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A population-based cohort study in Taiwan—use of insulin sensitizers can decrease cancer risk in diabetic patients?

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Background: The purpose of the study was to explore the possible association between the use of insulin sensitizers (thiazolidinediones, TZDs) and the risk of cancer in Taiwanese diabetic patients.

Patients and Methods: From the National Health Insurance Research Database (NHIRD) of Taiwan, we identified 22 910 diabetic patients newly diagnosed from 2001 to 2009 and 91 636 non-diabetic comparisons frequency matched with age, sex, and calendar year, excluding those with cancer at the baseline. Among the diabetics, 4159 patients were treated with TZDs and the rest of 18 752 patients were on other anti-diabetic medications (non-TZDs).

Results: In comparison to the non-diabetes group, the non-TZDs group had an increased risk of developing cancer [the adjusted hazard ratio (HR): 1.20 and 95% confidence interval (CI) = 1.11–1.30]. The TZDs group had a HR of 1.18 (95% CI = 0.98–1.42). Analysis of site-specific cancer risks showed that both TZDs and non-TZDs groups with elevated risks of colorectal and pancreatic cancer. However, the non-TZDs group had an increased risk of liver cancer when comparing with TZD and non-diabetes groups.

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Conclusion: This study suggests that patients with diabetes are at an elevated risk of cancer (especially in colorectal and pancreatic cancers), and the use of TZDs might decrease the liver cancer risk in diabetic patients. Further investigation using large samples and rigorous methodology is warranted.
Key words: cancer, population-based cohort study, thiazolidinediones

introduction

Thiazolidinediones (TZDs) are insulin sensitizers that bind and activate peroxisome proliferator-activated receptors gamma (PPARγ), a nuclear hormone receptor [1, 2] Conflicting results have been reported regarding the relationship between TZDs' use and subsequent cancer risk. A number of studies have found that TZDs modulate several cancer cell lines and probably inhibit tumor growth, progression, differentiation, and metastasis [3–5]. In contrast, an earlier study suggested a possible association between development of cancer and the use of TZDs, particularly rosiglitazone [6]. Experimental studies have revealed a link between pioglitazone and rat bladder cancer [7]. A subsequent PROactive (prospective pioglitazone clinical trial in macro-vascular events) study similarly detected more human bladder cancer cases than expected in the pioglitazone group [8]. The US Food and Drug Administration was concerned with these results, and in September 2010 announced an ongoing investigation into the possible risk of TZDs in humans. Recent research into reports of adverse events related to drug use also found a definite signal for bladder cancer associated with pioglitazone [9].

TZDs are currently widely used as oral agents for the treatment of type 2 diabetes. Thus, even a small magnitude of hazard could have important clinical implications, and such findings may hold interest for the general public as well as the medical profession. A population-based, large-scale study may help clarify this controversy. Therefore, we explored the issue using the database from the National Health Insurance (NHI) system of Taiwan.

patients and methods

data source

We obtained data on reimbursement claims from the Taiwanese NHI system, a mandatory health care plan that has provided affordable healthcare to all residents since March 1995. Since 2007, this system has covered >99% of the population. The NHI contracts with >90% of hospitals and clinics in Taiwan, and provides comprehensive medical services including outpatient and inpatient care, dental care, physical therapy, preventive care, and prescriptions. The National Health Research Institute is responsible for administering the NHI Research Database (NHIRD), which includes numerous randomly selected claims that are representative of the entire population, and which is used for administrative purposes and research. The data we used were a sub-dataset composed of one million randomly selected subjects (~5% of the entire population), drawn from the larger pool of all enrollees registered with the NHI from 1996 to 2009. The details of this population-based cohort database have been published previously [10]. Diagnoses were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

study sample

We identified patients who were ≥20 years of age with newly diagnosed type 2 diabetes (ICD-9-CM code 250.xx) and who were treated with anti-diabetic agents between 2001 and 2009, excluding the subjects with potential type 1 diabetes (code numbers 250.x1 and 250.x3). Subjects with cancer (code numbers 140.xx-208.xx) diagnosed before their date of diabetes diagnosis were further excluded, leaving 22 910 diabetic patients for data analysis. For patients with diabetes, the potential comparison subjects were persons with the same sex and birth year who had never been diagnosed with diabetes and cancer before the year of diagnosis of their matched diabetic counterparts. To identify the comparison group, we stratified the one million NHI beneficiaries using the distribution of birth year, sex, and calendar year of diabetes diagnosis among the diabetes patients. Within the strata, the comparison subjects were randomly selected in a 4:1 ratio to diabetic patients.

Among the diabetic subjects, those who have been prescribed for rosiglitazone and pioglitazone before the study's end date formed the TZDs group; all others were included in the non-TZDs group.

statistical analysis

We compared the event-free probabilities for cancer among the TZDs, non-TZDs and the non-diabetic comparison groups using Kaplan–Meier survival curves constructed using the current age as the time scale. The differences between these groups were tested using the log-rank test. The incidence density of cancer was calculated by using the number of cancer cases as the nominator and follow-up person-years as the denominator. Multivariable Cox proportional hazards models with the current age as the time scale and adjusted for sex were carried out to assess the association between anti-diabetic medications and the risk of developing cancer, quantified as hazard ratios (HRs) with 95% confidence intervals (CI). For the diabetic group, the entry time of this study was age at the first prescription of anti-diabetic drugs, and the follow-up ended at the age of diagnosis of malignant cancer (ICD-9-CM codes 140.xx-208.xx, the observed end-point of this study), withdrawal from NHI program, or the termination of this study on 31 December 2009, whichever came first. For subjects in the TZDs group previously treated with other anti-diabetic drugs, the follow-up duration before initiation of TZDs treatments was included in the non-TZDs group. For the non-diabetic comparison group, the entry time was age at the same year of diagnosis of their matched diabetic counterparts. The definition of the end of follow-up was the same as that applied to the diabetic group, but for the comparison subjects later diagnosed with diabetes, the follow-up ended at the age of diabetes diagnosis. Two sets of Cox regression analyses were carried out. One was to estimate the cancer risk for TZDs and non-TZDs groups, respectively, using the non-diabetic comparison group as the reference group. The other estimated the risk for the TZDs group relative to the non-TZDs group.

We also evaluated the dose–response relationship between TZDs and the risk of cancer. The dosage of TZDs was classified by the tertile of average prescription dose per year, which were at levels of <0.69 g, 0.69–5.29 g, and >5.29 g. Further Cox regression analysis was carried out by stratifying time since the initiation of treatments in order to evaluate whether the risk of cancer associated with TZDs and other anti-diabetic drugs differed over time.

All analyses were carried out using SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, North Carolina), and the significance level was set to 0.05.

results

Among the 22 910 subjects with diabetes, 4158 patients had been treated with TZDs (Table 1). More than half of the diabetic patients were men (55.1%) and aged between 45 and 64 years (54.2%). The frequency distribution of age and sex was the same between the diabetic group and the comparison group after matching. However, patients in the TZDs group were younger than those in the non-TZDs group with the mean age of 54.2 years versus 57.0 years.

During the follow-up period, 2952 patients in the comparison group, 781 in the non-TZDs group and 119 in the TZDs group had been diagnosed with cancer (Table 2). The Kaplan–Meier curves of cumulative event-free probability by age of cancer were similar among the non-TZDs, TZDs, and the comparison groups before 60 years of age (Figure 1). After that, the event-free probability was higher in the non-diabetic comparison group and the TZDs group than in the non-TZDs group after 80 years of age (log-rank test among the three groups, $P < 0.001$).

Compared with the non-diabetes group, the diabetes group had an increased risk of developing cancer (adjusted HR = 1.20; 95% CI = 1.11–1.29) (Table 2). The adjusted HR was 1.20 (95% CI = 1.11–1.30) for the non-TZDs group and 1.18 (95% CI = 0.98–1.42) for the TZDs group. The elevated risks of cancer in the non-TZDs group, relative to the comparison group, were observed in all the subgroups of age, except those ≥75 years of age at their first prescriptions. The risk of cancer associated with the TZDs group was greater among patients starting their prescription at 45–54 years of age (adjusted HR = 1.62, 95% CI = 1.16–2.27). The adjusted HR was at the same strength for patients aged <45 years at their first prescription but not statistically significant (95% CI = 0.88–2.99). A statistically non-significant decrease in the risk in the TZDs group was observed among subjects whose first prescription was at ≥75 years of age. (HR = 0.75, 95% CI = 0.37–1.51). No significant association was observed in the analysis comparing the risk of cancer in the TZDs with the non-TZDs group.

Site-specific cancer risks are presented in Table 3. When using the non-diabetes comparison group as a reference group, the risks were substantially increased in the non-TZDs diabetes group for colorectal cancer (HR = 1.27), liver cancer (HR = 1.79), and pancreatic cancer (HR = 2.78). In the TZDs group, the risks increased for colorectal cancer (HR = 1.82), pancreatic cancer (HR = 5.45), and lymphoma (HR = 2.50). Among the diabetic patients, no significant findings were observed for the risk of cancer in the TZDs group relative to the non-TZDs group, but a marginally lower risk of liver cancer was found in the TZDs group.

Analysis of the TZD dose showed that compared with the non-diabetes comparison group, the risk of cancer increased in the TZDs group prescribed for the lowest dosage (<0.69 g/year) (HR = 1.40; 95% CI = 1.09–1.80), but decreased to null for other TZD dosage, suggesting no dose–response trend on the risk of cancer (Table 4). Similar results were observed when we used non-TZDs diabetic patients as a reference group. Stratified analysis by time since the first prescription showed that the risks of cancer in both the non-TZDs and TZDs groups were the greatest within 1 year after initiation of prescription, when compared with the comparison group (supplementary Table S5, available at *Annals of Oncology* online).

discussion

The results from this population-based cohort study indicated that diabetic patients had a significant increase in the overall cancer risk, especially for patients not using TZDs. The risk depends on the cancer site. TZD users had significantly higher risks of colorectal, pancreatic cancers, and lymphoma. Non-TZD users had significantly higher risks of colorectal, liver,

Table 1. Baseline characteristics of the diabetes group and the comparison group

Variables	Diabetes						Comparison group N = 91 636	
	Non-thiazolidinediones (TZDs) N = 18 752		TZDs N = 4158		All N = 22 910			
	n	%	n	%	n	%	n	%
Sex								
Men	10 313	55.0	2303	55.4	12 616	55.1	50 462	55.1
Women	8439	45.0	1855	44.6	10 294	44.9	41 174	44.9
Age, years								
<45	3435	18.3	921	22.2	4356	19.0	17503	19.1
45–54	5286	28.2	1370	33.0	6656	29.1	26 667	29.1
55–64	4686	24.5	1068	25.7	5754	25.1	22 986	25.1
65–74	3428	18.3	593	14.3	4 021	17.6	15 991	17.5
≥75	1917	10.2	206	4.95	2123	9.27	8489	9.26
Mean (SD)[a]	57.0	(13.3)	54.2	(12.0)	56.5	(13.2)	56.5	(13.2)

Chi-square test.

[a]t-test.

Table 2. Incidence rate of and hazard ratios (HRs) for cancer, stratified by age at first prescription

Age at the first prescription, years	No. of cancer cases	Incidence[a]	HR (95% CI)	HR (95% CI) compared with the non- thiazolidinediones (TZDs) group
All				
Comparison group	2952	8.04	1.00 (reference)	
Diabetes				
All	900	9.60	1.20 (1.11–1.29)***	
Non-TZDs	781	9.66	1.20 (1.11–1.30)***	1.00 (reference)
TZDs	119	9.23	1.18 (0.98–1.42)	0.98 (0.81–1.19)
<45 years				
Comparison group	165	2.19	1.00 (reference)	
Diabetes				
All	59	3.12	1.42 (1.05–1.91)*	
Non-TZDs	48	2.99	1.38 (1.00–1.90)	1.00 (reference)
TZDs	11	3.89	1.62 (0.88–2.99)	1.21 (0.63–2.34)
45–54 years				
Comparison group	543	49.33	1.00 (reference)	
Diabetes				
All	189	6.70	1.35 (1.15–1.60)***	
Non-TZDs	153	6.39	1.30 (1.09–1.56)**	1.00 (reference)
TZDs	36	8.47	1.62 (1.16–2.27)**	1.30 (0.90–1.87)
55–64 years				
Comparison group	789	8.76	1.00 (reference)	
Diabetes				
All	239	10.12	1.15 (1.00–1.33)	
Non-TZDs	210	10.34	1.19 (1.03–1.39)*	1.00 (reference)
TZDs	29	8.75	0.93 (0.64–1.35)	0.80 (0.54–1.18)
65–74 years				
Comparison group	947	14.92	1.00 (reference)	
Diabetes				
All	285	17.37	1.16 (1.02–1.33)*	
Non-TZDs	250	17.23	1.16 (1.01–1.34)*	1.00 (reference)
TZDs	35	18.40	1.18 (0.84–1.65)	1.03 (0.73–1.47)
≥75 years				
Comparison group	508	17.93	1.00 (reference)	
Diabetes				
All	128	19.36	1.08 (0.89–1.31)	
Non-TZDs	120	19.94	1.12 (0.91–1.36)	1.00 (reference)
TZDs	8	13.47	0.75 (0.37–1.51)	0.68 (0.33–1.40)

Adjusted for sex.
[a]Per 1000 person-years.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

and pancreatic cancers. For patients with diabetes, the use of TZDs decreased the risk of liver cancer with a marginal statistical significance.

Cancer has been the leading cause of death in Taiwan since 1982. The age-adjusted incidence rate has increased steadily since then, and in 2007, 270 new cases per 100 000 individuals were reported in the general population [11]. This trend differs from that of the United States, where data from Surveillance Epidemiology and End Results showed that the overall cancer incidence rate decreased by 0.7% per year between 1999 and 2006 [12]. Because cancer continues to be a challenge for public health in Taiwan, it has come to the attention of the government, resulting in population-based investigations regarding cancer-preventive epidemiology. The NHI program provides comprehensive health care coverage, and the NHIRD contains data on ambulatory service records, hospital service records, and prescription claims. This database enabled us to select patients for study who were representative of the underlying population. Previously, we used the data to evaluate the risk of malignancy for patients with end-stage renal disease, and uncovered a number of positive findings, which have been published [13]. The current study used a similar design in an attempt to determine whether the use of TZDs is associated with the risk of cancer.

The factors affecting cancer incidence in the diabetic population are diverse and complex. Epidemiologic evidence suggests that the risk of cancer is increased in diabetic patients [14, 15]. Type 2 diabetes and cancer are well-known to share many risk factors. However, most observational studies have not examined the potential association between anti-diabetic medication use and cancer risk. Evidence from some observational studies suggests that some medications used to treat hyperglycemia are associated with either an increased or reduced risk of cancer [14]. To our knowledge, this was the first population-based study conducted in Taiwan to compare cancer rates among diabetic patients who were either using TZDs or those who were not. The data of large samples of TZD users (4158 patients) and non-TZD users (18 752 patients) among the type 2 diabetic patients were compared. To create a comparison group, we randomly matched each patient with four persons from the general population without diabetes, based on the demographic variables (year birthday, sex, and index year).

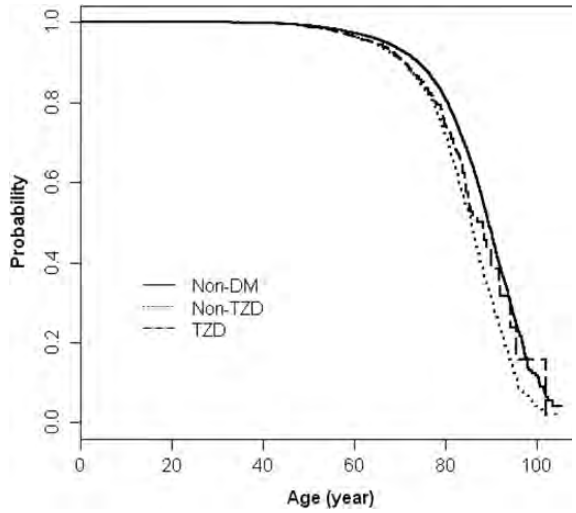

Figure 1. Kaplan–Meier curves of cumulative event-free probability for cancer among subjects in the non-thiazolidinediones (TZDs), TZDs, and the comparison groups ($P < 0.001$).

Using the non-diabetes comparison group as a reference, our data revealed that the risk of cancer for diabetic patients (TZDs + non-TZDs) was significantly higher than for the non-diabetes cohort by a 20% difference. The risks in the TZDs group and the non-TZDs group were of similar strength. However, the HRs were statistically significant in the non-TZDs group but not in the TZDs group possibly because of a relatively small sample size of the TZDs group. We thought that diabetes itself rather than anti-diabetic medications should be accounting for the risk of cancer. In contrast, studies have indicated that TZDs inhibit tumor growth, progression, and metastasis in numerous types of cancer by activating individual PPARγ, and may potentially play a chemopreventive role [3, 4, 16]. Although PPARγ activators show anticancer effects on cell lines, testing in human clinical trials with advanced cancer

Table 3. Site-specific cancer incident number and hazard ratios (HRs) for diabetes groups

	Comparison group	Compared with the comparison group				Compared with Non-thiazolidinediones (TZDs) group in diabetes patients
		Non-TZDs		TZDs		
	Event	Event	HR (95% CI)	Event	HR (95% CI)	HR (95% CI)
Oral cancer	184	50	1.23 (0.90–1.68)	5	0.76 (0.31–1.84)	0.61 (0.24–1.52)
Stomach cancer	163	34	0.95 (0.66–1.37)	2	0.37 (0.09–1.50)	0.39 (0.09–1.60)
Colorectal cancer	440	123	1.27 (1.04–1.55)*	27	1.82 (1.23–2.69)**	1.44 (0.95–2.18)
Liver cancer	379	150	1.79 (1.48–2.17)***	15	1.14 (0.68–1.19)	0.62 (0.37–1.06)
Lung cancer	412	82	0.90 (0.71–1.14)	14	1.01 (0.59–1.72)	1.11 (0.63–1.95)
Breast cancer[a]	237	53	1.01 (0.75–1.36)	10	1.16 (0.62–2.19)	1.16 (0.59–2.28)
Cervical cancer[a]	67	22	1.48 (0.91–2.40)	1	0.44 (0.06–3.14)	0.30 (0.04–2.22)
Gallbladder cancer	48	15	1.41 (0.79–2.52)	2	1.24 (0.30–5.10)	0.84 (0.19–3.69)
Pancreatic cancer	51	31	2.78 (1.78–4.34)***	9	5.45 (2.68–11.1)***	1.90 (0.90–3.99)
Prostate cancer[b]	170	33	0.79 (0.50–1.25)	4	1.17 (0.48–2.87)	0.86 (0.30–2.42)
Bladder cancer	126	22	0.89 (0.61–1.29)	5	0.74 (0.27–1.99)	1.48 (0.56–3.92)
Kidney cancer	91	20	0.99 (0.61–1.61)	1	0.32 (0.04–2.27)	0.32 (0.04–2.41)
Lymphoma	63	14	1.02 (0.57–1.81)	5	2.50 (1.00–6.22)*	2.55 (0.92–7.10)
Other cancers	521	132	1.15 (0.95–1.39)	19	1.05 (0.67–1.66)	0.92 (0.57–1.48)

Adjusted for sex.

ICD-9-CM: oral cancer, 140.xx, 141.xx, 143.xx–146.xx and 148.xx–149.xx; stomach cancer, 151.xx;colorectal cancer, 153.xx and 154.xx; liver cancer, 155.xx; lung cancer, 162.xx; breast cancer, 174.xx; cervical cancer, 180.xx; gallbladder cancer, 156.xx; pancreatic cancer, 157.xx; prostate cancer, 185.xx; bladder cancer, 188.xx; kidney cancer, 189.xx; lymphoma, 202.xx;

[a]For women.

[b]For men.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

Table 4. Hazard ratios (HRs) for incidence of cancer in relation to dosage of thiazolidinediones (TZDs) prescriptions

TZDs dosage (g/year)	*N*	Case	Incidence[a]	HR (95% CI)	HR (95% CI)
Compared group	91 636	2952	8.04	1.00 (reference)	
DM group					
Non-TZDs group	22 291	781	9.66	1.20 (1.11–1.30)***	1.00 (reference)
TZDs group (g/year)					
<0.69	1337	62	11.8	1.40 (1.09–1.80)**	1.17 (0.90–1.52)
0.69–5.29	1445	34	7.49	0.98 (0.70–1.37)	0.81 (0.57–1.14)
≥5.30	1376	23	7.44	1.06 (0.70–1.60)	0.86 (0.57–1.31)

Adjusted for sex.
[a]Per 1000 person-years.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

patients has met with limited success [17]. If we focused on the diabetes group patients, we found that TZDs' use reduced overall cancer risk only by 2% compared with non-TZDs' use. With regard to the age difference, the figure revealed some specific patterns and implied that a higher cancer risk can be expected for diabetic patients >60 years of age compared with non-diabetic subjects, and a lower cancer risk can be expected in the TZDs group than in the non-TZDs group after 80 years of age.

For site-specific cancer risk, our study showed that non-TZDs diabetic patients were at a significantly higher risk of colorectal, liver, and pancreatic cancers. For diabetic patients using TZDs, the risk of colorectal and pancreatic cancers and lymphoma was significantly higher. It is compatible with earlier studies, which found that diabetes is a risk factor for colorectal, liver, and pancreatic cancers, as well as lymphoma [14, 15, 18, 19]. PPARγ indeed has many faces and is well known for its role in the cellular proliferation [20]. Activation of individual PPARγ has been implicated in breast, cervical, colon, prostate, and lung cancers [3, 16, 17]. Once activated, PPARγ preferentially binds with retinoid X receptor α and signal antiproliferative, antiangiogenic, and prodifferentiation pathways in these cell types, thus making PPARγ a highly useful target for down-regulation of carcinogenesis [21, 22]. Our results did not reveal any chemopreventive effect by TZDs in these cancers, and the shared risk factors for cancer and diabetes may counteract its effect. On the other hand, earlier investigators found that TZDs promote growth in colon tumors with mutations in the APC gene [23, 24]. Furthermore, the published trials on TZDs demonstrate that they produce substantial body weight gain [25, 26], which consequently increases the risk of cancer of the breast, colon, prostate, endometrium, and kidney [27]. This factor may also offset the effect of chemopreventive role of TZDs on colon and prostate cancers, as shown by our results.

Recent studies on TZDs, particularly pioglitazone, have shown that the medication may increase bladder cancer risk, as evidenced by a higher-than-expected frequency of bladder cancer among pioglitazone users [9, 28, 29]. However, the current findings did not confirm this pattern, and are consistent with the report from Tseng [30].

When we focused on the diabetic patients, for those taking anti-diabetic drugs other than TZDs, our study revealed no significant difference in the overall cancer risk when compared with the TZDs group, but a marginally significantly higher risk of liver cancer in the non-TZDs group. The findings may support the potential chemopreventive effect of TZDs on liver development of cancer in diabetic patients, which has been suggested by Chang et al. [31]. Evidence from *in vivo* studies has also shown that TZDs inhibit tumor formation in the liver [32], providing a plausible biological basis for these findings.

For the dose–response relationship, Table 4 shows that the TZDs group significantly increased overall cancer risk at the lowest dose level when compared with non-diabetic subjects. It suggests that longer than 1-year medication of TZDs is preferred when development of cancer is concerned in diabetic patients. For the treatment duration, our data revealed that the significantly higher risk was only observed among patients taking TZDs or non-TZDs <1 year, or taking non-TZDs between 5 and 6 years. One study from Taiwan found that diabetes <2-year duration is associated with pancreatic cancer and long-standing diabetes was not a risk factor for pancreatic cancer [33], and our findings are partially compatible with this.

The study was subject to some limitations, which must be mentioned. First, the NHIRD does not provide detailed information on patients such as their smoking habits, alcohol consumption, body mass index (BMI), physical activity, socioeconomic status, and family history of cancer. All of these are major risk factors for numerous cancers, and could plausibly be associated with diabetes and anti-diabetic medications (either TZDs or non-TZDs). An earlier epidemiologic study of type 2 diabetes in Taiwan also showed that BMI, physical activity, and cigarette smoking were possible risk factors for newly diagnosed diabetes [34]. These shared risk factors for cancer and diabetes can induce the higher cancer incidence for TZDs and non-TZDs groups at the baseline, which may hinder the possible chemopreventive effect of cancer for TZDs. However, we still got some significantly different results between TZDs and non-TZDs groups in diabetic patients. Second, the evidence derived from a cohort study is generally of a lower methodological quality than that from randomized trials because a cohort study design is subject

to many biases related to adjustment for confounds. Despite our meticulous study design with adequate control of confounding factors, a key limitation was that bias could still remain because of possible unmeasured or unknown confounders (e.g. the difference in the stage of the disease or in risk factors between TZD users and non-TZD users). Third, the diagnoses in NHI claims primarily serve the purpose of administrative billing, and do not undergo verification for scientific purposes. We were unable to contact the patients directly to obtain more information on their use of TZDs because of the anonymity assured by the identification numbers. Furthermore, prescriptions for the study drugs issued before 1996 were excluded from our analysis. This omission could have resulted in the underestimation of the cumulative dosage and may have weakened the observed association. However, the data that we obtained on TZDs prescriptions and cancer diagnoses were highly reliable. Last, the small number of cancers in the TZD group, particularly in the analysis stratified by age and on the incidence of cancer at different sites, suggests cautious interpretation of the results of the study. Failure to find an association for types of cancer may be due to the small number of cancer cases.

In conclusion, this population-based retrospective cohort study found that diabetes is significantly associated with an increase in the risk for overall cancer incidence, and TZDs or non-TZDs correlated with the increased risks for some sites of cancer. However, the use of TZDs is probably associated with a decreased incidence of liver cancer risk in diabetic patients. These findings may be partially explained by a biologically plausible link between type 2 diabetes and cancer outcomes, as well as some plausibly pharmacologic mechanisms. However, underlying mechanisms must still be explored and identified. Additional large population-based unbiased studies are required, and it would be essential to confirm our current findings before drawing any firm conclusions.

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disclosures

The authors have declared no conflicts of interest.

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Cutaneous effects of BRAF inhibitor therapy: a case series

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Background: The cutaneous effects of rapidly accelerated fibrosarcoma kinase B (BRAF) inhibitors are not well understood. Squamous cell carcinoma (SCC), keratoacanthoma, and photosensitivity have been described in patients taking BRAF inhibitors.
Patients and methods: To characterize the timing and frequency of skin lesions in patients receiving BRAF inhibitor therapy, we utilized a retrospective case review of 53 patients undergoing treatment with BRAF inhibitors for 4–92 weeks of therapy. Patients were evaluated at baseline, and then followed at 4- to 12-week intervals. Charts were retrospectively reviewed, and the morphology and timing of cutaneous events were recorded.
Results: Thirty-three of the 53 charts met exclusion/inclusion criteria, 15 were treated with vemurafenib, and 18 were treated with GSK 2118436/GSK 1120212. Of 33 patients treated with BRAF inhibitor, 13 developed photosensitivity (39.4%), 10 developed actinic keratoses (30.3%), 10 developed warts (30.3%), and 6 developed SCC (18.2%).
Conclusions: Multiple cutaneous findings were observed in the 33 patients taking BRAF inhibitors. The previously described association with SCC and photosensitivity was observed in these patients as well. Over half of the observed SCCs were invasive in nature. Photosensitivity continues to be frequent with BRAF inhibitors. Patients taking BRAF inhibitors should have regular full body skin exams. Further studies are necessary to better elucidate the rates of these adverse cutaneous effects.
Key words: BRAF inhibitor, cutaneous squamous cell carcinoma, MEK inhibitor, photosensitivity, side effects

introduction

The inhibition of rapidly accelerated fibrosarcoma kinase B (BRAF), a serine/threonine-protein kinase in the RAS pathway of cell proliferation, was identified about a decade ago as a fruitful target for cancer treatment. With the finding by the Sanger institute that 59% of melanoma cell lines and 67% of melanoma clinical specimens harbored BRAF mutation [1], and the subsequent discovery that this mutation was seen in 50% of metastatic melanoma [2], the race was on to harness this discovery for clinical utility. As it turned out, 90% of BRAF mutant melanomas involve a glutamic acid to valine substitution at position 600 (V600E) [3], which results in sustained activation of the mitogen-activated protein kinase (MAPK) pathway in the absence of any growth factor signal. This finding allowed the development of targeted therapy towards this specific mutation, and the recent development of BRAF-targeted agents for the treatment of advanced melanoma has produced unprecedented response rates in several clinical trials. Figures 1 and 2, respectively, illustrate

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