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Original Research

Use of metformin and risk of kidney cancer in patients with type 2 diabetes

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Abstract ***Background:*** The anticancer effect of metformin has been reported in the literature but requires additional confirmation in epidemiologic studies. With respect to kidney cancer scarce data are available. This study investigates whether metformin use in patients with type 2 diabetes mellitus (T2DM) might affect kidney cancer risk.
Methods: The reimbursement database of the National Health Insurance in Taiwan was used. T2DM patients aged ≥40 years and newly treated with either metformin (n = 171,753, "ever users of metformin") or other antidiabetic drugs (n = 75,499, "never users of metformin") within 1998–2002 were followed for at least 6 months for kidney cancer until 31 December 2009. The treatment effect was estimated by Cox regression using propensity score weighting by inverse probability of treatment weighting approach. Hazard ratios were estimated for ever versus never users, and for tertiles of cumulative duration of metformin therapy.
Results: During follow-up, 917 ever users and 824 never users developed kidney cancer, with respective incidence of 80.09 and 190.30 per 100,000 person-years. The hazard ratio (95% confidence intervals) for ever versus never users is 0.279 (0.254–0.307); and is 0.598 (0.535–0.668), 0.279 (0.243–0.321) and 0.104 (0.088–0.124), respectively, for the first, second, and third tertile of cumulative duration of <14.5, 14.5–45.8 and >45.8 months. In subgroup analyses, the lower risk of kidney cancer associated with metformin use is consistently

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observed in both sexes, and in patients with or without concomitant use of other antidiabetic drugs.
Conclusion: Metformin use is associated with a decreased risk of kidney cancer in patients with T2DM.

1. Introduction

Renal cell carcinoma is the most common type of kidney cancer, representing approximately 85% of all kidney cancers [1,2]. It has a poor prognosis and nearly half of the patients die within 5 years after diagnosis [3]. The incidence of kidney cancer is increasing steadily throughout the world, but is generally higher in European and North American countries than in Asian and South American countries [1].

In Taiwan, renal cell carcinoma represented 92.4% and 90.4% of all kidney cancers in men and in women, respectively [4,5]. In a 10-year population-based follow-up from 1998 to 2007, the standardized incidence ratio for kidney cancer comparing patients with diabetes to the general population in Taiwan was 1.32 (95% confidence interval: 1.25–1.40), suggesting an excess risk of kidney cancer in patients with diabetes [6]. The most important risk factors for kidney cancer identified in Taiwan were age [7], male sex [7], chronic kidney disease [4,8] and urinary tract disease [4,9,10].

Studies suggest that the use of antidiabetic drugs might affect the risk of various cancers in patients with type 2 diabetes mellitus (T2DM). For example, pioglitazone has been associated with a higher risk of bladder cancer [11,12] and incretin-based therapies may increase the risk of pancreatic cancer and thyroid cancer [13]; but metformin has been associated with a lower risk of colon cancer [14], bladder cancer [15] and other malignancies involving the liver, pancreas, stomach and esophagus [16,17]. Whether metformin use can affect the risk of kidney cancer remains to be confirmed. While an observational study showed a non-significantly higher risk of kidney/pelvis cancer associated with metformin use [18], another study including two clinical trials showed a non-significantly lower risk of kidney cancer associated with metformin use [17,19].

Renal cell carcinoma is characterized by an overactivation of the mammalian target of rapamycin (mTOR), and activation of serine–threonine kinase AMP-activated kinase (AMPK) might inhibit the proliferation and growth of renal cell carcinoma [20]. Therefore, metformin is potentially protective against kidney cancer through its well-recognized effects on the activation of AMPK and inhibition of the mTOR pathway [21].

The purpose of the present study is to evaluate the association between metformin use and the risk of kidney cancer in Taiwanese patients with T2DM using the National Health Insurance (NHI) reimbursement database.

2. Materials and methods

The study was approved by the ethics review board of the National Health Research Institutes (registered approval number: 99274).

Since March 1995 a compulsory and universal system of NHI was implemented in Taiwan. According to this system, all contracted medical institutes must submit computerized and standard claim documents for reimbursement. More than 99% of citizens are enrolled in the NHI, and over 98% of the hospitals nationwide are under contract with the NHI.

The National Health Research Institutes is the only organization approved, as per local regulations, for handling the NHI reimbursement database for academic research. The identification information of individuals was de-identified for the protection of privacy. Diabetes was coded as 250.XX and kidney cancer as 189, based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

A cohort of T2DM patients newly treated with antidiabetic drugs during 1998–2002 and without a history of kidney cancer was retrieved from the NHI database for analyses ($n = 525{,}821$). To assure that diabetes was first diagnosed after 1998, patients who had a diagnosis of diabetes in 1996 and/or 1997 were not included. Patients who were on diet control only and had not been using one or more antidiabetic drugs after 1 January 1998 were also not included. After excluding patients with type 1 diabetes ($n = 2397$), those with a duplicated identification number ($n = 26$), unclear information on date of birth or sex ($n = 1782$), patients aged <40 years at entry ($n = 53{,}955$, they were excluded because both diabetes mellitus [22] and kidney cancer [5,7] are rare in individuals below 40 years of age), metformin users who had been using other antidiabetic drugs before metformin was prescribed ($n = 200{,}785$), or a follow-up duration of less than 6 months ($n = 11{,}375$), a total of 247,252 patients were identified.