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Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes

Chin-Hsiao Tseng[1,2,3]

[1]Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

[3]Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan, Taiwan

Correspondence
Chin-Hsiao Tseng, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.
Email: ccktsh@ms6.hinet.net

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Abstract

Background: Whether metformin may reduce hepatocellular carcinoma (HCC) risk requires confirmation.

Methods: Type 2 diabetes patients newly diagnosed during 1999-2005 and with 2 or more prescriptions of antidiabetic drugs were enrolled from the Taiwan's National Health Insurance database. A total of 173 917 ever-users and 21 900 never-users of metformin were identified (unmatched cohort). A 1:1 matched-pair cohort of 21 900 ever-users and 21 900 never-users based on a propensity score (PS) was created. Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using the PS. In addition, interactions with aspirin and statin were evaluated.

Results: In the unmatched cohort, 619 never-users and 2642 ever-users developed HCC, with a respective incidence of 668.0 and 330.7 per 100 000 person-years and an overall hazard ratio of 0.49 (95% confidence interval: 0.45-0.54). The hazard ratios for the first (<25.7 months), second (25.7-56.9 months) and third (>56.9 months) tertile of cumulative duration of metformin therapy were 0.89 (0.81-0.98), 0.50 (0.46-0.56) and 0.23 (0.21-0.26) respectively. Analyses of the matched cohort showed an overall hazard ratio of 0.76 (0.67-0.85), and the hazard ratios for the respective tertiles were 1.39 (1.19-1.62), 0.77 (0.65-0.91) and 0.37 (0.30-0.45). Aspirin and statin were observed to have a significant interaction with metformin.

Conclusions: Metformin was associated with a reduced risk of HCC in a dose-response pattern. Users of both metformin and aspirin or metformin and statin had the lowest risk.

KEYWORDS

diabetes mellitus, hepatocellular carcinoma, metformin, Taiwan

1 | INTRODUCTION

High incidence rates of hepatocellular carcinoma (HCC) are observed in countries in East and Southeast Asia and in Northern and Western Africa.[1] Taiwan is among the countries with a high incidence.[2] Viral hepatitis B and C are the main causes of HCC in countries with a high incidence, but alcohol, obesity and type 2 diabetes mellitus may be responsible in more developed countries.[3] Risk factors that have not yet been confirmed include *Helicobacter pylori* infection,[4] gallstones[5] and fibrate use.[6]

Patients with type 2 diabetes mellitus may have an increased risk of various types of cancer including HCC.[7,8] However, use of different

Abbreviations: AMPK, adenosine monophosphate kinase; HCC, hepatocellular carcinoma; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; mTOR, mammalian target of rapamycin; NHI, National Health Insurance; PS, propensity score.

classes of antidiabetic drugs may be associated with different risks of HCC. For example insulin and sulfonylurea are associated with a higher risk, but use of metformin has been reported to be associated with a lower risk.[9]

Two meta-analyses published in 2013 suggested a reduced risk of HCC in patients treated with metformin.[9,10] The first meta-analysis by Zhang et al,[10] which included 7 observational studies (3 cohort and 4 case-control), suggested a significant risk reduction of 76% (relative risk: 0.24%, 95% confidence interval: 0.13-0.46) in metformin users. The other meta-analysis published later in the same year by Singh et al[9] included 8 observational studies and reported an odds ratio of 0.50 (95% confidence interval: 0.34-0.73). These 2 meta-analyses were published in the same year but the magnitudes of the estimated risk reduction differed markedly. This could be because of the different studies included in the respective meta-analyses. These 2 meta-analyses shared 5 papers in common, but the meta-analysis by Zhang et al included a study by Lee et al[11] that reported an extremely low relative risk of 0.06 (95% confidence interval: 0.02-0.16). This study by Lee et al was not selected by Singh et al or by authors of later meta-analyses. The third meta-analysis, by Zhou et al[12] and published in 2016, included 13 studies (1 randomized controlled trial and 12 observational studies) and estimated a relative risk of 0.49 (95% confidence interval: 0.25-0.97). The most recent meta-analysis, published in 2017, included 19 studies and estimated a very similar odds ratio of 0.52 (95% confidence interval: 0.40-0.68).[13]

Although all meta-analyses reported a significantly lower risk of HCC associated with metformin use, not all studies reached the same conclusion. For example a study using the Clinical Practice Research Datalink did not support a role for metformin relative to HCC risk.[14] Singh et al[9] pointed out the considerable heterogeneity among the different studies in the meta-analyses, probably because of different study settings and the lack of concomitant consideration of the cancer-modifying effects of other antidiabetic drugs. The risk reduction associated with metformin use may also be because of a missing link with statins in some studies[15] and the lack of full consideration of potential confounders and biases commonly seen in pharmaco-epidemiological studies using administrative databases. Therefore, the beneficial effect of metformin on HCC should be interpreted more cautiously, and confirmation with additional studies that consider adequate confounders and avoid potential biases such as selection bias, prevalent user bias, immortal time bias and confounding by indication is needed.

This study further investigated whether the risk of HCC might differ between ever- and never-users of metformin among Taiwanese patients with type 2 diabetes mellitus, considering most confounders and addressing potential biases. Analyses of both an unmatched cohort and a cohort matched in terms of propensity score (PS) were conducted. In addition, potential interactions with aspirin and statin were also analyzed.

Key points

- Metformin use is associated with a reduced risk of various types of cancer
- Whether metformin use is associated with a reduced risk of hepatocellular carcinoma requires confirmation
- Previous studies may suffer from selection bias, prevalent user bias, immortal time bias or confounding by indication
- This study used a nationwide National Health Insurance database in Taiwan and addressed methodological limitations in earlier studies to confirm a beneficial effect of metformin and a synergistic effect between metformin and aspirin or statin on the prevention of hepatocellular carcinoma.

2 | MATERIALS AND METHODS

Taiwan's National Health Insurance (NHI) program was implemented in March 1995. It currently covers more than 99% of the population and has contracts with 93% of medical settings and with all hospitals nationwide. The reimbursement database of the NHI keeps all records of diseases diagnosed, medications prescribed and procedures performed. Researchers may use the database for academic purposes after approval by an ethics review board. This study was granted approval number 99274 by the Institutional Review Board of the National Health Research Institutes. Informed consent was not required according to local regulations because all personal data were de-identified before the release of the database for analyses.

The methods used in this study have been described in detail elsewhere.[16] Disease diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) during the study period. Diabetes was coded 250.XX and HCC 155 (excluding 155.1).

The unmatched original cohort and the matched cohort were created step-by-step following the procedures illustrated in Figure 1. In brief, 423 949 patients who were newly diagnosed as having diabetes mellitus during 1999-2005 and who had been followed up in outpatient clinics with ≥2 prescriptions of antidiabetic drugs were first identified. Exclusion criteria were the following: (i) use of other antidiabetic drugs before metformin was initiated among metformin users (n = 183 837); (ii) type 1 diabetes mellitus (n = 2062); (iii) missing data (n = 423); (iv) diagnosis of any cancer before entry or within 6 months of diabetes diagnosis (n = 26 637); and (v) follow-up duration of <6 months (n = 15 173). In the end, 173 917 ever-users and 21 900 never-users of metformin were identified in the unmatched original cohort. A PS matched-pair cohort (the matched cohort) of ever- and never-users of metformin was created using the Greedy 8→1 digit match algorithm.[17] All baseline characteristics listed in

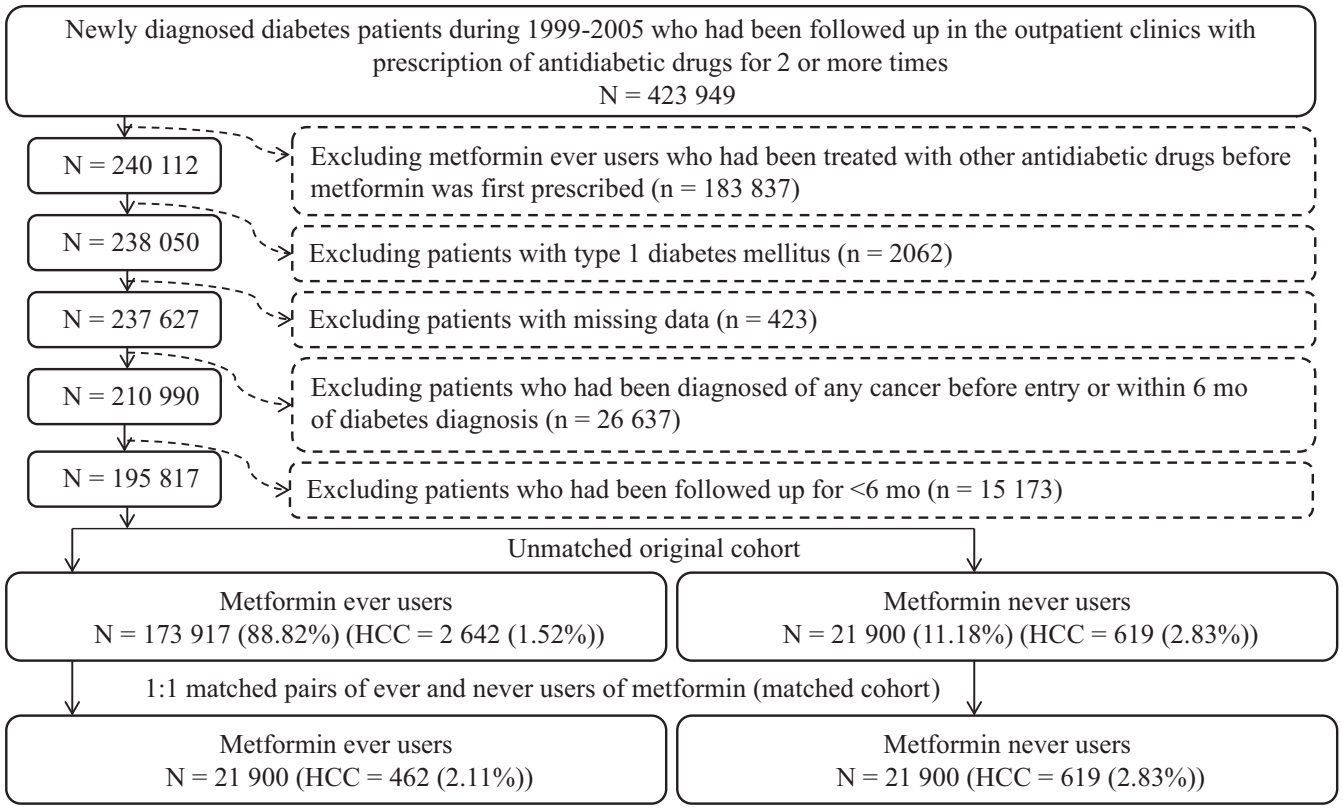

FIGURE 1 The procedures in creating the unmatched original cohort and the cohort of 1:1 matched-pair of ever- and never-users of metformin using the reimbursement database of the National Health Insurance (HCC: hepatocellular carcinoma)

Table 1 and the date of entry were used to create the PS by logistic regression.

Cumulative duration of metformin use (months) was calculated for each patient, and its tertiles were used for analyses. Potential confounders were categorized into demographic data (age, sex, occupation and residential area), major comorbidities (hypertension, dyslipidaemia and obesity), diabetes-related complications (nephropathy, eye disease, stroke, ischaemic heart disease and peripheral arterial disease), use of antidiabetic drugs (insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone and pioglitazone), potential risk factors for cancer (chronic obstructive pulmonary disease, tobacco abuse, alcohol-related diagnoses, gallstone, history of *Helicobacter pylori* infection, Epstein-Barr virus-related diagnoses, hepatitis B virus infection, hepatitis C virus infection, cirrhosis and other chronic non-alcoholic liver diseases) and medications that are commonly used among diabetes patients or that may affect cancer risk (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, statins, fibrates and aspirin). The patient's residential area and occupation were classified as detailed elsewhere.[18] Diagnoses of cirrhosis and other chronic non-alcoholic liver diseases were based on ICD-9-CM 571.5 and 571.8 respectively. The ICD-9-CM codes for other diagnoses have been described in previously published papers.[16,18]

Both the unmatched original cohort and the matched cohort were analyzed. Student's *t* test was used to compare the differences in age between the never- and ever-users, and the Chi-square test was used to compare the differences in other variables. Standardized difference was calculated for each covariate, as described by Austin and Stuart, who proposed a value >10% as an indication of potential confounding from the variable.[19]

Incidence was calculated for each subgroup of metformin exposure, that is never-users and ever-users, and for each tertile of cumulative duration of therapy. The numerator was the case number of newly diagnosed HCC identified during follow-up. The denominator was the person-years of follow-up, which ended at the time of HCC diagnosis or on the date of death, the last reimbursement record or December 31, 2011.

Hazard ratios and their 95% confidence intervals for ever-users and tertiles of cumulative duration versus never-users were estimated by Cox regression incorporated with the inverse probability of treatment weighting (IPTW) using the PS, as recommended by Austin, to reduce confounding from the differences in characteristics.[20] To further examine the consistency of the findings, models were also created after excluding patients aged <25 or >75 years in the unmatched cohort as sensitivity analyses, because HCC rarely occurs in patients younger than 25 years, and patients older than 75 years may represent a group of healthy survivors. Subgroup analyses were conducted for patients with and without liver diseases, including alcohol-related diagnoses, hepatitis B virus infection, hepatitis C virus infection, cirrhosis, other chronic non-alcoholic liver diseases and any of the above.

TABLE 1 Characteristics in metformin never-users and ever-users in the unmatched original cohort and in the propensity score matched cohort

	Unmatched original cohort					
	Never-users (n = 21,900)		Ever-users (n = 173,917)			
Variable	n	%	n	%	*P* value	Standardized difference
Demographic data						
Age* (years)	64.5 ± 13.5		59.6 ± 12.2		<.0001	−43.5
Sex (Men)	9983	45.6	82 145	47.2	<.0001	−3.5
Occupation						
I	7903	36.1	64 919	37.3	<.0001	
II	3685	16.8	36 777	21.1		12.3
III	5279	24.1	39 982	23.0		−2.6
IV	5033	23.0	32 239	18.5		−12.7
Residential area						
Taipei	7410	33.8	54 582	31.4	<.0001	
Northern	2331	10.6	20 083	11.5		3.0
Central	3813	17.4	31 784	18.3		2.0
Southern	3762	17.2	29 900	17.2		0.6
Kao-Ping and Eastern	4584	20.9	37 568	21.6		2.4
Major comorbidities						
Hypertension	17 136	78.2	125 271	72.0	<.0001	−16.2
Dyslipidaemia	12 970	59.2	118 751	68.3	<.0001	21.1
Obesity	428	2.0	5739	3.3	<.0001	8.9
Diabetes-related complications						
Nephropathy	6134	28.0	30 522	17.5	<.0001	−30.3
Eye disease	1949	8.9	27 233	15.7	<.0001	21.4
Stroke	6914	31.6	40 011	23.0	<.0001	−22.9
Ischaemic heart disease	9801	44.8	65 738	37.8	<.0001	−16.6
Peripheral arterial disease	3950	18.0	31 388	18.0	.9677	−1.1
Antidiabetic drugs						
Insulin	1920	8.8	3957	2.3	<.0001	−34.6
Sulfonylurea	15 620	71.3	123 841	71.2	.7180	8.8
Meglitinide	1981	9.0	6952	4.0	<.0001	−23.2
Acarbose	2471	11.3	9257	5.3	<.0001	−21.0
Rosiglitazone	622	2.8	8164	4.7	<.0001	10.6
Pioglitazone	513	2.3	4358	2.5	.1436	2.4
Potential risk factors for cancer						
Chronic obstructive pulmonary disease	10 091	46.1	71 850	41.3	<.0001	−12.2
Tobacco abuse	303	1.4	3457	2.0	<.0001	5.2
Alcohol-related diagnoses	1156	5.3	8859	5.1	.2422	−1.3
Gallstone	2475	11.3	16 656	9.6	<.0001	−6.9
History of *Helicobacter pylori* infection	5353	24.4	35 017	20.1	<.0001	−12.9
Epstein-Barr virus-related diagnoses	138	0.6	1141	0.7	.6536	0.3
Hepatitis B virus infection	376	1.7	2555	1.5	.0044	−2.2

Matched cohort					
Never-users (n = 21,900)		Ever-users (n = 21,900)			
n	%	n	%	*P* value	Standardized difference
64.5 ± 13.5		64.4 ± 12.1		.2694	−0.5
9983	45.6	9962	45.5	.8403	0.1
7903	36.1	7919	36.2	.8610	
3685	16.8	3710	16.9		0.2
5279	24.1	5204	23.8		−0.6
5033	23.0	5067	23.1		0.5
7410	33.8	7503	34.3	.8818	
2331	10.6	2338	10.7		0.0
3813	17.4	3781	17.3		−0.4
3762	17.2	3758	17.2		0.1
4584	20.9	4520	20.6		−0.6
17 136	78.2	17 132	78.2	.9631	0.1
12 970	59.2	12 933	59.1	.7191	−0.2
428	2.0	398	1.8	.2920	−1.1
6134	28.0	5933	27.1	.0316	−2.4
1949	8.9	1888	8.6	.3026	−1.4
6914	31.6	6833	31.2	.4043	−0.6
9801	44.8	9742	44.5	.5706	−0.4
3950	18.0	3890	17.8	.4545	−0.9
1920	8.8	1756	8.0	.0047	−4.5
15 620	71.3	16 205	74.0	<.0001	5.0
1981	9.0	1910	8.7	.2331	−1.6
2471	11.3	2644	12.1	.0101	0.6
622	2.8	686	3.1	.0724	0.9
513	2.3	547	2.5	.2904	0.1
10 091	46.1	10 069	46.0	.8330	−0.1
303	1.4	305	1.4	.9349	0.1
1156	5.3	1179	5.4	.6247	0.4
2475	11.3	2400	11.0	.2545	−1.0
5353	24.4	5252	24.0	.2599	−1.1
138	0.6	161	0.7	.1820	1.3
376	1.7	381	1.7	.8545	0.2

(Continues)

TABLE 1 (Continued)

	Unmatched original cohort					
	Never-users (n = 21,900)		Ever-users (n = 173,917)			
Variable	n	%	n	%	*P* value	Standardized difference
Hepatitis C virus infection	909	4.2	5847	3.4	<.0001	−4.4
Cirrhosis	1122	5.1	5739	3.3	<.0001	−10.7
Other chronic non-alcoholic liver diseases	1636	7.5	14 656	8.4	<.0001	3.9
Medications that are commonly used among diabetes patients or that may affect cancer risk						
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	14 014	64.0	105 330	60.6	<.0001	−8.5
Calcium channel blockers	13 461	61.5	92 733	53.3	<.0001	−18.6
Statins	8573	39.1	78 722	45.3	<.0001	13.9
Fibrates	5855	26.7	57 217	32.9	<.0001	14.8
Aspirin	11 597	53.0	87 348	50.2	<.0001	−7.2

*Age is expressed as mean ± standard deviation.

To investigate the interactions between metformin and aspirin or statin, hazard ratios and their 95% confidence intervals and *P*-values for interaction were estimated. Users of aspirin or statin for <2 years were excluded to allow a potential incubation period.

SAS statistical software (version 9.3, SAS Institute, Cary, NC) was used for statistical analyses. $P < .05$ was considered statistically significant.

3 | RESULTS

The median follow-up time was 5.3 years in both the unmatched cohort (range: 0.50-5.92 years) and the matched cohort (range: 0.50-5.92 years). In the unmatched original cohort, age and sex differed significantly. The mean age of the never-users was older (64.5 ± 13.5 versus 59.6 ± 12.2 years, $P < .0001$) and the proportion of men was lower (45.6% versus 47.2%, $P < .0001$). All other variables, except peripheral arterial disease, sulfonylurea, pioglitazone, alcohol-related diagnoses and Epstein-Barr virus-related diagnoses, differed significantly in the unmatched original cohort. However, in the matched cohort, age and sex were similar and most variables did not differ significantly (except for nephropathy, insulin, sulfonylurea and acarbose; Table 1). The standardized differences in the matched cohort suggested that the 2 groups were well-matched and none of the covariates had a value >10%.

The overall hazard ratios by metformin exposure suggested a significantly reduced risk of HCC in both the unmatched original cohort and the matched cohort. In the tertile analyses, there was a trend towards a decreasing risk of HCC with an increasing cumulative duration of metformin use (Table 2). The *P*-values suggested a reduced risk in all tertiles of cumulative duration in the unmatched cohort, but a significantly higher risk was observed in the first tertile in the matched cohort (hazard ratio: 1.39, 95% confidence interval: 1.19-1.62).

Sensitivity analyses after excluding patients aged <25 or >75 years did not change the findings remarkably. The overall hazard ratio was 0.45 (0.41-0.49) and the hazard ratios for the first, second and third tertiles of cumulative duration of metformin therapy were 0.84 (0.75-0.93), 0.45 (0.41-0.51) and 0.21 (0.19-0.24) respectively.

In the subgroup analyses of patients with and without liver diseases, a significantly lower risk of HCC associated with metformin use could be seen in all subgroups, and none of the *P*-interactions were statistically significant (Table 3).

Users of metformin with or without the use of aspirin/statin had a significantly lower risk of HCC, compared to the reference groups. There was a significant interaction between metformin and aspirin or statin (Table 4).

4 | DISCUSSION

This study found that metformin use in patients with type 2 diabetes mellitus was associated with a significantly lower risk of HCC. In addition, the findings supported an interaction between metformin and aspirin or statin.

Although analyses by Chi square test showed significant *P*-values for nephropathy, insulin, sulfonylurea and acarbose in the matched cohort, these probably would not lead to residual confounding because all their values of standardized difference were <10% (Table 1). In addition, a significantly lower risk of HCC associated with metformin use could be seen in all subgroups of patients with or without these characteristics in secondary analyses (data not shown).

Matched cohort					
Never-users (n = 21,900)		Ever-users (n = 21,900)			
n	%	n	%	*P* value	Standardized difference
909	4.2	883	4.0	.5306	−0.6
1122	5.1	1072	4.9	.2734	−1.1
1636	7.5	1667	7.6	.5748	0.5
14 014	64.0	13 977	63.8	.7128	−0.3
13 461	61.5	13 465	61.5	.9687	0.2
8573	39.1	8539	39.0	.7392	−0.4
5855	26.7	5768	26.3	.3464	−0.9
11 597	53.0	11 515	52.6	.4326	−0.6

It is worth noting that only approximately 11.2% of the patients were never-users of metformin (Figure 1). This low percentage is understandable, for the following reasons. Before 1995, only insulin, sulfonylurea and metformin were available in Taiwan. In 1995, acarbose was introduced in Taiwan, and several newer drugs including meglitinide, rosiglitazone and pioglitazone were introduced during the NHI enrolment period from 1999 to 2005. Although more choices were available during the enrolment period, sulfonylurea and metformin remained the main oral antidiabetic drugs prescribed by physicians at that time. In addition, metformin has always been recommended as the first-line therapy for type 2 diabetes in several guidelines, including the guideline of the American Diabetes Association,[21] which is always followed in clinical practice in Taiwan. In consideration of the fact that the guidelines for the

TABLE 2 Incidence rates of hepatocellular carcinoma and hazard ratios by metformin exposure

Metformin use	n	N	Person-years	Incidence rate (per 100 000 person-years)	HR	95% CI
I. Unmatched cohort						
Never-users	619	21 900	92 665.8	668.0	1.00	
Ever-users	2642	173 917	798 951.5	330.7	0.49	0.45-0.54
Tertiles of cumulative duration of metformin therapy (months)						
Never-users	619	21 900	92 665.8	668.0	1.00	
<25.7	1168	57 435	192 207.8	607.7	0.89	0.81-0.98
25.7-56.9	929	57 345	272 782.8	340.6	0.50	0.46-0.56
>56.9	545	59 137	333 961.0	163.2	0.23	0.21-0.26
II. Matched cohort						
Never-users	619	21 900	92 665.8	668.0	1.00	
Ever-users	503	21 900	99 108.0	507.5	0.76	0.67-0.85
Tertiles of cumulative duration of metformin therapy (months)						
Never users	619	21 900	92 665.8	668.0	1.00	
<25.8	228	7228	23 735.6	960.6	1.39	1.19-1.62
25.8-56.6	174	7221	33 662.3	516.9	0.77	0.65-0.91
>56.6	101	7451	41 710.1	242.1	0.37	0.30-0.45

CI, confidence interval; HR, hazard ratio (weighted for propensity score); N, cases followed; n, new cases of hepatocellular carcinoma during follow-up.

TABLE 3 Subgroup analyses in patients with and without liver diseases

Subgroup	N	HR	95% CI
1. Alcohol-related diagnoses			
Yes	10 015	0.40	0.32-0.51
No	185 802	0.50	0.46-0.55
2. Hepatitis B virus infection			
Yes	2931	0.52	0.37-0.74
No	192 886	0.49	0.45-0.54
3. Hepatitis C virus infection			
Yes	6756	0.47	0.39-0.57
No	189 061	0.51	0.47-0.57
4. Cirrhosis			
Yes	6861	0.51	0.43-0.60
No	188 956	0.54	0.49-0.60
5. Other chronic non-alcoholic liver disease			
Yes	16 292	0.49	0.37-0.64
No	179 525	0.49	0.45-0.54
6. Any of the above			
Yes	34 238	0.44	0.39-0.50
No	161 579	0.53	0.47-0.60

P-interaction is not significant for any of the above analyses.
CI, confidence interval; HR, hazard ratio (weighted for propensity score); N, cases followed.

use of antidiabetic drugs have evolved over the years, secondary analyses were conducted to calculate the proportions of never-users of metformin and to estimate the PS-weighted hazard ratios for patients enrolled during each specific year from 1999 to 2005 in the unmatched original cohort. It was noted that the proportions of never-users of metformin increased gradually from 7.4% in 1999 to 18.3% in 2005. However, the hazard ratios remained statistically significant for each specific year, ranging from 0.43 to 0.67 (data not shown).

It is not known whether some unmeasured confounders could be associated with the reasons for the 21 900 never-users in the study never being treated with metformin. The main contraindication for the use of metformin is renal dysfunction that may potentially lead to fatal lactic acidosis. However, this did not seem to be a potential confounder because, as discussed previously, the lower risk of HCC associated with metformin use could also be observed in patients with or without a diagnosis of nephropathy in the secondary analyses. For patients with a diagnosis of nephropathy, the estimated hazard ratio (95% confidence interval) was 0.56 (0.47-0.67), and for those without such a diagnosis, it was 0.48 (0.43-0.53).

Obesity is an important risk factor for HCC.[3] In the tertile analysis of the matched cohort, a significantly increased risk was observed in the first tertile (Table 2). Since metformin is always considered as first-line treatment for obese patients, a residual confounding by obesity could not be excluded in this subgroup of patients who had used metformin for a short period, and the impact of obesity on HCC could be carried over from a non-pharmacological control status to metformin initiation. However, the prevalence of obesity (defined by ICD-9-CM code 278) in the secondary analyses did not differ among the 3 subgroups of tertiles, in both the unmatched cohort (3.3% in each subgroup) and the matched cohort (2.0% in each subgroup), so the potential impact of some unknown factors could not be completely excluded.

Statin has been shown to reduce the risk of HCC,[22] and combined metformin and statin treatment may also reduce the risk of HCC.[23] It is true that patients with type 2 diabetes mellitus have a high risk of dyslipidaemia and the use of statin is very common. Therefore, the potential confounding effect of statin and the interaction between

TABLE 4 Interactions between metformin and aspirin/statin on hepatocellular carcinoma

Model	n	N	Person-years	Incidence rate (per 100 000 person-years)	HR	95% CI	*P* value
Metformin and aspirin (excluding users <2 y)							
Metformin (−)/Aspirin (−)	335	10 303	45 732.6	732.5	1.00		
Metformin (−)/Aspirin (+)	236	9574	38 064.1	620.0	0.83	0.69-0.99	.0412
Metformin (+)/Aspirin (−)	632	36 070	180 388.9	350.4	0.62	0.54-0.71	<.0001
Metformin (+)/Aspirin (+)	547	32 955	158 973.8	344.1	0.58	0.50-0.68	<.0001
						P-interaction	<.0001
Metformin and statin (excluding users <2 y)							
Metformin (−)/Statin (−)	475	13 327	56 426.8	841.8	1.00		
Metformin (−)/Statin (+)	90	5532	22 427.4	401.3	0.66	0.52-0.84	.0006
Metformin (+)/Statin (−)	906	40 569	199 279.7	454.6	0.66	0.59-0.74	<.0001
Metformin (+)/Statin (+)	279	25 668	125 023.0	223.2	0.46	0.39-0.54	<.0001
						P-interaction	<.0001

CI: confidence interval; HR, hazard ratio (weighted for propensity score); N, cases followed; n, new cases of hepatocellular carcinoma during follow-up.

metformin and statin should not be neglected. Although the effect of aspirin on HCC is not well established,[24] this study suggested a potential beneficial effect of aspirin and its interaction with metformin (Table 4).

This study has carefully considered the adjustment for potential confounders (Table 1), and has addressed several potential biases that have not been fully considered in previous studies. These may include selection bias, prevalent user bias, immortal time bias and confounding by indication.

Selection bias can be avoided using Taiwan's NHI, a universal healthcare plan that covers more than 99% of Taiwan's population. Prevalent user bias can be avoided by enrolling new users of the drug. Immortal time bias may be introduced by inappropriately assigning treatment status and follow-up time to the patients.[25] By including patients who had been followed up and prescribed antidiabetic drugs 2 or more times in outpatient clinics (Figure 1), the diagnosis of diabetes and the assignment of treatment status should not be erroneous. Patients with immortal time between diabetes diagnosis and the use of antidiabetic drugs were not included in the analyses. Furthermore, in the calculation of person-years, the chance of inappropriate assignment of follow-up time within the initial period of antidiabetic treatment was further reduced by including only those patients who had been followed up for at least 6 months (Figure 1).

Confounding by indication was less likely in the matched cohort analyses because never-users and ever-users were balanced in potential confounders as indicated by the fact that none of the covariates had a standardized difference >10% (Table 1). The use of Cox regression incorporated with IPTW was also aimed at reducing such a potential confounding by indication.

This study has the merit of using the large NHI database, so the findings can be generalized to the whole population. Potential bias related to self-reporting can also be reduced using medical records. Biases from disparity in healthcare accessibility and differences in disease detection are less likely in Taiwan than in many other countries, because the NHI is a universal healthcare system and drug cost-sharing is low. Furthermore, the Bureau of the NHI considers cancer a catastrophic illness and most copayments by patients with cancer can be waived.

Limitations of the study may include the lack of measurement data on some potential risk factors such as biochemistry, abdominal ultrasound data, anthropometric factors, lifestyle, smoking, alcohol drinking, nutritional status, dietary patterns, family history, biomarkers of viral hepatitis and genetic markers. This study did not have data on the pathology, grading and staging of HCC. Whether the findings derived from the diabetes patients can be applied to non-diabetes patients awaits additional confirmation.

In summary, this study supports a beneficial effect of metformin use and a synergistic effect of metformin and aspirin/statin use on the prevention of HCC in patients with type 2 diabetes mellitus. Since metformin, aspirin and statin are inexpensive and commonly used in clinical practice, additional studies, especially clinical trials, are urgently needed to confirm their beneficial effects on the prevention and treatment of HCC in both diabetes and non-diabetes patients.

CONFLICT OF INTEREST

The author does not have any disclosures to report.

ORCID

Chin-Hsiao Tseng http://orcid.org/0000-0001-9545-7123

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