Association of Thiazolidinediones With Liver Cancer and Colorectal Cancer in Type 2 Diabetes Mellitus

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The objective of this nationwide case-control study was to evaluate the risk of specific malignancy in diabetic patients who received thiazolidinediones (TZDs). A total of 606,583 type 2 diabetic patients, age 30 years and above, without a history of cancer were identified from the Taiwan National Health Insurance claims database during the period between January 1 2000 and December 31 2000. As of December 31 2007, patients with incident cancer of liver, colorectal, lung, and urinary bladder were included as cases and up to four age- and sex-matched controls were selected by risk-set sampling. Logistic regression models were applied to estimate the odds ratio (OR) and 95% confidence interval (CI) between TZDs and cancer incidence. A total of 10,741 liver cancer cases, 7,200 colorectal cancer cases, and 70,559 diabetic controls were included. A significantly lower risk of liver cancer incidence was found for any use of rosiglitazone (OR: 0.73, 95% CI: 0.65-0.81) or pioglitazone (OR: 0.83, 95% CI: 0.72-0.95), respectively. The protective effects were stronger for higher cumulative dosage and longer duration. For colorectal cancer, rosiglitazone, but not pioglitazone, was associated with a significantly reduced risk (OR: 0.86; 95% CI: 0.76-0.96). TZDs were not associated with lung and bladder cancer incidence, although a potential increased risk for bladder cancer with pioglitazone use $\geq$3 years could not be excluded (OR: 1.56; 95% CI: 0.51-4.74). *Conclusion:* The use of pioglitazone and rosiglitazone is associated with a decreased liver cancer incidence in diabetic patients. The effects on occurrence of specific cancer types may be different for pioglitazone and rosiglitazone. (HEPATOLOGY 2012;55:1462-1472)

Both diabetes and cancer are common diseases that have tremendous impacts on health worldwide and the prevalence of both diseases is increasing globally. The diagnosis of cancer and diabetes in the same individual occurs more frequently than would be expected by chance.[1,2] Diabetes has been consistently associated with an increased risk of cancers of the liver, pancreas, and endometrium, despite an association with the occurrence of other cancers being inconclusive.[3] A recent meta-analysis reported that the hazard ratio among persons with diabetes compared with those without diabetes was 1.25 (95% confidence interval [CI]: 1.19 to 1.31) for death from cancer, moderately associated with death from cancers of the liver, pancreas, ovary, colorectal, lung, bladder, and breast.[4]

Many factors may affect the positive association between diabetes and cancers. Potential risk factors common to both diseases include age, sex, obesity, physical activity, diet, alcohol, and smoking.[5-10] Furthermore, diabetes treatment might influence cancer risk and cancer prognosis. Evidence from observational studies indicates that oral hypoglycemic agents and

Abbreviations: DDD, defined daily dose; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione.

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Received June 8, 2011; accepted November 17, 2011.

Supported in part by Taiwan Department of Health grant DOH098-TD-D-113-098016, which did not play any role in our study design, collection, analysis, and interpretation of data, in report writing, or in the decision to submit the article for publication. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Department of Health, Executive Yuan, Taiwan.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.25509

Potential conflict of interest: Nothing to report.

Additional Supporting Information may be found in the online version of this article.

insulin are associated with either an increased or reduced risk of cancer.[2]

Thiazolidinediones (TZDs) are insulin-sensitizing peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, available drugs including pioglitazone and rosiglitazone in this class. Laboratory studies showed that PPAR-γ agonists might have anti-cancer activities, such as growth inhibition, induction of apoptosis, and cell differentiation.[11-13] In contrast, preclinical studies showed that bladder tumors were observed in male rats receiving doses of pioglitazone that produced blood drug levels equivalent to those resulting from a clinical dose.[14] Additionally, results from a 3-year placebo-controlled trial of pioglitazone demonstrated a higher incidence of bladder neoplasm in patients receiving pioglitazone.[15] Although a meta-analysis of randomized clinical trials found that rosiglitazone was not associated with a significant modification of cancer risk, epidemiologic data regarding individual sites of cancer risk associated with different TZDs were inconsistent.[16-20] Therefore, the objective of this study was to conduct a nested case-control study based on a nation-wide health insurance claims database in Taiwan to assess the association between TZDs (both pioglitazone and rosiglitazone) and the occurrences of liver, colorectal, lung, and urinary bladder cancers.

Materials and Methods

Data Source. The Taiwan National Health Insurance (NHI) claims database includes complete outpatient visits, hospital admissions, prescriptions, disease, and vital status for 99% of the population of 23 million in Taiwan. We established the longitudinal medical history of each beneficiary by linking several computerized administrative and claims datasets to National Cancer and Death Registry through the date of birth and the civil identification number unique to each beneficiary. The protocol of this study was approved by the National Taiwan University Hospital Research Ethics Committee.

Source Population. Data for all patients with any diabetes diagnostic codes (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), ICD-9-CM code 250 and A code 181) in the claims database between January 1 2000 and December 31 2000 were retrieved. An algorithm including age, number of outpatient visits, number of hospitalizations, and the hospital level was used to identify potential diabetic patients with improved accuracy. This definition of diabetes was evaluated by a study sampling 9,000 patients with a diagnosis of diabetes in the NHI claims data in 2000. The diagnostic accuracy of diabetes was assessed based on patient response to a questionnaire concerning (1) being told by doctors they have diabetes or (2) ever use of oral hypoglycemic agents or insulin injections. Subjects who gave negative or uncertain answers but were using hypoglycemic agents in the pharmacy claims database were also classified as diabetic. Validation of this algorithm by which 640,173 patients were identified demonstrated 93.2% sensitivity and 92.3% positive predictive value.

Study Design. Because diabetic patients may receive highly variable antidiabetic therapies in terms of drug regimens, dosage, duration, and other concomitant drugs, and confounding factors are constantly changing over time in a long-term observational follow-up study, there are complex analytical difficulties for a cohort analysis to be attempted. Instead, a nested case-control approach is a useful alternative of cohort analysis to study time-dependent exposures.[21] The risk estimates from cohort and nested case-control analyses should be identical if confounding is fully controlled in both analyses. The superior computational efficiency by nested case-control study design may be particularly useful in case rare outcomes are encountered.[22]

Study Groups. First, we excluded patients age <30 and >100 years old. To enroll patients with type 2 diabetes, we further excluded those who (1) had a hospital admission with a discharge diagnosis of insulin dependent diabetes mellitus (ICD-9-CM code 250.x1, 250.x3), or (2) received a catastrophic illness certificate issued by the Department of Health for type 1 diabetes (Fig. 1). Patients were classified as having prevalent or newly diagnosed type 2 diabetes according to the criteria in 1999. Those who had a history of cancer recorded in the National Cancer Registry any time before the cohort entry date, that is, date of diabetes diagnosis for newly diagnosed patients and January 1 2000 for prevalent patients, were also excluded. Patients were followed from January 1 2000 (for prevalent type 2 diabetes patients) or the date of diabetes diagnosis in 2000 (for newly diagnosed type 2 diabetes patients) to the earliest of cancer diagnosis, death, disenrollment from the national health insurance, or December 31 2007.

All individuals in the study cohort with the first occurrence of liver, colorectal, lung, and urinary bladder cancer were included as cases. All potential cases were validated by a linkage through National Cancer Registry.

A risk-set sampling (that is, controls sampled from those in the original study cohort who remained free

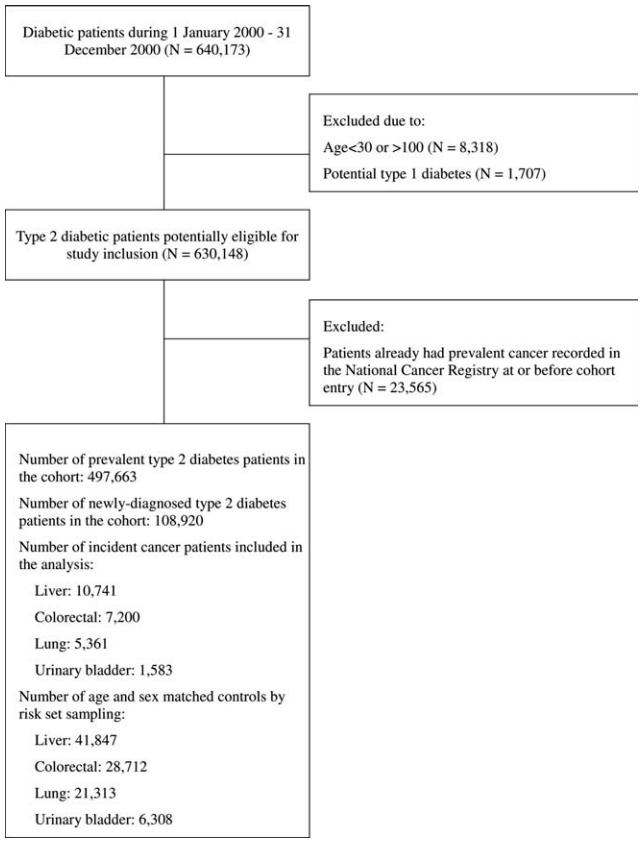

Fig. 1. Study flow.

of outcome at the time point when a case occurred) matched by age (within 5 years), sex, and the number of days of follow-up was used to find controls for the cohort. For newly diagnosed type 2 diabetes patients, cases and controls were also matched on antidiabetic treatment duration (within 30 days) at cancer diagnosis. For newly diagnosed diabetic patients, this scheme that matched follow-up duration would have, by design, also taken diabetes duration into consideration. For prevalent patients with unknown duration, we selected controls with the same follow-up duration to reduce the confounding effect by diabetes duration. Up to four controls were selected for each case.

Exposure Ascertainment and Covariates Adjustment. The main exposure of interest was the use of rosiglitazone and pioglitazone, which entered Taiwan's market in March 2000 and June 2001, respectively. We collected information of prescribed drug types (according to the anatomic therapeutic chemical [ATC] classification system, A10BG02 for rosiglitazone and A10BG03 for pioglitazone), dosage, date of prescription, supply days, and total number of pills dispensed from the outpatient pharmacy prescription database. The mean daily dose for each individual was calculated as dividing the cumulative number of pills by the follow-up duration. Subsequently, the defined daily dose (DDD) was then established by an expert panel according to the relative amount compared to the typical maintenance dose for an adult. Other medications, including biguanides (ATC code A10BA), sulfonylurea (A10BB), alpha glucosidase inhibitors (A10BF), glinides (A10BX02, A10BX03), fast-acting insulins (A10AB01, A10AB02, A10AB03, A10AB30), insulin glargine (A10AE04), statins (C10AA), and low-dose aspirin (B01AC06), angiotensin converting enzyme inhibitors (C09AA), angiotensin receptor blockers (C09CA), beta-blockers (C07A), and calcium channel blockers (C08C, C08D, C08E), were also recorded and reported.

We also incorporated inpatient and outpatient diagnosis files to ascertain the history of cardiovascular disease, peripheral vascular disease, cerebrovascular disease, retinopathy, nephropathy, neuropathy, depression, chronic kidney disease, chronic liver disease, and chronic lung disease based on ICD-9-CM codes. Patients were classified as having chronic liver disease if they had at least one hospital admission or outpatient visit with a diagnostic code of hepatitis B virus infection (ICD-9-CM codes 070.2x, 070.3x, V02.61), hepatitis C virus infection (070.41, 070.44, 070.51, 070.54, V02.62), chronic hepatitis (571.4), liver cirrhosis (571.2, 571.5, 571.6), or alcoholic liver disease (571.0x, 571.1x, 571.2, 571.3x). A previous validation study using hospital administrative database reported a positive predictive value of 90% with this definition.[23] Covariate information included age, gender, and socioeconomic status (i.e., using monthly income as a proxy).

Statistical Analysis. Conditional logistic regression was used to estimate the crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for the association between rosiglitazone/pioglitazone and cancer occurrence with "nonuse" as the reference group. Potential covariates, including socioeconomic status (monthly income level), diabetes complications and comorbidities at cancer diagnosis, other antidiabetic agents, antihypertensive medications, statin, and aspirin were examined. In the multivariate analysis, we adjusted for the use of short-acting human insulin, sulfonylurea, metformin, as these antidiabetic agents were reported to be associated with cancer risks and could potentially confound the association. Other variables were chosen by using stepwise selection with P values < 0.10 for model entry and > 0.05 for removal. The association between rosiglitazone/pioglitazone and individual cancer incidence was separately estimated after adjustment for potential confounders specific to

that cancer type. In the dose- and duration-response analyses, we calculated the ORs for higher (≥120 DDD) and lower cumulative dose (<120 DDD) use, and for cumulative treatment duration ≥3, 2-3, 1-2, and ≤1 years. A two-sided P value < 0.05 was considered statistically significant.

Approximately 15% participants claimed at lease one prescription for pioglitazone. Assuming a correlation coefficient for pioglitazone use between case and control was 0.5 and an ORs was 0.8, a study of 2,500 cases and 4 controls for each case would have a power ≥80% at $\alpha = 0.05$.

Results

During the period between January 1 2000 and December 31 2000, a total of 640,173 patients were initially identified by the algorithm (Fig. 1). Among them, 606,583 patients, including 497,663 prevalent type 2 diabetes and 108,920 newly diagnosed type 2 diabetes, were included in the analysis after excluding those who were age <30 or >100 years, who were type 1 diabetes, or who already had prevalent cancer. These patients were followed for a median of 7.9 years. Meanwhile, a total of 174,800 (27.3%) patients died, whereas only 1,566 (0.2%) were lost to follow-up due to discontinuation from or drop-out of health insurance.

During the study period the number of oral antidiabetic agents (mean ± standard deviation) was 2.62 ± 1.07 and the mean daily dosage was 1.18 ± 0.92 DDD per day. Metformin and sulfonylurea were the most commonly used oral antidiabetic medications (83.5% and 88.4% of the study population, respectively). In the diabetic cohort, 324,773 (50.7%) had ever used insulin therapy during the study period.

Approximately 26.1% of the patients ever received rosiglitazone and 14.1% pioglitazone. The mean cumulative duration was 522 days and the mean daily dosage was 0.14 DDD/day for rosiglitazone, as compared with 375 days and 0.11 DDD/day for pioglitazone. Because of the concern that physicians might preferentially prescribe TZDs to patients with normal liver function, we compared the proportion of diabetic patients with chronic liver disease (hepatitis B virus infection, hepatitis C virus infection, chronic hepatitis, liver cirrhosis, and alcoholic liver disease) among control subjects (a representative sample of the study population) who received different types of antidiabetic therapies. A significantly higher proportion of patients with chronic liver disease were found to have received insulin, rosiglitazone, and/or pioglitazone than those receiving sulfonylureas, metformin, or diet therapy (Supporting Table A).

A total of 10,741 incident liver cancer, 7,200 colorectal cancer, 5,361 lung cancer, and 1,583 bladder cancer cases were identified. These cases were age- and sex-matched with 99,538 controls (at least one and up to four eligible controls for each case) by the risk-set sampling scheme. In general, cancer cases were more likely to be of lower socioeconomic status and more likely to have diabetes-associated complications (retinopathy, neuropathy, and nephropathy), cardiovascular disease, chronic kidney diseases, liver diseases, and lung diseases. The cases were also more likely to have received fast-acting insulin and insulin glargine and glinides, whereas fewer of them have received statins before cancer diagnosis as compared with controls (Table 1 for liver cancer and Table 2 for colorectal cancer). Despite a similar proportion of overall cancer cases and controls who received metformin and sulfonylurea, the mean daily dosage of these two antidiabetic agents in overall cancer cases were significantly higher than those for matched controls (data not shown). (Associations with specific cancer sites are reported below.) Regarding antihypertensive therapy, a higher proportion of cancer cases had ever used beta-blockers and calcium channel blockers.

In the univariate analyses, we found a negative association between pioglitazone/rosiglitazone and liver cancer incidence, and a positive one between rosiglitazone and lung cancer. After controlling for potential confounding variables including short-acting human insulin, metformin (mean daily dosage in quartiles), sulfonylurea (mean daily dosage in quartiles), number of oral antidiabetic agents, chronic liver disease, statins, aspirin, beta-blockers, chronic kidney disease, glinides, nephropathy, cerebrovascular disease, calcium channel blockers, cardiovascular disease, and chronic lung disease, a significantly decreased risk of liver cancer incidence was found for any use of rosiglitazone (OR: 0.73, 95% CI: 0.65-0.81) and pioglitazone (OR: 0.83, 95% CI: 0.72-0.95), respectively (Table 3), in contrast to the adjusted ORs of 2.35 (95% CI: 2.21-2.49) for short-acting insulin, 1.05 (95% CI: 0.93-1.18) for sulfonylurea, and 0.77 (95% CI: 0.69-0.85) for metformin. The protective effects were even stronger for higher cumulative dosage ≥120 DDD (OR 0.64; 95% CI: 0.56-0.72 for rosiglitazone and OR 0.80; 95% CI: 0.67-0.95 for pioglitazone) and for cumulative treatment duration ≥3 years (OR 0.64; 95% CI: 0.49-0.85 for rosiglitazone and OR 0.44; 95% CI: 0.23-0.86 for pioglitazone). Risk estimates were similar between prevalent and newly diagnosed type 2 diabetes

Table 1. Characteristics, Comorbidities, and Medication Use Among Incident Liver Cancer Cases and Matched Controls

	Cases (N = 10,741)	Controls (N = 41,847)	Crude Odds Ratio (95% CI)
Age at cancer diagnosis (mean ± SD)	66.66 ± 9.88	66.71 ± 9.98	–
Male (%)	64.03	63.86	–
Diagnosis year			
2000	1,314	5,144	–
2001	1,458	5,613	–
2002	1,386	5,397	–
2003	1,353	5,277	–
2004	1,364	5,379	–
2005	1,341	5,225	–
2006	1,349	5,162	–
2007	1,176	4,650	–
Socioeconomic status (monthly income in NTD, %)			
≤17,280	36.91	37.15	Reference
17,281∼22,800	45.95	41.99	1.10 (1.05-1.15)
22,801∼28,800	5.05	5.49	0.92 (0.83-1.02)
28,801∼36,300	5.01	5.61	0.89 (0.81-0.99)
36,301∼45,800	4.11	5.13	0.80 (0.72-0.89)
>45,800	2.97	4.63	0.64 (0.56-0.72)
Comorbidities (%)			
Cardiovascular disease	79.67	80.90	0.91 (0.86-0.97)
Peripheral vascular disease	6.28	5.46	1.17 (1.07-1.28)
Cerebrovascular disease	25.95	27.25	0.93 (0.89-0.98)
Retinopathy	27.99	26.18	1.10 (1.05-1.16)
Neuropathy	43.63	40.34	1.16 (1.11-1.21)
Nephropathy	61.13	51.05	1.60 (1.53-1.68)
Depression	8.00	6.31	1.30 (1.20-1.41)
Chronic kidney disease	11.67	8.25	1.48 (1.38-1.59)
Chronic liver disease	82.59	30.04	12.80 (12.04-13.61)
Chronic lung disease	15.84	14.63	1.10 (1.04-1.17)
Charlson's index (mean ± SD)	5.25 ± 2.89	3.43 ± 2.26	1.39 (1.38-1.40)
Medication use before cancer diagnosis (%)			
Metformin	79.00	79.98	0.93 (0.88-0.99)
Mean daily dosage among users	0.26 ± 0.29	0.18 ± 0.21	5.59 (5.09-6.14)
Sulfonylurea	91.61	90.58	1.16 (1.07-1.25)
Mean daily dosage among users	0.68 ± 0.58	0.41 ± 0.43	3.37 (3.21-3.53)
Alpha-glucosidase inhibitors	17.64	15.64	1.18 (1.11-1.25)
Thiazolidinediones	17.04	17.79	0.94 (0.88-1.00)
Pioglitazone	4.41	5.03	0.87 (0.78-0.96)
Rosiglitazone	14.78	15.56	0.93 (0.87-0.99)
Glinides	15.36	11.89	1.38 (1.29-1.47)
Mean number of oral anti-diabetic agents (mean ± SD)	2.22 ± 1.10	2.17 ± 1.08	1.05 (1.03-1.08)
Short-acting human insulin	47.31	26.57	2.64 (2.53-2.77)
Insulin glargine	0.80	0.59	1.38 (1.07-1.77)
Statins	16.53	29.02	0.45 (0.43-0.48)
Aspirin	42.07	46.74	0.81 (0.77-0.85)
ACE inhibitors	52.14	52.26	0.99 (0.95-1.04)
Angiotensin receptor blockers	28.41	28.25	1.01 (0.96-1.06)
Beta-blockers	56.21	48.90	1.38 (1.32-1.44)
Calcium channel blockers	64.10	60.68	1.18 (1.13-1.24)

patients. Due to the high prevalence of hepatitis B and C infection, the analysis was further stratified to those with and without chronic liver disease. The risk reduction (especially in high and prolonged dosage of rosiglitazone and pioglitazone) in liver cancer was mostly seen in the patients with prevalent chronic liver disease (Table 4).

For colorectal cancer, rosiglitazone was associated with a significantly decreased risk (OR: 0.86; 95% CI: 0.76-0.96) with a more prominent effect among those with the highest cumulative dose (OR: 0.83; 95% CI: 0.73-0.95) (Table 5). In contrast, pioglitazone was not associated with a significantly protective effect for colorectal cancer, although a trend of negative association was also found. The characteristics for cases and controls of lung and bladder cancer are summarized in Supporting Tables B and C. No relation between rosiglitazone/pioglitazone and lung or bladder cancer was found, although the ORs were above 1.0 (Supporting Tables D, E). A dosage and duration response

Table 2. Characteristics, Comorbidities, and Medication Use Among Incident Colorectal Cancer Cases and Matched Controls

	Cases (N = 7,200)	Controls (N = 28,712)	Crude Odds Ratio (95% CI)
Age at cancer diagnosis (mean ± SD)	70.17 ± 9.41	70.24 ± 9.41	–
Male (%)	54.21	54.16	–
Diagnosis year			
2000	864	3,424	–
2001	818	3,283	–
2002	898	3,574	–
2003	922	3,657	–
2004	971	3,888	–
2005	890	3,542	–
2006	900	3,626	–
2007	937	3,718	–
Socioeconomic status (monthly income in NTD, %)			
≤17,280	42.47	40.85	Reference
17,281∼22,800	39.86	41.76	0.91 (0.86-0.97)
22,801∼28,800	4.46	4.62	0.92 (0.81-1.05)
28,801∼36,300	4.94	5.16	0.92 (0.81-1.04)
36,301∼45,800	4.39	4.09	1.03 (0.90-1.18)
>45,800	3.88	3.52	1.05 (0.92-1.21)
Comorbidities (%)			
Cardiovascular disease	86.69	84.59	1.21 (1.12-1.31)
Peripheral vascular disease	5.58	6.03	0.92 (0.82-1.03)
Cerebrovascular disease	31.71	30.37	1.07 (1.01-1.13)
Retinopathy	27.81	27.25	1.03 (0.97-1.10)
Neuropathy	42.40	42.28	1.01 (0.95-1.06)
Nephropathy	61.85	54.29	1.43 (1.35-1.51)
Depression	6.21	7.15	0.86 (0.77-0.96)
Chronic kidney disease	11.40	8.65	1.37 (1.26-1.49)
Chronic liver disease	32.38	28.93	1.19 (1.12-1.26)
Chronic lung disease	16.31	16.79	0.96 (0.90-1.03)
Charlson's index (mean ± SD)	4.86 ± 3.19	3.60 ± 2.31	1.24 (1.22-1.25)
Medication use before cancer diagnosis (%)			
Metformin	80.07	79.60	1.03 (0.97-1.11)
Mean daily dosage among users	0.29 ± 0.30	0.18 ± 0.21	7.97 (7.12-8.93)
Sulfonylurea	91.57	90.26	1.20 (1.09-1.33)
Mean daily dosage among users	0.69 ± 0.59	0.42 ± 0.44	3.42 (3.23-3.62)
Alpha-glucosidase inhibitors	16.17	15.86	1.03 (0.95-1.11)
Thiazolidinediones	17.35	17.78	0.97 (0.90-1.04)
Pioglitazone	5.25	5.09	1.03 (0.92-1.17)
Rosiglitazone	14.90	15.48	0.95 (0.88-1.03)
Glinides	15.31	12.72	1.26 (1.17-1.36)
Mean number of oral anti-diabetic agents (mean ± SD)	2.22 ± 1.09	2.18 ± 1.09	1.05 (1.02-1.08)
Short-acting human insulin	48.31	27.70	2.62 (2.48-2.77)
Insulin glargine	0.88	0.62	1.42 (1.06-1.90)
Statins	27.63	29.52	0.90 (0.85-0.96)
Aspirin	51.06	50.18	1.04 (0.99-1.10)
ACE inhibitors	56.58	55.40	1.05 (1.00-1.11)
Angiotensin receptor blockers	31.94	30.57	1.07 (1.01-1.14)
Beta-blockers	57.00	51.94	1.25 (1.18-1.32)
Calcium channel blockers	71.51	65.73	1.35 (1.27-1.43)

relationship was not evident between the use of rosiglitazone and pioglitazone and these two types of cancer. An increase in bladder cancer risk was observed with pioglitazone use ≥3 years (OR: 1.56, 95% CI: 0.51-4.74), which did not reach statistical significance.

The cancer risk associated with antidiabetic therapies other than TZD are also reported (Supporting Table F). In general, short-acting human insulin, sulfonylureas, and glinides were significantly associated with an increased risk for liver, colorectal, and lung cancer. In contrast, metformin was associated with a decreased risk for liver cancer.

Discussion

Consistent with previous *in vitro* studies on TZDs which showed antiproliferation and prodifferentiation effects, our data have provided an association between

Table 3. Risk of Liver Cancer Associated With Pioglitazone or Rosiglitazone Use in Type 2 Diabetic Patients

	Pioglitazone				Rosiglitazone			
	Number of Cases	Number of Controls	Crude Odds Ratio	Adjusted* Odds Ratio	Number of Cases	Number of Controls	Crude Odds Ratio	Adjusted* Odds Ratio
Nonuse	10,267	39,741	Reference	Reference	9,154	35,336	Reference	Reference
Any use	474	2,106	0.87 (0.78-0.96)	0.83 (0.72-0.95)	1,587	6,511	0.93 (0.87-0.99)	0.73 (0.65-0.81)
Cumulative dosage								
$<$ 120 DDD	225	915	0.95 (0.81-1.10)	0.87 (0.72-1.05)	725	2,483	1.11 (1.02-1.22)	0.86 (0.75-0.98)
$\geq$ 120 DDD	249	1,191	0.81 (0.70-0.93)	0.80 (0.67-0.95)	862	4,028	0.81 (0.75-0.88)	0.64 (0.56-0.72)
Cumulative duration								
$\leq$1 year	352	1,463	0.93 (0.82-1.04)	0.87 (0.74-1.02)	1,034	3,856	1.02 (0.95-1.10)	0.78 (0.69-0.88)
1-2 years	79	387	0.78 (0.61-1.00)	0.80 (0.59-1.07)	330	1,457	0.86 (0.76-0.98)	0.66 (0.56-0.79)
2-3 years	30	159	0.73 (0.49-1.08)	0.71 (0.45-1.14)	135	697	0.73 (0.60-0.88)	0.59 (0.46-0.74)
$\geq$3 years	13	97	0.52 (0.29-0.93)	0.44 (0.23-0.86)	88	501	0.65 (0.52-0.82)	0.64 (0.49-0.85)

*Multivariate model with stepwise selection of covariates, including pioglitazone, rosiglitazone, short-acting human insulin, metformin (mean daily dosage in quartiles), sulfonylurea (mean daily dosage in quartiles), number of oral antidiabetic agents, chronic liver disease, statins, aspirin, beta-blockers, chronic kidney disease, glinides, nephropathy, cerebrovascular disease, calcium channel blockers, cardiovascular disease, chronic lung disease.

the clinical use of TZDs and a reduced risk for several cancer incidences, in particular liver cancer. The association became stronger when the duration of TZD use was longer and the dosage was higher. Rosiglitazone, but not pioglitazone, was associated with a significantly reduced risk for colorectal cancer. No association between both TZDs and lung and bladder cancer was observed.

Previous reports on the association between TZD use and cancer incidence have been inconsistent. The report from the data obtained from the Veterans Integrated Services Network 16 (VISN 16) cohort of 87,678 individuals showed a 33% reduction in lung cancer risk among TZD users compared with nonusers (relative risk: 0.65, 95% CI: 0.51-0.87). However, as rosiglitazone and pioglitazone were combined, the risk reduction for colorectal cancer did not reach statistical significance.[18] In contrast, the present study results did not show a decreased risk for lung cancer. Although numerous *in vitro* studies support the protective effect of TZDs in lung cancer, the specific tissue or type of cancer and its stage might contribute to the efficacy or failure of TZDs as antineoplastic agents.[19,20,24-29] Because the risk factors, genetic expressions, and pharmaceutical responses of lung cancer of the Taiwanese differ significantly from those in the Western countries, there might also be a differential response to TZDs.[30]

On the contrary, our analysis showed a protective effect of rosiglitazone on colorectal cancers, which was not evident in the VISN 16 cohort. In animal studies, PPAR-γ agonists inhibited tumor growth and colon carcinogenesis through induction of apoptosis and suppression of the cell cycle.[31-34] The current study, to the best of our knowledge, provides the first evidence that rosiglitazone but not pioglitazone might reduce the risk of colorectal cancer.

It is initially surprising that both pioglitazone and rosiglitazone are associated with a reduced risk for liver cancer. Hepatocellular carcinoma, one of the most incident, prevalent, and lethal malignancies in Taiwan, is regarded as a late-stage sequel of chronic infection of hepatitis B and C.[35,36] With only a few exceptions, the development of hepatocellular carcinoma almost exclusively follows the sequence of chronic hepatic inflammation, cirrhosis of the liver, repair and regeneration of hepatic cells, and then carcinogenesis.[37] This might explain the finding that risk reduction was more evident in the patients with chronic liver disease. Despite the concern that physicians may preferentially prescribe TZDs to patients with better liver function (i.e., confounding by contraindication), the present study showed that among patients receiving rosiglitazone and/or pioglitazone there was a significantly higher proportion of patients with chronic liver disease as compared with those receiving sulfonylureas, metformin, or diet therapy. This finding suggests that in Taiwan diabetic patients with abnormal liver function, on the contrary, are more likely to have ever received TZDs. One explanation of this contradiction was that other antidiabetic medications, such as sulfonylurea and metformin, might be associated with more frequent adverse effects among these patients. Although the possibility of residual confounding by contraindication among those with abnormal liver function tests cannot be excluded, the observed protective effects of rosiglitazone and pioglitazone were less likely due to physicians' reluctance to prescribe rosiglitazone and/or pioglitazone to patients with chronic liver disease. Currently, there are many clinical investigations concerning

Table 4. Risk of Liver Cancer Associated With Pioglitazone or Rosiglitazone Use in Type 2 Diabetic Patients With and Without Chronic Liver Disease

	Diabetic Patients Without Chronic Liver Disease				Diabetic Patients With Chronic Liver Disease			
	Pioglitazone		Rosiglitazone		Pioglitazone		Rosiglitazone	
	Crude Odds Ratio	Adjusted* Odds Ratio	Crude Odds Ratio	Adjusted* Odds Ratio	Crude Odds Ratio	Adjusted* Odds Ratio	Crude Odds Ratio	Adjusted* Odds Ratio
Nonuse	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any use	1.11 (0.85-1.44)	0.99 (0.72-1.36)	1.00 (0.85-1.18)	0.85 (0.66-1.09)	0.81 (0.71-0.93)	0.76 (0.64-0.90)	0.88 (0.81-0.96)	0.73 (0.64-0.83)
Cumulative dosage								
< 120 DDD	0.94 (0.63-1.40)	0.85 (0.54-1.34)	1.07 (0.84-1.37)	0.92 (0.67-1.27)	0.89 (0.73-1.08)	0.88 (0.70-1.11)	1.10 (0.97-1.24)	0.93 (0.79-1.10)
≥ 120 DDD	1.25 (0.89-1.74)	1.10 (0.74-1.63)	0.96 (0.78-1.17)	0.80 (0.61-1.07)	0.75 (0.62-0.91)	0.68 (0.54-0.84)	0.74 (0.67-0.83)	0.60 (0.51-0.70)
Cumulative duration								
≤1 year	1.08 (0.79-1.47)	0.98 (0.68-1.42)	1.02 (0.83-1.24)	0.87 (0.65-1.15)	0.87 (0.74-1.02)	0.82 (0.68-0.99)	0.96 (0.87-1.07)	0.80 (0.69-0.93)
1-2 years	1.05 (0.60-1.86)	0.85 (0.45-1.61)	0.95 (0.68-1.31)	0.83 (0.56-1.22)	0.82 (0.59-1.14)	0.76 (0.53-1.08)	0.83 (0.70-0.98)	0.64 (0.52-0.79)
2-3 years	1.26 (0.54-2.94)	1.16 (0.44-3.06)	0.93 (0.60-1.44)	0.81 (0.49-1.35)	0.59 (0.35-1.00)	0.51 (0.28-0.91)	0.66 (0.51-0.85)	0.51 (0.38-0.69)
≥3 years	1.93 (0.53-6.99)	1.70 (0.40-7.26)	1.13 (0.66-1.95)	0.83 (0.45-1.53)	0.38 (0.17-0.82)	0.30 (0.13-0.68)	0.64 (0.47-0.87)	0.63 (0.45-0.90)

*Multivariate model with stepwise selection of covariates, including pioglitazone, rosiglitazone, short-acting human insulin, metformin (mean daily dosage in quartiles), sulfonylurea (mean daily dosage in quartiles), number of oral antidiabetic agents, statins, aspirin, beta-blockers, chronic kidney disease, glinides, nephropathy, cerebrovascular disease, calcium channel blockers, cardiovascular disease, chronic lung disease.

antiviral therapy and interferon-α in the treatment of chronic hepatitis, aiming to stop the progression to cirrhosis and hepatocellular carcinoma.[38-40] TZDs may be considered a new component in the combination therapy because the protective effect is most prominent in the patients with chronic liver disease.

The present study also demonstrated that use of insulin, sulfonylurea, and glinides also increased the risk of cancer. The finding that both insulin and oral insulin secretagogues confer an increased risk suggests that an increasing insulin level plays an important role in carcinogenesis.[41] Insulin sensitizers (metformin and TZDs) do not increase insulin concentrations and, theoretically, may not influence the risk of cancer occurrence. The finding that metformin was associated with a decreased risk for liver cancer was comparable to the results in previous reports.[42] Further studies are warranted to elucidate the potential role of metformin to reduce the cancer risk among diabetic patients.

The strength of the current study includes that, on a national scale, there are far more cancer cases compared to previous epidemiological studies. As rosiglitazone and pioglitazone entered Taiwan's market in 2000 and 2001, respectively, diabetic patients in this study were all new-users to these two drugs and hence allowed us to capture all cancer occurrences following TZD treatment initiation.[43] Furthermore, this case-control study was designed to be nested within a clearly defined diabetic cohort. Each diabetic patient was followed from cohort entry (date of diabetes diagnosis for newly diagnosed patients and January 1 2000 for prevalent diabetes) to the earliest of cancer diagnosis, death, or December 31 2007. The cumulative dosage of TZDs and other antidiabetic therapy during the follow-up period was calculated and drug exposure experiences were compared between cancer cases and controls selected by risk-set sampling matched on age, sex, and follow-up time. This analysis accounted for the individual and time-varying nature of different glucose-lowering treatments and eliminated the bias introduced by defining treatment groups based on follow-up information.

There are also limitations in this study. First, we did not have the information of lifestyle risk factors or family history of cancer; there might be residual confounding by duration or severity of diabetes, as well as by obesity, smoking, and physical inactivity. Due to lack of data about patients' level of glycemic control, we could not examine whether a better glucose-lowering effect by TZDs as compared with nonuse may explain the association with a reduced cancer risk. Second, as our average cumulative treatment duration of

Table 5. Risk of Colorectal Cancer Associated With Pioglitazone or Rosiglitazone Use in Type 2 Diabetic Patients

	Pioglitazone				Rosiglitazone			
	Number of Cases	Number of Controls	Crude Odds Ratio	Adjusted* Odds Ratio	Number of Cases	Number of Controls	Crude Odds Ratio	Adjusted* Odds Ratio
Nonuse	6,822	27,250	Reference	Reference	6,127	26,267	Reference	Reference
Any use	378	1,462	1.03 (0.92-1.17)	1.04 (0.91-1.20)	1,073	4,445	0.95 (0.88-1.03)	0.86 (0.76-0.96)
Cumulative dosage								
$<$ 120 DDD	170	592	1.15 (0.96-1.37)	1.15 (0.95-1.39)	434	1,785	0.96 (0.86-1.07)	0.89 (0.77-1.03)
$\geq$ 120 DDD	280	870	0.96 (0.82-1.12)	0.97 (0.82-1.16)	639	2,660	0.94 (0.86-1.04)	0.83 (0.73-0.95)
Cumulative duration								
$\leq$1 year	278	981	1.13 (0.99-1.30)	1.15 (0.98-1.34)	678	2,671	0.99 (0.91-1.09)	0.91 (0.80-1.04)
1-2 years	60	267	0.90 (0.68-1.19)	0.82 (0.61-1.11)	220	950	0.91 (0.78-1.05)	0.78 (0.65-0.94)
2-3 years	26	133	0.79 (0.51-1.20)	0.86 (0.55-1.33)	99	476	0.81 (0.65-1.02)	0.69 (0.54-0.88)
$\geq$3 years	14	81	0.69 (0.39-1.22)	0.77 (0.43-1.39)	76	328	0.91 (0.70-1.17)	0.83 (0.63-1.10)

*Multivariate model with stepwise selection of covariates, including pioglitazone, rosiglitazone, short-acting human insulin, metformin (mean daily dosage in quartiles), sulfonylurea (mean daily dosage in quartiles), number of oral antidiabetic agents, glinides, nephropathy, neuropathy, chronic liver disease, statins, retinopathy, calcium channel blockers, ACE inhibitors, peripheral vascular disease, depression, beta-blockers, aspirin, chronic kidney disease, chronic lung disease, cerebrovascular disease.

TZDs was relatively short, we were not able to examine the long-term effect of TZDs on cancer occurrence. Third, we observed differential associations between pioglitazone and rosiglitazone with specific sites of cancer. Despite numerous *in vitro* and animal studies support the protective effects of TZDs, we are not able to identify the exact underlying physiological pathways that result in a reduced cancer risk and that differentiate pioglitazone and rosiglitazone. Fourth, one of the most recent studies included 193,099 patients in the Kaiser Permanente Northern California diabetes registry who were $\geq$40 years of age demonstrated that short-term use of pioglitazone was not associated with an increased incidence of bladder cancer (hazard ratio [HR] 1.2, 95% CI 0.9-1.5), but use for more than 2 years was weakly associated with increased risk (HR: 1.4, 95% CI: 1.03-2.0). Our results did not show a significant association despite a tendency to an increased risk. Due to the limited case number in bladder cancer, we could not exclude the possibility that a prolonged use of pioglitazone might potentially increase the risk for bladder cancer.[44] Fifth, PPAR-γ is one member of the nuclear receptor superfamily that contains in excess of 80 described receptors. Once activated, PPAR-γ will preferentially bind with retinoid X receptor α and signal antiproliferative, antiangiogenic, and prodifferentiation pathways in several tissue types, thus making it a highly useful target for down-regulation of carcinogenesis.[13] Rosiglitazone has PPAR-γ activity but pioglitazone has both PPAR-α and PPAR-γ activities. The mediation of cancer initiation and progression through dependent and independent pathways may also differ between rosiglitazone and pioglitazone.[45] The differential selectivity in activating PPAR signaling pathways might explain the cancer risk of different sites, but the true mechanisms remain to be clarified. Finally, TZDs are contraindicated in patients with congestive heart failure.[46] Pioglitazone and rosiglitazone show different cardiovascular safety profiles.[15,47-50] We are not sure whether the reduced cancer risk could compensate for the potentially increased cardiovascular risk. The overall risks and benefits of TZD should be evaluated.

In conclusion, the results of this study show that both pioglitazone and rosiglitazone reduce the risk of incident liver cancer in type 2 diabetic patients. There is a better protection against cancer occurrence associated with a longer use and higher doses of TZDs. The association with individual sites of specific cancer differs between pioglitazone and rosiglitazone and the underlying mechanisms merit further investigations.

Acknowledgment: The corresponding authors have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chang C.H., Lin J.W.; Acquisition of data: Lai M.S.; Analysis and interpretation of data: Chang C.H., Lin J.W.; Drafting of the article: Lin J.W., Chang C.H.; Critical revision of the article for important intellectual content: Chuang L.M., Chan K.A.; Statistical analysis: Wu L.C.; Obtained funding: Lai M.S.; Study supervision: Lai M.S.

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