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ORIGINAL REPORT

Cancer risks in thiazolidinedione users compared to other anti-diabetic agents†

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SUMMARY

Purpose We conducted three nested case-control studies to evaluate the risk of breast, colon, and prostate cancers developing in patients exposed to thiazolidinediones (TZDs) compared with other anti-diabetic agents.

Methods Cancer cases were matched to five controls by age, gender, calendar year, and time in the database from a cohort of 126971 diabetic patients taking anti-diabetic medication in the US Integrated Healthcare Information Services database. Five hundred thirteen breast cancer cases were matched with 2557 controls, 408 cases of colon cancer were matched with 2027 controls and 643 cases of prostate cancer were matched with 3176 controls. Exposure to an anti-diabetic agent within 90 days preceding the index date was defined as recent exposure and at any time during the follow-up was defined as ever exposed.

Results The adjusted odds ratios and 95%CI of cancer from ever exposure to TZDs compared to oral monotherapy, oral dual therapy, oral triple therapy, insulin monotherapy, insulin and oral therapy and all non-TZD anti-diabetic agents were, respectively for breast cancer: 0.91 (0.69–1.20), 0.80 (0.56–1.14), 0.87 (0.32–2.35), 1.27 (0.61–2.67), 0.71 (0.36–1.37), 0.89 (0.68–1.15); for colon cancer: 1.06 (0.80–1.40), 1.12 (0.77–1.63), 1.73 (0.39–7.78), 4.46 (1.05–19.00), 1.06 (0.50–2.26) 1.03 (0.80–1.32) and for prostate cancer: 1.08 (0.85–1.37), 0.89 (0.66–1.21); 0.82 (0.33–2.06); 1.80 (0.79–4.07), 1.10 (0.55–2.18), 1.04 (0.83–1.31). Results for exposure within 90 days of the date of the cancer were similar.

Conclusions Our findings suggest that the effect of TZDs on the likelihood of development of the cancers studied (colon, prostate and breast) appears to be neutral and do not support a beneficial or deleterious effect of TZD on the cancers studied.

KEY WORDS — thiazolidinediones; cancer; breast; colon; prostate; risk; cohort; database

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INTRODUCTION

The influence of various anti-diabetic therapies on the risk of developing cancer has not been explored in epidemiological studies.

In vitro and animal data suggest that thiazolidinediones (TZDs) may potentially reduce the risk of developing cancer or alter the natural history of established cancer, though there are limited data for common cancers. TZDs inhibited in vitro growth and viability of human neuroblastoma cell lines in a dose-dependent manner showing considerable effects only at high concentrations.[1] Rosiglitazone led to a decrease in cell viability, a decrease of cellular proliferation and an increase in apoptosis in the adrenocortical tumor cell line NCI h295.[2] TZD treatment in pancreatic cancer cells had potent inhibitory effects on growth by a PPAR-dependent induction of pancreatic ductal differentiation.[3] TZDs inhibited mitogen-induced cellular proliferation in normal

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mouse skin primary keratinocytes and in the C50 keratinocyte cell line.[4] TZDs completely inhibited lymph node and lung metastases in the xenograft animal model of colon cancer, and TZDs inhibited growth of primary xenografts by 40%.[5]

A few genetic epidemiological studies have explored the association of PPAR genes with common cancers. In a nested case-control analysis of 193 cases and 188 controls, from a cohort study of Finnish male smokers, no association was found between the PPAR-g Pro12Ala polymorphism and the risk of prostate cancer or tumour stage or grade.[6] In a case control study to examine the association of PPARg Pro12Ala polymorphism with colorectal adenoma, the adjusted odds ratio indicated a reduced risk for those with the Pro12Ala or Ala12Ala genotype compared with those with the Pro12Pro genotype.[7]

We are not aware of any epidemiological studies which have explored the risk of cancer from exposure to anti-diabetic agents and, therefore, conducted three nested case-control studies from a diabetic cohort to assess the risk of the common cancers of breast, colon and prostate in patients exposed to TZDs compared to other anti-diabetic agents in diabetic patients. We chose these cancers as they are important and common enough to be addressed with good statistical power in a claims database. Our primary interest was in the comparison between TZD therapy, alone or combined with other anti-diabetic agents, and oral dual antidiabetic therapy, as TZDs are often started as an addition to other first line therapy.

METHODS

Data source

The study was conducted in the Integrated Healthcare Information Services (IHCIS) managed care database. IHCIS is a comprehensive, de-identified United States healthcare claims database that is representative of the non-elderly, insured population in the USA. It contains inpatient, outpatient and pharmacy claims data and laboratory results and enrollment information on over 38 million lives, from over 30 different healthcare plans across nine census regions.

Study population

Within the database, we conducted three matched nested case-control studies, one for each cancer of interest. Among participants aged 18 years or older, who had at least 6 months of continuous enrolment in the database between 1st January 1997 and 31st December 2004 and who were eligible for pharmacy benefit with prescription drug coverage, a study cohort population was identified that consisted of all patients with type 2 diabetes defined as those with at least one ICD-9 code of 250.x. To improve diagnostic accuracy, we ensured that all of these diabetic patients had at least one record of a claim for the prescription of an anti-diabetic agent at some time in their follow-up in the database. Within the base cohort population, each participant was followed from the start of the patient's follow up time until the earliest of: the cancer of interest, death, leaving the health care plan, or 31st December 2004. For the analysis of each cancer, we excluded subjects who had had a previous cancer of the same type recorded before the diagnosis of diabetes. We also excluded patients assigned a diagnosis of cancer within 90 days of cohort entry to ensure that the diagnosis of the cancer was made after the diagnosis of diabetes had been assigned. Other cancers were not excluded from the cohort.

We identified cases of incident cancer as those participants with an ICD-9 diagnosis of breast cancer (174.xx), cancer of the prostate and seminal vesicles (185.x and 187.8x) and colon cancer (153.xx). To be considered a case, the first mentioned diagnosis of cancer had to be recorded at least 3 months after the diagnosis of diabetes. The date of the first cancer diagnosis was termed the index date.

Up to five controls were individually matched for each case on age (within 5 years), gender, calendar year of the cancer diagnosis and length of follow-up in the database. Selected controls did not have a record of the relevant cancer at any time during their follow-up in the database. Controls were assigned the same index date as the case to which they were matched.

Prescriptions were used as a proxy for drug exposure. Exposure was defined in two ways. A prescription for an anti-diabetic agent recorded (yes/no) within 90 days preceding the index date for cases and controls was termed recent exposure. Ever exposure was defined as prescriptions for anti-diabetic agents during their entire follow-up prior to the index date. Mutually exclusive anti-diabetic agent exposure groups were defined as oral monotherapy (excluding TZDs); oral dual therapy (excluding TZDs); oral triple therapy (excluding TZDs); TZDs (rosiglitazone and pioglitazone) monotherapy or in combination with other anti-diabetic agents; insulin monotherapy; insulin and oral therapy (excluding TZDs) and untreated. A group of untreated patients arose from patients who after being selected from the cohort, started their anti-diabetic agent after the index date.

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A further non-mutually exclusive group comprised all non-TZD anti-diabetic agents.

Statistical analysis

Owing to the matched study design, we used conditional logistic regression to assess the risk of each cancer according to the exposure groups. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for cancer were calculated. Matching was used to control for age, sex, calendar time and years of recorded history in the database before the index date. Participants who were exposed to TZDs, alone or in combination with other anti-diabetic drugs, were compared with other mutually exclusive anti-diabetic drug regimes and to the non-mutually exclusive category of all non-TZD anti-diabetic agents. Identical analyses were conducted using the time window of exposure of 90 days before the index date of cancer diagnosis and of exposure at any time in the follow-up period. Unadjusted incidence rates for the three cancers were also calculated from the cohort. The analysis was conducted identically for each cancer. We used SAS version 8.1 (SAS Institute, Inc., Cary, NC) to conduct all the analyses.

RESULTS

The diabetes cohort from which the cases and controls arose consisted of 126971 patients at baseline (Table 1). The mean follow up of the entire cohort was 21.7 months (SD = 16.0) and the median follow up was 17.8 months. Males comprised 56.6% and the largest age group was 45–64 (62.9%) with people aged 65 and over representing 15.6% of the entire cohort. The majority of patients were exposed to oral monotherapy (excluding TZDs) (56%) followed by those exposed to TZD (24.2%) at some point during their follow-up, and then followed by oral dual therapy (excluding TZDs) (14.9%). Insulin monotherapy was used in only 0.02% and insulin plus oral therapy (excluding TZDs) was used in 3.2%. There were 290 subjects (0.23%) in the untreated category, which represented those who were exposed to an anti-diabetic agent at a time in the follow-up period that started after the time of the index date of cancer diagnosis for cases and the corresponding time for controls.

The incidence rates, per 1000 patient-years, and 95% confidence intervals (CI), of the cancers of interest in the diabetes cohort were: 2.26 (95%CI: 2.07–2.47) for breast, 1.80 (95%CI: 1.63–1.98) for colon and 2.84 (95%CI: 2.62–3.06) for prostate.

Table 1. Characteristics of the diabetes cohort

	Diabetes cohort	
	No.	%
Total	126971	100.00
Age group		
18–44	27339	21.53
45–64	79866	62.90
>=65	19766	15.57
Gender:		
Male	71884	56.61
Female	55087	43.39
Follow-up		
Mean in months (SD)	21.74 (15.97)	
Median in months	17.83	
Ever exposure to diabetic medication*		
Oral monotherapy (excluding TZDs)	71514	56.32
Oral dual therapy (excluding TZDs)	18894	14.88
Oral triple therapy (excluding TZDs)	1376	1.08
TZD mono- or combination therapy	30780	24.24
Insulin monotherapy	20	0.02
Insulin and oral therapy(excluding TZDs)	4097	3.23
Untreated	290	0.23

*Categories are mutually exclusive.

Breast cancer developed in 513 patients, and they were matched with 2557 controls. The distribution of age groups and length of follow-up were similar in cases and controls (Table 2). The adjusted odds ratios and 95%CI for breast cancer from ever exposure to TZD (mono- or combination therapy) compared to oral monotherapy, oral dual therapy, oral triple therapy, insulin monotherapy, insulin and oral therapy and all non-TZD anti-diabetic agents were, respectively: 0.91 (0.69–1.20), 0.80 (0.56–1.14), 0.87 (0.32–2.35), 1.27 (0.61–2.67), 0.71 (0.36–1.37), 0.89 (0.68–1.15). The results for exposure 90 days prior to the date of the cancer were similar (Table 2).

Colon cancer developed in 408 patients, and they were matched with 2027 controls. The distribution of age groups and length of follow-up were similar in cases and controls (Table 3). The adjusted odds ratios and 95% CI for colon cancer from ever exposure to TZD (mono- or combination therapy) compared to oral monotherapy, oral dual therapy, oral triple therapy, insulin monotherapy, insulin and oral therapy, and all non-TZD anti-diabetic agents were, respectively: 1.06 (0.80–1.40), 1.12 (0.77–1.63), 1.73 (0.39–7.78), 4.46 (1.05–19.00), 1.06 (0.50–2.26), 1.03 (0.84–1.32). The results for exposure within 90 days of the date of the cancer were similar (Table 3).

Prostate cancer developed in 643 patients, and they were matched with 3176 controls. The distribution of age groups and length of follow-up were similar in cases and controls (Table 4). The adjusted odds ratios

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Table 2. Odds ratios for breast cancer from anti-diabetic therapies

	Breast cancer				Odds ratios for TZD compared with other non-TZD anti-diabetic regimes	
	Cases		Controls		Adjusted odds ratio	95%CI
	No.	%	No.	%		
Total	513	100.00	2557	100.00		
Age group						
18–44	48	9.36	240	9.39	—	—
45–64	365	71.15	1874	73.29	—	—
>=65	100	19.49	443	17.32	—	—
Gender						
Male	0	0.0	0	0.0	—	—
Female	513	100.0	2557	100.0	—	—
Follow-up						
Mean in months (SD)	16.66 (12.80)		16.62 (12.75)		—	—
Median in months	12.93		12.93		—	—
Ever exposure to diabetic medication						
Oral monotherapy	245	47.76	1209	47.28	0.91	0.69–1.20
Oral dual therapy	66	12.87	287	11.22	0.80	0.56–1.14
Oral triple therapy	5	0.97	24	0.94	0.87	0.32–2.35
TZD mono- or combination therapy	83	16.18	449	17.56	1.00	—
Insulin monotherapy	9	1.75	62	2.42	1.27	0.61–2.67
Insulin and oral therapy	13	2.53	52	2.03	0.71	0.36–1.37
Untreated	92	17.93	474	18.54	0.96	0.69–1.34
All anti-diabetic agents minus TZD	333	65.89	1634	63.90	0.89	0.68–1.15
Recent exposure to diabetic medication						
Oral monotherapy	227	44.25	1163	45.48	0.90	0.67–1.21
Oral dual therapy	48	9.36	199	7.78	0.74	0.49–1.11
Oral triple therapy	0	0.0	8	0.31	—	—
TZD mono– or combination therapy	66	12.87	377	14.74	1.00	—
Insulin monotherapy	18	3.51	102	3.99	1.00	0.56–1.77
Insulin and oral therapy	4	0.78	16	0.63	0.69	0.22–2.12
Untreated	150	29.24	692	27.06	0.81	0.59–1.12
All anti–diabetic agents minus TZD	297	57.89	1488	58.19	0.87	0.66–1.18

and 95%CI for prostate cancer from ever exposure to TZD (mono- or combination therapy) compared to oral monotherapy, oral dual therapy, oral triple therapy, insulin monotherapy, insulin and oral therapy and all non-TZD anti-diabetic agents were, respectively: 1.08 (0.85–1.37), 0.89 (0.66–1.21); 0.82 (0.33–2.06); 1.80 (0.79–4.07), 1.10 (0.55–2.18), 1.04 (0.83–1.31). The results for exposure within 90 days of the date of the cancer were similar (Table 4).

CONCLUSIONS

This study, the first and only epidemiological analysis of the risks of cancer in TZDs versus other anti-diabetic agents (or between anti-diabetic agents) that we are aware of, found that the effect of TZDs on the likelihood of development of the cancers studied (colon, prostate and breast) appears to be neutral and does not support a beneficial or deleterious effect of TZDs on the cancers studied. The risk of these cancers from use of TZDs was not statistically or materially different from exposure to any other single or combined anti-diabetic regime of an oral antidiabetic agent or insulin therapy. The only exception was risk of colon cancer from TZDs compared with insulin monotherapy, which contained only two cases and an extremely wide 95% confidence interval from 1.05 to 19.00. We consider this result to be due to the play of chance on a non-primary comparison. Support for this deduction comes from the recent exposure analysis in which the odds ratio risk of those exposed to insulin monotherapy, based on 15 cases, was 1.25 (95%CI: 0.68–2.32) and not statistically significant. The remaining results were similar in analyses of ever exposure and within the 3 months preceding the date of diagnosis of the cancer of interest. The results apply

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Table 3. Odds ratios for colon cancer from anti-diabetic therapies

	Colon cancer				Odds ratios for TZD compared with other non-TZD anti-diabetic regimes	
	Cases		Controls		Adjusted odds ratio	95%CI
	No.	%	No.	%		
Total	408	100.00	2027	100.00		
Age group						
18–44	21	5.15	103	5.08	—	—
45–64	259	63.48	1373	67.74	—	—
>=65	128	31.37	551	27.18	—	—
Gender						
Male	237	58.09	1185	58.46	—	—
Female	171	41.91	842	41.54	—	—
Follow-up						
Mean in months (SD)	19.65 (13.42)		19.68 (13.41)		—	—
Median in months	15.97		16.1		—	—
Ever exposure to diabetic medication						
Oral monotherapy	196	48.04	926	45.68	1.06	0.80–1.40
Oral dual therapy	53	12.99	262	12.93	1.12	0.77–1.63
Oral triple therapy	2	0.49	16	0.79	1.73	0.39–7.78
TZD mono- or combination therapy	90	22.06	401	19.78	1.00	—
Insulin monotherapy	2	0.49	38	1.87	4.46	1.05–19.00
Insulin and oral therapy	9	2.21	45	2.22	1.06	0.50–2.26
Untreated	56	13.73	339	16.72	1.38	0.95–2.01
All anti-diabetic agents minus TZD	262	64.22	1287	63.49	1.03	0.84–1.32
Recent exposure to diabetic medication						
Oral monotherapy	181	44.36	892	44.01	1.20	0.89–1.62
Oral dual therapy	41	10.05	190	9.37	1.15	0.75–1.76
Oral triple therapy	0	0.0	4	0.2	—	—
TZD mono- or combination therapy	77	18.87	316	15.59	1.00	—
Insulin monotherapy	15	3.68	74	3.65	1.25	0.68–2.32
Insulin and oral therapy	1	0.25	11	0.54	2.29	0.29–17.98
Untreated	93	22.79	540	26.64	1.42	1.01–1.99
All anti-diabetic agents minus TZD	238	58.33	1171	57.77	1.21	0.90–161

to rosiglitazone and pioglitazone, the two TZDs currently available on the market, combined as there were not sufficient data to analyse the two drugs separately.

Proving a negative conclusively is difficult but the narrow confidence intervals of most of the comparisons confidently exclude any important large or moderate risks for these durations of exposure for any of these three common cancers. Excess risks above 1.14 for breast cancer, 1.63 for colon cancer and 1.21 for prostate cancer can be reliably ruled out from this analysis for the primary comparison of interest between TZD therapy (mono- or combination therapy) and non-TZD oral dual therapy. We believe this comparison to be the most appropriate, as most TZD prescribing is second line therapy after use of other oral anti-diabetic agents.[8] Also, although the evidence is mixed, diabetes itself may have an influence on the risk of these cancers,[9–27] and hence comparison with dual therapy provides the best assurance of comparing similar stages of diabetes, which may have an influence on risk. Matching by duration of follow-up from the date of diagnosis of diabetes (cohort entry) in this claims database does not guarantee comparability of the duration of diabetes between TZDs and comparators. We did not have enough data to conduct a duration response analysis and it is possible that the TZD exposure group did not have sufficient duration of exposure to assess any protective or excess risk for these three cancers. The median duration of follow-up for the cohort in general and for the time to diagnosis of cancer from the time of diagnosis of diabetes is rather short for the development of cancers. However, the mean and standard deviation are longer suggesting

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Table 4. Odds ratios for prostate cancer from anti-diabetic therapies

	Prostate cancer				Odds ratios for TZD compared with other non-TZD anti-diabetic regimes	
	Cases		Controls		Adjusted odds ratio	95%CI
	No.	%	No.	%		
Total	643	100.00	3176	100.00		
Age group						
18–44	15	2.33	91	2.87	—	—
45–64	398	61.9	2145	67.54	—	—
>=65	230	35.77	940	29.60	—	—
Gender						
Male	643	100.00	3176	100.00	—	—
Female	0	0.00	0	0.00	—	—
Follow-up						
Mean in months (SD)	19.37 (13.33)		19.37 (13.26)		—	—
Median in months	15.77		15.77		—	—
Ever exposure to diabetic medication						
Oral monotherapy	294	45.72	1522	47.92	1.08	0.85–1.37
Oral dual therapy	89	13.84	400	12.59	0.89	0.66–1.21
Oral triple therapy	6	0.93	26	0.82	0.82	0.33–2.06
TZD mono- or combination therapy	123	19.13	600	18.89	1.00	—
Insulin monotherapy	7	1.09	56	1.76	1.80	0.79–4.07
Insulin and oral therapy	11	1.71	58	1.83	1.10	0.55–2.18
Untreated	113	17.57	514	16.18	0.94	0.70–1.26
All anti-diabetic agents minus TZD	407	63.30	2062	64.92	1.04	0.83–131
Recent exposure to diabetic medication						
Oral monotherapy	281	43.7	1498	47.17	1.06	0.82–1.37
Oral dual therapy	63	9.8	298	9.38	0.91	0.64–1.29
Oral triple therapy	2	0.31	2	0.06	0.17	0.02–1.25
TZD mono- or combination therapy	98	15.24	493	15.52	1.00	—
Insulin monotherapy	16	2.49	84	2.64	1.09	0.61–1.95
Insulin and oral therapy	4	0.62	21	0.66	1.00	0.33–3.02
Untreated	179	27.84	780	24.54	0.87	0.66–1.14
All anti-diabetic agents minus TZD	366	56.92	1903	59.92	1.03	0.80–1.32

that there are patients who had the cancer diagnosed a few years after the diagnosis of diabetes. Nevertheless, this analysis cannot exclude the possibility of a reduced or excess risk much greater than found here for these three cancers from much longer duration of therapy and follow-up. Cancers occurring within 90 days of the diagnosis of diabetes were few, did not affect the analysis and were unlikely to be associated with exposure, given the time span of the process of carcinogenesis in these cancers.

The cases and controls were well matched for age group, sex and follow-up period prior to the occurrence of the breast, colon and prostate cancers. As the controls were matched for age up to 5 years either side of a case, we further adjusted for age in the analysis, as age is such an important determinant of cancer risk. We could not adjust for other potential confounders for the three cancers, such as diet, age at menarche, age at menopause, number of births, age at first pregnancy, as these kinds of data are not captured well in claims databases. Therefore, it is conceivable, though improbable, that negative confounding could explain our negative results. Furthermore, we have no knowledge that information on these potential confounders for cancer risk would influence prescribing in diabetes. Cases and controls arising from the same base population consisting of diabetic patients further reduced selection bias.

The age distribution of the entire diabetic cohort and the cancers bear witness to the lack of representativeness of this, and most managed care, databases to the US population. However, the IHCIS database is representative of people insured in such plans in the US and our results should apply to, at least, other diabetes patients in other health plans. Nevertheless, we have no prior biological reasons for

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thinking that the results would be dissimilar for type 2 diabetes patient outside of US managed care. Although there were fewer subjects over age 65 than the national average, there were still sufficient subjects in this age group in the analysis (approximately 20% breast cancer, and about 30% for colon and prostate cancers) to justify generalisation of the results to this age group.

We used ICD-9 codes to assign patients with the diagnoses and these codes were reviewed independently by two clinicians. However, a limitation of the study is that we did not conduct a validation with chart review to confirm the cancer and diabetes diagnoses and exposures. Given the nature of these three common cancers we believe that our presumption to take at face value the recorded diagnosis is justified. Furthermore, by making the diagnosis of diabetes conditional on use of an antidiabetic agent we believe we ensured that all the patients in the cohort did indeed have diabetes.

Cancer of the seminal vesicles is not cancer of the prostate and may well have different aetiological and triggering factors in its development. However, clinically, cancer of the seminal vesicles may be confused with cancer of the prostate due to their proximity and for this reason we combined it together with cancer of the prostate. There were six cases of cancer of the seminal vesicles and their exclusion did not alter materially the results.

We did not exclude other cancers at baseline, and it is conceivable that metastases of other cancers could have been mistaken for primary cancers of breast, colon and prostate. However, we believe that this was unlikely as the sites of these cancers are unusual sites for secondaries.

Currently, there are no other relevant epidemiological data of cancer risks with the various anti-diabetic agents with which to compare our findings.

KEY POINTS

- Pre-clinical data suggest that TZDs may reduce the risk of several cancers.
- There is no information on the risks of common cancers from different classes of anti-diabetic agents.
- This is the first epidemiological study to examine the risks of common cancers associated with the TZD class of anti-diabetic agents.
- The effect of TZDs on the likelihood of development of the cancers studied (colon, prostate and breast) appears to be neutral and does not support a beneficial or deleterious effect of TZDs on the cancers studied.

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