Association of hepatocellular carcinoma with thiazolidinediones use
A population-based case-control study
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Abstract
The study aimed to investigate the association between the risk of hepatocellular carcinoma and thiazolidinediones use among type 2 diabetic patients who had risk factors for hepatocellular carcinoma.

A population-based case-control study was performed using the database of the Taiwan National Health Insurance Program. The cases consisted of 23580 type 2 diabetic subjects aged 20 to 84 years with newly diagnosed hepatocellular carcinoma between 2000 and 2011. The sex- and age-matched controls consisted of 23580 randomly selected type 2 diabetic subjects without hepatocellular carcinoma between 2000 and 2011. Ever use of thiazolidinediones was defined as subjects who had at least 1 prescription of thiazolidinediones before the index date. Never use of thiazolidinediones was defined as subjects who did not have a prescription of thiazolidinediones before the index date. The odds ratio and 95% confidence interval for the association between hepatocellular carcinoma and cumulative duration of thiazolidinediones use was measured by a multivariable logistic regression model.

Among subjects with any 1 of the comorbidities including alcohol-related disease, cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis, a multivariable logistic regression model demonstrated that there was a negative association between hepatocellular carcinoma and every 1-year increase of cumulative duration of thiazolidinediones use (adjusted odds ratio 0.94, 95% confidence interval 0.92–0.97).

There was a negative association in a duration-dependent manner between the risk of hepatocellular carcinoma and thiazolidinediones use among type 2 diabetic patients who had risk factors for hepatocellular carcinoma.

Abbreviation: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: case-control study, hepatocellular carcinoma, thiazolidinediones

1. Introduction
Thiazolidinediones are commonly used to treat patients with type 2 diabetes mellitus.\cite{1} Current evidence shows that insulin-like growth factor-1 (IGF-1) signaling is aberrantly regulated in numerous cancers.\cite{2} Thiazolidinediones can appropriately regulate IGF-1 receptor signaling,\cite{2,3} and therefore anti-cancer effects of thiazolidinediones are at least partially mediated by regulation of IGF-1 receptor signaling.\cite{3} Epidemiological studies have demonstrated that thiazolidinediones use is associated with reduced risk of various cancers, including hepatocellular carcinoma, colorectal cancer, and breast cancer,\cite{4–8} but a modestly increased risk of bladder cancer associated with pioglitazone use (a thiazolidinedione) was found.\cite{9–11}

In Taiwan, hepatocellular carcinoma was the second leading cause of cancer-related death in 2018.\cite{12} Hepatitis B infection, hepatitis C infection, heavy alcohol consumption and diabetes mellitus are significantly associated with increased risk for hepatocellular carcinoma in Taiwan.\cite{13–15} In the absence of these risk factors, it is less likely to develop hepatocellular carcinoma in Taiwan. In view of previous studies only focusing on patients with type 2 diabetes mellitus, we conducted a population-based case-control study to investigate whether there was an association between the risk of hepatocellular carcinoma and thiazolidinediones use among type 2 diabetic patients who had risk factors for hepatocellular carcinoma.
2. Methods

2.1. Data source

We performed a population-based case-control study using the database of the Taiwan National Health Insurance Program. The insurance program was launched in March 1995 and the enrollment rate exceeded 99.7% of 23 million people living in Taiwan.\textsuperscript{16,17} The details of the program have been recorded in previous studies.\textsuperscript{18–20}

2.2. Selection of cases and controls

The cases consisted of type 2 diabetic subjects aged 20 to 84 years with newly diagnosed hepatocellular carcinoma between 2000 and 2011 (based on International Classification of Diseases, 9th Revision, Clinical Modification, [ICD-9 codes] 155, 155.0, and 155.2). The date of a subject being diagnosed with hepatocellular carcinoma was defined as the index date. For each 1 case with hepatocellular carcinoma, 1 type 2 diabetic subject without hepatocellular carcinoma between 2000 and 2011 was randomly selected as the control. The cases and controls were matched for sex, age (5-year interval), and the year of the index date. Subjects who had any other cancers (ICD-9 codes 140–208) before the index date were excluded from the study (Fig. 1).

2.3. Comorbidities

Comorbidities were selected as follows: alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, as well as chronic liver diseases including cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis. All comorbidities were diagnosed based on ICD-9 codes. The accuracy of ICD-9 codes has been evaluated in previous studies.\textsuperscript{21–23}

2.4. Measurements of thiazolidinediones use and other anti-diabetic drugs use

Thiazolidinediones available in Taiwan between 2000 and 2011 were pioglitazone and rosiglitazone. Other anti-diabetic drugs available in Taiwan between 2000 and 2011 were listed as follows: metformin, sulfonylureas, α-glucosidase inhibitors, DPP-4 inhibitors, and insulins. Prescription histories of medications studied were collected. Ever use of medications was defined as subjects who had at least 1 prescription of medications studied before the index date. Never use of medications was defined as subjects who did not have a prescription of medications studied before the index date.\textsuperscript{24–26}

2.5. Statistical analysis

We compared the distributions of sex, age group, thiazolidinediones use, other anti-diabetic drugs use, and comorbidities between the cases and the controls using the Chi-square test for categorized variables, and the \( t \)-test for continuous variables. The odds ratio and 95% confidence interval for the association between hepatocellular carcinoma and cumulative duration of thiazolidinediones use was measured by a multivariable logistic regression model. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, North Carolina), and the results were considered statistically significant when 2-tailed \( P \) values were less than .05.

2.6. Ethical statement

Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers were scrambled to ensure confidentiality. Patient informed consent was not required. This study was approved by the Research
3. Results

3.1. Characteristics of the study population

In Table 1, we identified 23580 type 2 diabetic cases with newly diagnosed hepatocellular carcinoma and 23580 type 2 diabetic controls without hepatocellular carcinoma. The cases and controls had similar distributions of sex and age. The mean ages (standard deviation) were 65.3 (10.2) years in cases and 65.3 (10.3) years in controls, without statistical significance (t-test, \( P = .43 \)). The mean durations (standard deviation) of thiazolidinediones use were 15.7 (18.6) months in cases and 20.0 (21.9) months in controls, with statistical significance (t-test, \( P < .001 \)). The proportions of ever use of thiazolidinediones were 18.9% in cases and 18.6% in controls, without statistical significance (Chi-square test, \( P = .40 \)). In addition, the proportions of ever use of other anti-diabetic drugs, alcohol-related disease, chronic kidney disease and chronic liver diseases were higher in the cases than the controls, with statistical significance (Chi-square test, \( P < .001 \) for all). Approximately 88% of cases with hepatocellular carcinoma (20701/23580) had an alcohol-related disease or/and chronic liver diseases (including cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis). These subjects were classified as high risk subjects.

3.2. Association between hepatocellular carcinoma and cumulative duration of thiazolidinediones use among high risk subjects

Among high risk subjects, a multivariable logistic regression model demonstrated that after adjustment for multiple variables, there was a negative association between hepatocellular carcinoma and every 1-year increase of cumulative duration of thiazolidinediones use (adjusted OR 0.94, 95% CI 0.92–0.97, Table 2).

4. Discussion

Hepatitis B infection, hepatitis C infection, heavy alcohol consumption, and diabetes mellitus are well-known risk factors for hepatocellular carcinoma in Taiwan.[13–15] In the absence of these risk factors, it is less likely to develop hepatocellular carcinoma. Therefore, the key point of our study was to focus on type 2 diabetic patients who had these established risk factors. Among these high risk patients, we observed that there was a negative association between hepatocellular carcinoma and every 1-year increase of cumulative duration of thiazolidinediones use (Table 2). This finding indicates that there is a duration-dependent effect of thiazolidinediones use on the risk of hepatocellular carcinoma. Longer the duration of thiazolidinediones use, lower the risk of hepatocellular carcinoma. One case-control study by Chang et al demonstrated that there was a negative association between the risk of hepatocellular carcinoma and the cumulative dosage of thiazolidinediones use ≥120 DDD (defined daily dose).[31] Chang et al study demonstrated that there was a negative association between the risk of hepatocellular carcinoma and the cumulative duration of thiazolidinediones use ≥3 years.[31] Chang et al study indicates that there were the dose-dependent and duration-dependent effects of thiazolidinediones on the risk of hepatocellular carcinoma. However, Chang et al study only focused on type 2 diabetic patients but without stratification of risk factors. Our study focused on type 2 diabetic patients who also had risk factors for hepatocellular carcinoma. It highlights that thiazolidinediones still have a protective effect on the risk of hepatocellular carcinoma among those patients.

### Table 1

Information between cases with hepatocellular carcinoma and controls.

| Variable                        | Controls N=23580 | Cases N=23580 | \( P \) value* |
|--------------------------------|-----------------|--------------|----------------|
| **Sex**                         |                 |              | .90            |
| Female                         | 8307 (35.2)     | 8303 (35.2)  |                |
| Male                           | 15273 (64.8)    | 15277 (64.8) |                |
| **Age group, yr**               |                 |              | .99            |
| 20–49                          | 1754 (7.4)      | 1754 (7.4)   |                |
| 50–64                          | 9236 (39.2)     | 9240 (39.2)  |                |
| 65–84                          | 12590 (53.4)    | 12586 (53.4) |                |
| **Age, yr, mean (standard deviation)** |             |              | .43            |
| 20.0 (21.9)                    | 15.7 (18.6)     | 15.7 (18.6)  | < .001         |
| **Thiazolidinediones use**      | 4376 (18.6)     | 4447 (18.9)  | .40            |
| **Other anti-diabetic drugs use** | 19721 (83.6)   | 20970 (88.9) | < .001         |
| **Comorbidities before index date** |         |              |                |
| Alcohol-related disease         | 1509 (6.40)     | 4077 (17.3)  | < .001         |
| Cardiovascular disease          | 12735 (54.0)    | 11213 (47.6) | < .001         |
| Chronic kidney disease          | 3226 (13.7)     | 3712 (15.7)  | < .001         |
| Chronic liver diseases          | 6250 (26.5)     | 20471 (86.8) | < .001         |
| Chronic obstructive pulmonary disease | 6043 (25.6)   | 5960 (25.3)  | .38            |
| Hyperlipidemia                  | 14450 (61.3)    | 9312 (39.5)  | < .001         |
| Hypertension                    | 17751 (75.3)    | 16451 (69.8) | < .001         |

* Data are presented as the number of subjects n each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

* Chi-square test, test.

† Test comparing cases with hepatocellular carcinoma and controls.
who had at least 2 risk factors for hepatocellular carcinoma (diabetes mellitus and others).

4.1. Strengths and limitations

Some strengths should be discussed. The whole population of Taiwan is well represented in a well recognized database with a large sample size and high participation rates in the National Health Insurance Program. We focused on patients who had risk factors for hepatocellular carcinoma, including alcohol-related disease, cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis. We have adjusted for these established risk factors and therefore under-adjustment is less likely. The study design and results are more compatible with clinical needs.

Some limitations should be discussed. First, a causal-relationship cannot be determined by a case-control study. Second, due to the natural limitation of the database, the records of alcohol consumption, tobacco use, and body mass index were not documented. Thus, we included alcohol-related disease and chronic obstructive pulmonary disease as surrogate variables. This point was mentioned in previous studies. Third, the study findings remain inconclusive, and should be interpreted more cautiously. More prospective cohort studies focusing on high risk populations are required to determine a causal-relationship.

5. Conclusion

There is a negative association in a duration-dependent manner between the risk of hepatocellular carcinoma and thiazolidinediones use among type 2 diabetic patients who have risk factors for hepatocellular carcinoma. Due to study limitations, definitive conclusions for clinical practice cannot be drawn. Further methodologically well-constructed research is needed to clarify whether there is a causal relationship between thiazolidinediones use and the risk of hepatocellular carcinoma.

Author contributions

Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and has approved the final draft submitted. Cheng-Li Lin and Kuan-Fu Liao conducted data analysis.

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