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Metformin and breast and gynecological cancer risk among women with diabetes

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ABSTRACT

Objective: We investigated if metformin lowers breast, endometrial, and ovarian cancer risk in women with type 2 diabetes mellitus compared with women who used other antidiabetic medications.

Research design and methods: We followed a cohort of 66 778 female patients with diabetes for a maximum of 12 years (median 6 years). We examined breast, endometrial, and ovarian cancer risk, and the composite cancer risk. We examined drug categories using pharmacy records: metformin only; metformin combination regimens; non-metformin regimens; and non-users. We used χ^2 analyses to examine categorical variables. We conducted multivariable Cox regression models with time-dependent drug use status.

Results: Women who used metformin combination regimens versus metformin only had a 15% lower breast cancer risk (adjusted HR=0.85, 95% CI 0.69 to 1.04). After stratifying by glycated hemoglobin (HbA1c), the association attenuated in those who had poorly controlled HbA1c (adjusted HR=1.06, 95% CI 0.73 to 1.55). Given the small numbers of ovarian and endometrial cancer outcomes, we examined these as a composite. The risk of all cancers combined was similar in those who used metformin combination regimens versus metformin only (adjusted HR=0.92, 95% CI 0.78 to 1.10). We found no significant differences for breast cancer or all cancers combined when we compared risks in non-metformin users versus metformin only users.

Conclusions: Women who used metformin and other antidiabetic drugs had a lower breast cancer risk compared with women who used metformin only, but the results were not significant. We also found no difference in overall cancer risks when we compared women who used other antidiabetic drugs (no metformin) versus metformin users.

Key messages

- We conducted a study that used comprehensive pharmacy longitudinal records from an integrated healthcare delivery system of nearly 67 000 female patients with type 2 diabetes who were followed for a maximum of 12 years, and exposed to various antidiabetic medications.
- Metformin alone was not associated with lower breast, endometrial, or ovarian cancer risks.
- Overall, our results do not support the beneficial role of metformin monotherapy in lowering the risk of developing breast or gynecological cancer.

INTRODUCTION

Epidemiological studies suggest that hyperinsulinemia, insulin resistance, and diabetes are associated with increased cancer risks.[1–3] Metformin improves glycemic control and is used to treat type 2 diabetes, and based on in vitro studies, the drug may have anticancer effects,[4–7] particularly for breast cancer.[8] While several studies described a lower cancer risk among patients with type 2 diabetes using metformin, other studies have disputed metformin's protective effect.[9–16] One case–control study of 11 000 women with type 2 diabetes in Scotland showed that overall cancer incidence was lower in patients taking metformin, and also suggested that there was a dose–response relationship.[2] This study was later expanded into a cohort study to confirm this overall reduction and found a lower incidence of all cancers from 11% to 8% as well as lower overall and cancer-related mortality in metformin users. Another prospective study of 1353 patients in the Netherlands similarly demonstrated lower cancer mortality among those with type 2 diabetes using metformin compared with non-users.[17] These observations have also been generally found when analyzing the impact of metformin use on specific cancers. A case–control analysis of 22 621 women with type 2 diabetes found an adjusted OR of 0.44 for developing breast cancer in those on long-term metformin treatment when compared to women with diabetes not using metformin.[18] In contrast, other studies have found no association with metformin,[11–16] while one found an increased risk of various cancers among metformin users.[19] However, prior studies were limited by self-reported

medication use data, short follow-up duration, inclusion of patients without diabetes, or limited covariate data.[1–4 8] With little data available on metformin use in gynecological cancers, our goal was to examine whether metformin use had an impact on breast, endometrial, or ovarian cancer incidence in a large cohort of adult women with type 2 diabetes with pharmacy and healthcare coverage.

RESEARCH DESIGN AND METHODS

Design, setting, and study population

We assembled a large cohort of female patients with type 2 diabetes using the membership of Kaiser Permanente Southern California (KPSC), a large not-for-profit integrated healthcare delivery system that serves over 3.3 million members in the region. All data elements were extracted from the KPSC comprehensive electronic health records. Potential subjects were patients with newly diagnosed diabetes from 1998 to 2004 as identified from the health plan's diabetes registry (N=232 637 with peak glycated hemoglobin (HbA1c)>7.5%; 58 mmol/mol). This group included new users of antidiabetic medications (those exposed to diabetic medications prior to study entry date were ineligible) and patients not treated with any antidiabetic medications. We also excluded males, those who were <18 years of age, and who were enrolled for less than 1 year in the health plan during the study, and who had a history of cancer prior to the diabetes diagnosis date (N=165 805). The final cohort consisted of 66 778 adult women with diabetes.

Outcomes and follow-up

The cohort was followed (using electronic health records) from the time of diabetes diagnosis (study entry date) to one of four end points, whichever occurred first: (1) diagnosis of breast, endometrial, or ovarian cancer, (2) disenrollment from the health plan, (3) study's end (December 31, 2009) or (4) patient death. Thus, the maximum follow-up was 12 years post-cohort entry. We identified incident cancer cases by linking the cohort with the KPSC National Cancer Institute's Surveillance Epidemiology and End Results (SEER)-affiliated cancer registry. Deaths (censored events) were ascertained by linking with an electronic database based on California's master file of death certificates using the patients' social security number.

Pharmacy records: antidiabetic medications

Antidiabetic medications (type, prescription dates, days supplied) were captured from the KPSC pharmacy records. Initially, women were classified into mutually exclusive groups based on their overall pattern of drug use over the study period (table 1): (1) single-agent metformin users ('metformin only'); (2) combination users (used metformin concurrently or sequentially with sulfonylureas, insulin, and 'other' hypoglycemic agents, which were less frequently prescribed, such as α-glucosidase inhibitors, incretin mimetics, amylinomimetics, meglitinides, dipeptidyl peptidase-4); and (3) non-metformin users (never used antidiabetic drugs; eg, controlled with lifestyle modifications or diet). We further divided the combination users in the analysis.

Table 1 Distribution of antidiabetic medication use in a cohort of 66 778 women with type 2 diabetes

Antidiabetic medication	N	Per cent
Metformin		
Metformin only	4887	7.32
Metformin combinations		
Metformin+sulfonylureas only	11 193	16.76
Metformin+insulin only	655	0.98
Metformin+other non-metformin drugs*	10 189	15.26
Non-metformin		
Sulfonylureas only	8253	12.36
Insulin only	4705	7.05
Other non-metformin drugs*	1907	2.86
Non-antidiabetic medication users	24 989	37.42
Total	66 778	

*Exposed to one or more of these classes: α-glucosidase inhibitors; amylinomimetics; biguanides; dipeptidyl peptidase-4 inhibitors; incretin mimetics; insulin; meglitinides; sulfonylureas; thiazolidinediones (glitazones).

We also examined the drug exposure as a time-dependent variable in tables 2 and 3. Given that patients often switched medications, we calculated the cumulative person-years of drug exposure for each patient (denominator of the rates). This was calculated as the sum of the cumulative number of days from the start date of the first antidiabetic prescription to the next prescription, or to the end of a patient's follow-up. The time between diabetes diagnosis and start date of the first antidiabetic drug prescription contributed to the 'non-antidiabetic users' category, thereby reducing immortal time bias in the time-dependent analyses (table 2). This enabled the patient's person-time to contribute to both the antidiabetic user or non-user categories. The cancer outcomes (numerator of the rates) were assigned to the most recent drug exposure category.

Covariates

Baseline covariates for which each patient was evaluated included: age at baseline (entry into cohort), race/ethnicity, geocoded income categories, prior use of estrogen replacement therapy (ERT), ever statin use, Charlson comorbidity index (1 year prior to entry into cohort), and number of outpatient visits during study period. The peak HbA1c level ascertained during follow-up was used as a surrogate marker for diabetes severity, and stratified into three groups (<7% (53 mmol/mol), 7–9.4% (53–80 mmol/mol), and ≥9.5% (80 mmol/mol)). Since multiple HbA1c levels were found per patient, we used the peak value to determine the level of control.

Table 2 Characteristics of women with type 2 diabetes at baseline by medication use

	Metformin users		Combination users		Non-metformin users		Non-antidiabetic users		Total	
	N	%	N	%	N	%	N	%	N	%
Total women	**4887**	**7.32**	**22 037**	**33.00**	**14 865**	**22.26**	**24 989**	**37.42**	**66 778**	**100**
Age at index DM date										
<30	120	2.46	689	3.13	1592	10.71	1576	6.31	3977	5.96
30–39	349	7.14	2375	10.78	3172	21.34	3006	12.03	8902	13.33
40–49	934	19.11	5652	25.65	1995	13.42	3336	13.35	11 917	17.85
50–59	1589	32.51	7168	32.53	2485	16.72	4329	17.32	15 571	23.32
60–69	1287	26.34	4228	19.19	2557	17.20	4729	18.92	12 801	19.17
70–79	535	10.95	1671	7.58	2086	14.03	4792	19.18	9084	13.60
80+	73	1.49	254	1.15	978	6.58	3221	12.89	4526	6.78
p Value*	<0.0001									
Mean±SD	56.2±12.1		53.1±12.1		52.7±18.0		59.1±18.0		55.5±16.1	
Range	18–92		18–99		18–101		18–103		18–103	
Race/ethnicity										
Non-Hispanic caucasian	1592	32.58	7054	32.01	4988	33.56	10 746	43.00	24 380	36.51
Hispanic	1321	27.03	6975	31.65	4662	31.36	6145	24.59	19 103	28.61
African American	568	11.62	3267	14.83	2022	13.60	3192	12.77	9049	13.55
Asian/PIs	500	10.23	1875	8.51	1390	9.35	1621	6.49	5386	8.07
Others/unknown	906	18.54	2866	13.01	1803	12.13	3285	13.15	8860	13.27
p Value*	<0.0001									
Geocoded income										
Lower 25% (≤US$43 022)	1100	22.51	5508	24.99	3935	26.47	5920	23.69	16 463	24.65
>25–50% (>US$43 023–US$58 415)	1224	25.05	5420	24.59	3677	24.74	6141	24.57	16 462	24.65
>50–75% (>US$58 416–US$77 536)	1181	24.17	5631	25.55	3597	24.20	6054	24.23	16 463	24.65
Top 25% (≥US$77 537)	1320	27.01	5242	23.79	3429	23.07	6468	25.88	16 459	24.65
Unknown/missing	62	1.27	236	1.07	227	1.53	406	1.62	931	1.39
p Value*	<0.0001									
Estrogen replacement treatment during study period										
Yes	1359	27.81	7301	33.13	3050	20.52	6019	24.09	17 729	26.55
No	3528	72.19	14 736	66.87	11 815	79.48	18 970	75.91	49 049	73.45
p Value*	<0.0001									
Parity (live births)										
0	58	1.19	409	1.86	941	6.33	726	2.91	2134	3.20
1–2	128	2.62	985	4.47	2443	16.43	2032	8.13	5588	8.37
3–4	31	0.63	329	1.49	611	4.11	535	2.14	1506	2.26
5+	5	0.10	47	0.21	92	0.62	66	0.26	210	0.31
Missing	4665	95.46	20 267	91.97	10 778	72.51	21 630	86.56	57 340	85.87
p Value*	<0.0001									

Continued

Table 2 Continued

	Metformin users		Combination users		Non-metformin users		Non-antidiabetic users		Total	
Total women	**N 4887**	**% 7.32**	**N 22 037**	**% 33.00**	**N 14 865**	**% 22.26**	**N 24 989**	**% 37.42**	**N 66 778**	**% 100**
Number of outpatient visits during study period										
None	11	0.23	48	0.22	213	1.43	526	2.10	798	1.20
Quartile 1 (1–24)	1069	21.87	2081	9.44	4709	31.68	8167	32.68	16 026	24.00
Quartile 2 (25–55)	1451	29.69	5504	24.98	3906	26.28	5716	22.87	16 577	24.82
Quartile 3 (56–102)	1324	27.09	7172	32.55	3142	21.14	5177	20.72	16 815	25.18
Quartile 4 (≥103)	1032	21.12	7232	32.82	2895	19.48	5403	21.62	16 562	24.80
p Value*	<0.0001									
Charlson index 1 year prior to index DM date										
0	4118	84.26	18 795	85.29	11 394	76.65	17 927	71.74	52 234	78.22
1–2	708	14.49	2924	13.27	2596	17.46	5373	21.50	11 601	17.37
3+	61	1.25	318	1.44	875	5.89	1689	6.76	2943	4.41
p Value*	<0.0001									

*Based on χ^2 test.
DM, diabetes mellitus.

Statistical analysis

We compared the covariate distributions by antidiabetic drug use status using contingency tables and χ^2 analysis. Rates of cancer incidence (per 1000 woman-years) were also estimated (table 2). Overall and adjusted HRs were estimated using multivariate Cox regression analysis (table 2) for the subset of patients who used antidiabetic medications to minimize confounding by indication, using the metformin only group as the reference group (ie, to examine the associations in the antidiabetic medication 'user' groups). In addition, separate Cox models were conducted for each cancer type, and also for all the three cancers combined. We further conducted sensitivity analyses by examining the HRs by level of HbA1c control. All analyses were performed using SAS V.9.1.

RESULTS

Overall, we identified 66 778 eligible women with type 2 diabetes for this study followed up to 12 years post-study entry. Of these 66 778 women, 41 789 who used antidiabetic medications were followed for a median of 6.5 years (range 0–12 years; interquartile 3.9–8.8 years). The non-user group (N=24 989) was followed for a median of 5.2 years (range 0–12 years; IQR 1.7–7.4 years). Table 1 shows the distribution of the cohort based on the patients' final combination of exposure to antidiabetic drugs in mutually exclusive categories. Among patients who used antidiabetic medications, 4887 (7.3%) were single-agent metformin users, 11 193 (16.8%) used metformin with sulfonylureas, 655 (0.9%) used metformin with insulin, 10 189 (15.3%) used metformin with other hypoglycemic medications, 8253 (12.4%) used sulfonylureas only, 4705 (7.1%) used insulin only, 1907 (2.9%) used other hypoglycemic medications only, and 24 989 (37.4%) did not use any antidiabetic medication (table 1). Since our primary objective was to examine the independent and combined effects of metformin use, we further categorized the aforementioned groups as follows: metformin only (n=4887); combination users (used metformin with other antidiabetic medications concurrently or sequentially, n=22 037); non-metformin users (n=14 865); and non-antidiabetic medication users ('non-users', n=24 989; table 1).

Table 2 displays the demographic covariates at baseline (diabetes cohort study entry date) by the patient' final combination of exposure to antidiabetic drugs in mutually exclusive categories. The mean age of the cohort was 56 years (range of 18–103 years). Women who used antidiabetic medications were slightly younger than non-users (p<0.0001). The cohort consisted of mainly non-Hispanic caucasian (36.5%) and Hispanic women (28.6%). A greater fraction of non-Hispanic caucasians tended to be non-users of antidiabetic medications (p<0.0001). Women who used metformin and other medications ('combination users') were more likely to have used ERT (p<0.0001).

Table 3 Incidence rate and rate ratio for cancer among patients who used antidiabetic medications and those who did not use antidiabetic drugs

Cancer site	Number of cases	Woman-years	Crude rate (per 1000)	95% CI
Breast cancer				
Metformin only	143	28 571	5.01	4.22 to 5.90
Metformin+sulfonylureas	215	57 577	3.73	3.25 to 4.27
Metformin+insulin	6	2613	2.30	0.84 to 5.00
Metformin and other diabetic meds	339	67 723	5.01	4.49 to 5.57
Sulfonylureas only	55	24 316	2.26	1.70 to 2.94
Insulin only	125	32 658	3.83	3.19 to 4.56
Other non-metformin drugs only	46	8560	5.37	3.93 to 7.17
Non-antidiabetic users	643	162 820	3.95	3.65 to 4.27
Endometrial cancer				
Metformin only	36	28 571	1.26	0.88 to 1.74
Metformin+sulfonylureas	60	57 577	1.04	0.80 to 1.34
Metformin+insulin	1	2613	0.38	0.01 to 2.13
Metformin and other diabetic meds	71	67 723	1.05	0.82 to 1.32
Sulfonylureas only	6	24 316	0.25	0.09 to 0.54
Insulin only	33	32 658	1.01	0.70 to 1.42
Other non-metformin drugs only	11	8560	1.29	0.64 to 2.30
Non-antidiabetic users	130	162 820	0.80	0.67 to 0.95
Ovarian cancer				
Metformin only	5	28 571	0.18	0.06 to 0.41
Metformin+sulfonylureas	20	57 577	0.35	0.21 to 0.54
Metformin+insulin	0	2613		
Metformin and other diabetic meds	29	67 723	0.43	0.29 to 0.61
Sulfonylureas only	11	24 316	0.45	0.23 to 0.81
Insulin only	12	32 658	0.37	0.19 to 0.64
Other non-metformin drugs only	7	8560	0.82	0.33 to 1.68
Non-antidiabetic users	79	162 820	0.49	0.38 to 0.60
All cancers combined				
Metformin only	184	28 571	6.44	5.54 to 7.44
Metformin+sulfonylureas	295	57 577	5.12	4.56 to 5.74
Metformin+insulin	7	2613	2.68	1.08 to 5.52
Metformin and other diabetic meds	439	67 723	6.48	5.89 to 7.12
Sulfonylureas only	72	24 316	2.96	2.32 to 3.73
Insulin only	170	32 658	5.21	4.45 to 6.05
Other non-metformin drugs only	64	8560	7.48	5.76 to 9.55
Non-antidiabetic users	852	162 820	5.23	4.89 to 5.60

In terms of parity, women who were non-metformin users were more likely to have had one to two pregnancies. Non-users were more likely to have a higher comorbidity index ($p<0.0001$). The distribution of geocoded income levels did not vary substantially with medication categories. In examining the Charlson comorbidity index, women who used metformin (with or without other antidiabetic medications) were less likely to have a comorbidity than non-metformin users or non-users. As expected, outpatient utilization was somewhat lower in women who were not treated with diabetic medications.

Of the 66 778 cohort members, 1572 developed breast cancer; 348 developed endometrial cancer; and 163 developed ovarian cancer; 7826 died; 22 943 disenrolled from the health plan; and 33 926 reached the study's end. Median follow-up was 6 years (range of 0–12 years) for the overall cohort. The median age at cancer diagnosis was 55.3 years (range of 18–103 years).

Incidence rates for breast, endometrial, ovarian cancer, and all cancers combined are shown by mutually exclusive antidiabetic medication use categories in table 3. Cancer incidence rates varied by drug use categories, with non-metformin combination users having the greatest breast cancer rate (5.37/1000 person-years) followed by metformin only users (5.01/1000 person-years) as compared with non-users (3.95/1000 person-years). Breast cancer incidence rates were lowest among those who used sulfonylureas only (2.26/1000 person-years). Similarly, the endometrial cancer incidence rate was the highest among non-metformin combination users (1.29/1000 person-years) and metformin only users (1.26/1000 person years), and lowest among sulfonylurea users (0.25/1000 person-years). Given that there were only five cases of ovarian cancer in the metformin only group, inferences are not feasible. In all cancers combined, the pattern of cancer incidence rates was again similar to the pattern found for breast and endometrial cancer in the

metformin only group (6.44/1000 person-years) and non-user group (5.23/1000 person-years).

We further examined the association of breast cancer risk and all cancer risk (given the larger number of events) in the antidiabetic drug user groups using time-dependent medication variables in separate Cox models (table 4). The drugs were categorized as combinations with metformin, combinations without metformin, and metformin only (reference group). The HRs were adjusted for age of index diabetes diagnosis, race/ethnicity, estrogen status, statin use, Charlson comorbidity index, and outpatient utilization. Among the user groups, combination users (with metformin) had a lower overall risk of breast cancer compared with metformin only users (adjusted HR=0.85, 95% CI 0.69 to 1.04), but the results were not significant. In the sensitivity analysis, we examined the risk stratified by the level of HbA1c control. Breast cancer risk was somewhat lower in those with better controlled HbA1c groups (<7% and 7–9.4% HbA1c), but not protective among those with higher HbA1c levels (≥9.5%; ≥80 mmol/mol; adjusted HR=1.06, 95% CI 0.73 to 1.55). However, CIs overlapped and crossed the null across all HbA1c categories. Similar patterns emerged for non-metformin combinations. Again, all CIs crossed the null, and are consistent with no associations. Regarding all cancers combined, we found no difference between combination users (either with or without metformin) versus metformin only users, even after stratifying by HbA1c.

DISCUSSION

Using comprehensive pharmacy longitudinal records of an integrated healthcare delivery system, in our cohort of nearly 67 000 female patients with type 2 diabetes who were followed for a maximum of 12 years and who were exposed to metformin and other antidiabetic drugs, our results do not support that metformin monotherapy was associated with lower breast cancer risk. Metformin only use was also not associated with a lower risk of endometrial or ovarian cancer, but this finding could have been due to the small numbers of women who developed these outcomes in the metformin only category. In general, compared with non-users of antidiabetic medications, those exposed to single therapies did not have lower cancer risks.

Our findings were generally consistent with studies that examined the antidiabetic drug categories with time-dependent analyses (ie, methods that we employed for the present study.[10–16] In addition, we were able to account for drug switching and statin use. The existing literature on the protective role of metformin is unclear. For example, a few prior studies that accounted for time-related bias produced conflicting results for metformin, with some finding lower risks from metformin,[17 20–27] and one finding an increased risk.[19] Reasons for the conflicting findings include the short follow-up time; different study populations (some might have included healthier populations than others); or inability to account for changes in drug therapy over time.

Although in vitro and in vivo studies support metformin's role in reducing cancer risks via AMP-activated protein kinase pathways to lower blood glucose and decreasing hepatic gluconeogenesis;[6] inhibition of the mTOR pathway (involved in cell profileration);[28 29] stimulation of p53 tumor suppression[29]; or affecting ki-67, which plays a role in tumor profileration, our

Table 4 HRs for cancer among women who used antidiabetic medications (using time-dependent variables), stratified by HbA1c

	Overall		HbA1c <7.0% (<53 mmol/mol)		HbA1c 7.0–9.4% (53–80 mmol/mol)		HbA1c ≥9.5% (≥80 mmol/mol)	
	Adjusted HR*	95% CI	Adjusted HR*	95% CI	Adjusted HR*	95% CI	Adjusted HR*	95% CI
Breast cancer								
Combination† vs metformin only	0.85	0.69 to 1.04	0.96	0.51 to 1.82	0.83	0.62 to 1.11	1.06	0.73 to 1.55
Non-metformin drugs vs metformin only	0.89	0.74 to 1.09	0.87	0.55 to 1.37	0.98	0.75 to 1.30	0.84	0.57 to 1.25
All cancers combined								
Combination† vs metformin only	0.92	0.77 to 1.10	1.07	0.61 to 1.88	0.85	0.66 to 1.10	1.15	0.83 to 1.60
Non-metformin drugs vs metformin only	0.93	0.79 to 1.11	0.98	0.65 to 1.48	1.00	0.78 to 1.28	0.85	0.60 to 1.20

*Adjusted for: age of index diabetes diagnosis, race/ethnicity, ERT status, statin use, Charlson comorbidity index, and outpatient utilization.
†Combination includes metformin use.
ERT, estrogen replacement therapy; HbA1c, glycated hemoglobin.

study did not support these hypotheses.[30] Our results suggest that taking a combination of antidiabetic drugs generally lowered cancer risk overall, although the results did not reach statistical significance. Of note, none of the monotherapies (metformin only, sulfonylureas only, insulin only) were associated with a significant reduction of gynecological cancer incidence rates compared with non-users. Although the biological mechanism of how antidiabetic medications affect cancer risk is not clear, some evidence suggests that insulin signaling and lipid deregulation in patients with type 2 diabetes may enhance cancer development.[31] Hence, a combination of antidiabetic medications that counter these mechanisms may contribute to the overall cancer risk reduction. Thus, it is possible that the protection is related more to improved glycemic control overall among these patients via multiple mechanisms. It is also possible that these patients who used multiple antidiabetic medications included patients with type 2 diabetes with a lower body size; cancer is postulated to be a secondary consequence of obesity.[31–33]

Our results are consistent with a few prior studies of metformin. For example, some authors have disputed the concept of metformin monotherapy as an antineoplastic agent altogether.[9–16] A similar study using pharmacy records of a large managed care organization also did not find an association between metformin and breast cancer, although it did not examine endometrial or ovarian cancer risk.[34] It has been suggested that the reduced cancer rates seen among metformin users may be attributed to patients with type 2 diabetes using insulin or insulin secretagogues. In our study, we found that women with type 2 diabetes using metformin with insulin had a lower incidence for breast cancer, but the rates were not different from those for women who used metformin with other (non-insulin) antidiabetic medications.

Table 3 shows that metformin only users had generally similar high cancer rates as did the non-metformin combination users, while sulfonylurea users had the lowest rates. This may be related to the American Diabetes Association and the European Association for the Study of Diabetes; the recommended approach to management of hyperglycemia in patients with type 2 diabetes begins with lifestyle modification and low-dose metformin.[35 36] From there, clinicians are encouraged to check blood glucose and HbA1c levels and titrate the metformin dosing, so as to minimize gastrointestinal side effects from the medication. If patients are not achieving target HbA1c levels, recommendations then include adding other medications from different drug classes, typically starting with sulfonylureas and then switching to other hypoglycemics based on tolerability and effectiveness. Thus, patients on a regimen which included metformin with sulfonylureas or other antidiabetic medications likely represent a subpopulation exposed to metformin for a longer duration and at the maximal metformin dosing. In contrast, single-agent metformin users may represent a population whose glucose management was maintained at lower doses of metformin, or were earlier in their treatment course. We addressed this potential confounding by adjusting for comorbidity status (using the Charlson score), the number of outpatient visits, and the HbA1c level as surrogates for diabetes severity. In addition, to minimize confounding by indication, we also conducted sensitivity analyses restricted to the women who were ever prescribed antidiabetic medications (table 3). Sulfonylureas only users generally had the lowest cancer rates (table 2). Our results are also consistent with the results of a recent meta-analysis that reviewed the relationship between metformin and sulfonylureas and their relationship to cancer risks.[37] Our cohort demonstrated that while metformin users had some of the highest cancer rates, use of metformin with sulfonylureas mitigated that risk. Hence, since sulfonylureas are insulin secretagogues, the mechanism by which metformin lowers cancer risk is not simply by reducing circulating insulin.

As with any study, certain limitations must be considered. We were not able to adjust for some important covariate data, including body mass index. Since body mass index was not available in the KPSC electronic health records until 2006, residual confounding might be possible. However, another large study of patients with diabetes in a managed care system determined that the inclusion of body mass index did not confound their results.[34] Although we used time-dependent medication variables in the Cox model, this method did not fully statistically address the complicated issue of drug switching. Nonetheless, we were able to apportion person-time into several different antidiabetic drug combination categories, as well as count person-years of exposure starting from drug initiation, thereby reducing immortal time bias. A substantial percentage (34%) disenrolled from the health plan. Disenrolled patients were more likely to be younger at baseline, of minority backgrounds, and have less comorbidity (although their distributions of antidiabetic medications at baseline were similar to those patients whose end points were ascertained). Therefore, the generalizability of this study may be limited. Our study was also limited by an inability to distinguish between premenopausal and postmenopausal estrogen use, which has implications for endometrial and breast cancer risk. Again, we believe this limitation to be minimal as ERT is unlikely to be associated with a particular type of hypoglycemic prescribing within the cohort of women with diabetes. Also, given that carcinogenesis has a long latency, the effects of the antidiabetic drugs may not be observed months or years after that exposure at which point a patient might have been on additional or different diabetic medications. Therefore, exposure might have been misclassified for some individuals. However, in a breast cancer prevention trial of estrogen and progestin in the Women's Health Initiative, Santen and colleagues estimated that nearly 94% of women who developed breast cancer during the 5-year follow-up study actually had occult tumor lesions at baseline.[38]

Taking these two points together, antidiabetic drugs may act as promoters of carcinogenesis rather than initiators.

Aside from these drawbacks, this study has several key strengths. An important strength was the large size of our cohort; this population-based cohort study of patients with type 2 diabetes is larger than many found in European national databases. We were able to account for several confounders not available in other observational cohort studies. In addition, we were able to compare cancer incidence across various mutually exclusive antidiabetic drug use categories. Further, the study cohort is also unique in its racial/ethnic diversity. With nearly 50% minority women, this makes our findings more broadly applicable. Another important advantage was that the study was based on an integrated healthcare delivery system with comprehensive access to pharmacy utilization that modeled risks using time-dependent drug variables. Many of the prior observational studies were limited by self-reports of the cancer outcomes, covariates, lack of pharmacy data, or inadequate statistical analyses.[4–8] Given the insured study population, the results may not be generalizable to all settings; however, the characteristics of the KPSC membership are similar to the communities it serves in southern California. Future studies should consider examining the cancer risk according to the dose and timing of the antidiabetic medications, and if body mass index modifies this risk.

In summary, we observed a slightly lower breast cancer risk among women with type 2 diabetes who used a combination of antidiabetic medications with metformin compared with metformin only users; however, the results were not statistically significant. Overall, our results do not strongly support metformin monotherapy for cancer chemoprevention. Larger studies with a longer follow-up are needed to evaluate metformin's potential effect on other gynecological cancers.

Contributors All authors contributed to the conception and design. RH, SEL, JS, and JC were responsible for data collection and assembly. All authors contributed to data analysis and interpretation, and manuscript preparation, and approved the final manuscript.

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Data sharing statement The authors welcome inquiries from external investigators for collaborations. Collaborations may require data use agreements with KPSC as authors are not free to release participants' personal data under KPSC's promise to safeguard confidentiality. Requests for collaboration must be submitted to the corresponding author. Before collaborations can be initiated, proposals require a review and approval by the study team and the KPSC contracts office. Additionally, funding may be required to support the future analyses conducted by KPSC staff. This purpose of the study committee is to: (A) ensure accurate reporting of KPSC data, (B) maintain the scientific integrity, and (C) safeguard the rights and confidentiality of the KPSC health plan members.

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