMIs and to be African-Americans than the patients without diabetes.

The patients with diabetes received the same treatment for ovarian cancer as the patients without diabetes. The rate of primary cytoreductive surgery with residual disease <1 cm after surgery, the type of chemotherapy agent used, and the mean number of chemotherapy cycles was comparable among the groups. Despite the long study interval (18 years), 95% of patients received both platinum and taxane based chemotherapy, the most common agents were carboplatin (72%) and taxol (94%). The response to chemotherapy was assessed using the clinical parameter of platinum sensitivity, defined as ≥ 6 months without recurrence of disease after the end of chemotherapy. The group using metformin had the highest percentage of patients sensitive to platinum chemotherapy, although the difference did not reach statistical significance ($p=0.18$) (Table 1).

Despite similar ovarian cancer treatment, the type II diabetic patients who used metformin had longer progression-free and overall survival. The progression-free survival at five years for diabetic patients who used metformin was 51% (median 72 months; 95% CI: 13.3-not

estimable) compared to 23% (median 16 months; 95% CI: 13.9–19.5 months) for patients without diabetes and 8% (median 10 months; 95% CI: 13.3–37.2 months) for the diabetic patients who did not use metformin (log rank test $P=.03$; Fig 1A). The overall survival at 5 years for diabetic patients who used metformin was 63% (median 138 months; 95% CI: 31.1–not estimable) compared to 37% (median 42 months; 95% CI: 35.1–49.6 months) for patients without diabetes and 23% (median 35 months; 95% CI: 24.6–54.3 months) for the diabetic patients who did not use metformin (log rank test $P=.03$; Fig 1B). The difference in survival could not be explained by stage, grade or histologic subtype, since the tumor characteristics of the three groups were similar (Table 2).

In a survival analysis adjusted for confounders, when comparing diabetics who took metformin to diabetics who did not take metformin, the metformin group had a significantly decreased hazard for disease recurrence (hazard ratio 0.38; 95% CI: 0.16, 0.90). The metformin group also had a decreased hazard of dying (hazard ratio 0.43; 95% CI: 0.16, 1.19), but this difference was not statistically significant. Variables significantly predictive of progression-free and/or overall survival and included in the models were: age, BMI, creatinine, FIGO stage, tumor grade, residual implants >1cm after surgery, and histological subtype. The variables that were not significant predictors of survival and excluded from the models were: ASA class, ethnicity, and history of cardiovascular disease. The hazards for both disease recurrence and dying were also lower in patients with diabetes who used metformin when compared to the group without diabetes, but this reduction was not statistically significant. In contrast, patients with diabetes who did not take metformin had an increased hazard of ovarian cancer recurrence (hazard ratio 1.42; 95% CI: 0.87–2.37) and an increased hazard of dying from ovarian cancer (hazard ratio 1.33; 95% CI: 0.77–2.28) when compared to patients without diabetes (Table 3).

DISCUSSION

In a single institution retrospective cohort we found that ovarian cancer patients with type II diabetes who used metformin had increased progression-free survival, but not overall survival, when compared to type II diabetics who did not use metformin. These findings are consistent with those of Landman et al, who analyzed a prospective diabetic cohort and found that diabetic patients who used metformin had an adjusted overall cancer mortality hazards ratio of 0.43 (95% CI: 0.23, 0.80) when compared to diabetics not using metformin.¹³ In fact, we report a similar magnitude of risk reduction in ovarian cancer patients.

The suggestion that metformin use is associated with improved ovarian cancer outcomes may not be intuitive to most gynecologists. However, our findings are congruent with the translational research which has demonstrated a distinct anti-cancer effect of the drug in several cancers (e.g. breast, prostate, colon), including ovarian cancer.^{15–19} Three possible mechanisms have been proposed. First, metformin's anti-cancer effect may be a result of the activation of a critical energy sensor in cancer cells, AMP-activated protein kinase (AMPK). Upon activation, AMPK contributes to energy conservation by decreasing cancer cell proliferation.²³ Second, insulin and glucose promote tumorigenesis^{6,8} and through inhibiting hepatic gluconeogenesis and increasing insulin sensitivity metformin decreases both insulin and glucose levels.²⁴ Finally, clinical and laboratory studies indicate that metformin may improve response to chemotherapy.²⁵ In a study of neo-adjuvant chemotherapy for breast cancer, Jiralerspong et al, reported that diabetic patients who took metformin had a pathological complete response rate of 24% compared to an 8% pathological complete response rate among diabetic patients who did not use metformin.²⁶ In our ovarian cancer cohort, we also noted that the type II diabetics who used metformin had the best response to chemotherapy.

The findings reported here are provocative, but given the retrospective study design, they can only be considered hypothesis generating and should not be generalized to clinical practice at this time. That being said, the study has some notable strengths. We include an analysis of the association of metformin use and ovarian cancer survival where previous studies have only examined the association of diabetes and ovarian cancer survival without consideration of diabetic medications.⁵ Also, by using a large ovarian cancer dataset that contained detailed chemotherapy and platinum sensitivity data, we were able to estimate the relationship between metformin use and response to chemotherapy. Finally, the homogeneity of ovarian cancer treatment among diabetics and non-diabetics in the cohort allowed us to make relatively strong inferences about the effects of metformin.

An important limitation of the study was the small sample size. The sample size limited our ability to detect a difference in survival between diabetic patients taking metformin and patients without diabetes. Based on retrospective power calculations, assuming a true hazard ratio of the magnitude reported here and that 5% of ovarian cancer patients have type II diabetes and use metformin, for progression-free survival a total sample size of 870 patients would be required to have 80% statistical power. For overall survival, 1570 patients would be required. The sample size also prohibited an analysis of the effects of diabetic medications other than metformin. A final limitation was that due to lack of available data we could not control for diabetes severity, which may represent an independent risk factors for death.

In summary, the findings in this ovarian cancer cohort of improved progression-free survival among type II diabetic patients who used metformin add to a growing body of evidence from epidemiologic and pre-clinical studies indicating that metformin may have anti-tumorigenic effects. The idea that specific diabetic treatments affect cancer survival is clinically relevant given the increasing prevalence of diabetes. According to the World Health Organization, 171 million people worldwide have type II diabetes and this number is expected to double by 2030.²⁷ If future studies continue to support the protective effect of metformin in cancer this will be an important consideration when managing diabetic patients with cancer.

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Fig. 1.

Kaplan-Meier estimates of survival outcomes. The three groups are: ovarian cancer patients with type II diabetes taking metformin (n=16); ovarian cancer patients without type II diabetes (n=297); and ovarian cancer patients with type II diabetes not taking metformin (n=28). *P* values are from the log-rank test. **(A)** Progression-free survival; **(B)** overall survival.

Table 1**Baseline Characteristics and Ovarian Cancer Treatment of Study Cohort**

	Nondiabetic Patients	Diabetic Patients Not Taking Metformin	Diabetic Patients Taking Metformin	P
Cases	297 (87)	28 (8)	16 (5)	
Age at diagnosis (year)	59±12	67±9	60±10	.07
BMI (kg/m ²)	27±7	31±6	34±6	<.05
Not recorded	14 (5)	0	0	
Current smoker	40 (14)	4 (15)	2 (13)	.93
Not recorded	20 (7)	2 (7)	2 (13)	
Race				.03
White	216 (73)	15 (53)	8 (50)	
African American	51 (17)	12 (43)	7 (44)	
Other	15 (5)	0	1 (6)	
Not recorded	15 (5)	1 (4)	0	
ASA class				.36
I–II	145 (49)	10 (36)	5 (31)	
III–IV	120 (40)	17 (60)	10 (63)	
Not recorded	32 (11)	1 (4)	1 (6)	
Type of Surgery				.11
Primary	253 (85)	27 (96)	12 (75)	
Interval	44 (15)	1 (4)	4 (25)	
Not recorded	0	0	0	
Residual disease after surgery				.68
Less than 1 cm	182 (61)	17 (61)	11 (69)	
More than 1 cm	101 (34)	11 (39)	4 (25)	
Not recorded	14 (5)	0	1 (6)	
Platinum*				.88
Carboplatin	196 (71)	18 (69)	12 (80)	
Cisplatin	76 (28)	8 (31)	3 (20)	
None	3 (1)	0	0	
Not recorded	0	0	0	
Taxane*				.74
Paclitaxel injection	258 (94)	24 (92)	14 (93)	
Docetaxel injection	5 (2)	1 (4)	0	
None [†]	12 (4)	1 (4)	1 (7)	
Not recorded	0	0	0	
Mean no. of cycles	6.1	6.3	6.8	.46
Not recorded	5 (2)	1 (4)	0	
Platinum sensitivity [‡]				.18
Sensitive	165 (61)	11 (44)	9 (69)	
Resistant	102 (38)	14 (56)	4 (31)	

	Nondiabetic Patients	Diabetic Patients Not Taking Metformin	Diabetic Patients Taking Metformin	<i>P</i>
Not recorded	0	0	0	

BMI, body mass index; ASA, American Society of Anesthesiologists.

Data are n (%) or mean±standard deviation. ASA class was determined at time of surgery.

* Patients were excluded from the analysis if they declined chemotherapy or chemotherapy was not indicated (eg, International Federation of Gynecology and Obstetrics [FIGO] 1A).

[†] Among the patients that did not receive a taxane, all received cytoxan except 5 patients in the non-diabetic group

[‡] Platinum Sensitive = no recurrence of disease for 6 months or more after the end of chemotherapy. Patients that did not receive platinum agent or did not complete 6 cycles of chemotherapy were excluded from platinum sensitivity analysis.

Table 2

Tumor Characteristics

	Nondiabetic Patients	Diabetic Patients Not Taking Metformin	Diabetic Patients Taking Metformin	P
Cases	297 (87)	28 (8)	16 (5)	
FIGO stage				.34
I	36 (12)	1 (4)	4 (25)	
II	17 (6)	3 (11)	1 (6)	
III	177 (60)	16 (57)	9 (57)	
IV	66 (22)	8 (28)	2 (12)	
Not recorded	1 (0)	0	0	
Grade of tumor				.37
I	17 (6)	1 (4)	1 (6)	
II	56 (19)	4 (14)	6 (37)	
III	217 (73)	22 (78)	9 (57)	
Not recorded	7 (2)	1 (4)	0	
Pathology				.37
Serous-papillary	223 (75)	20 (72)	9 (57)	
Endometrioid	31 (10)	2 (7)	4 (25)	
Clear cell	27 (9)	4 (14)	2 (12)	
Mucinous	16 (6)	2 (7)	1 (6)	
Not recorded	0	0	0	

FIGO. International Federation of Gynecology and Obstetrics.

Data are n (%).

Table 3

Cox Proportional Model Hazard Ratios for Progression-Free and Overall Survival

	Progression-Free Survival		Overall Survival	
	Hazard Ratio for Recurrence (95% CI)	P	Hazard Ratio for Survival (95% CI)	P
Cohort				
Nondiabetic patients	1		1	
Diabetic patients not taking metformin	1.42 (0.87–2.33)	.17	1.33 (0.77–2.28)	.30
Diabetic patients taking metformin	0.53 (0.27–1.15)	.11	0.58 (0.23–1.46)	.25
Using alternative parameterization *				
Diabetics no metformin	1		1	
Diabetics metformin	0.38 (0.16–0.90)	.03	0.43 (0.16–1.19)	.11
FIGO Stage				
I/II	1		1	
III/IV	3.73 (2.14–6.5)	<.05	2.86 (1.56–5.26)	<.05
Grade				
I	1		1	
II/III	2.20 (1.01–4.80)	.05	1.98 (0.79–4.99)	.14
Histological subtype				
Serous-papillary	1		1	
Other	0.77 (0.53–1.13)	.19	0.94 (0.62–1.43)	.79
Largest residual implant				
Less than 1cm	1		1	
More than 1cm	2.07 (1.55–2.77)	<.05	1.52 (1.10–2.10)	.01
Age [†]	1.0 (0.99–1.01)	.72	1.01 (0.99–1.03)	.16
BMI [†]	0.99 (0.96–1.01)	.29	0.98 (0.95–1.00)	.07
Creatinine ^{†‡}	NA		1.24 (0.76–2.01)	.39

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index.

* Alternative parameterization with diabetics not using metformin as a reference group is presented to show the direct comparison between diabetics not using metformin and diabetics using metformin.

[†] Modeled as continuous variables.[‡] Creatinine level at the time of ovarian cancer diagnosis. Creatinine predicted overall survival but not progression-free survival.