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Metformin decreases lung cancer risk in diabetic patients in a dose-dependent manner

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ABSTRACT

Objectives: Higher risk of lung cancer has been noted in patients with type 2 diabetes mellitus (DM). Some observational studies have shown a reduced risk of lung cancer in DM patients taking metformin, but a dose–response relationship has never been reported. The aim of this study is to exam the association between the dose of metformin and the incidence of lung cancer in a Chinese population.
Materials and methods: The dataset used for this nationwide population-based study is a cohort of 1 million subjects randomly sampled from individuals enrolled in the Taiwan National Health Insurance system. We enrolled all subjects with newly diagnosed type 2 DM between 1997 and 2007. Subjects with a diagnosis of neoplasm before DM diagnosis, those using metformin before DM diagnosis, those with polycystic ovary syndrome, and those with a DM diagnosis before their 15 years of age were excluded. The demographic data and duration, cumulative dose and intensity of metformin use were compared between patients developing lung cancer and those without lung cancer.
Results: Totally, 47,356 subjects were identified. After adjusting for age, gender, and modified Charlson Comorbidity Index score, the utilization of metformin was an independent protecting factor, and the risk of developing lung cancer decreased progressively with either the higher cumulative dose or the higher intensity of metformin use.
Conclusions: This study revealed that the use of metformin decreased the risk of lung cancer in a dose-dependent manner in patients with type 2 DM. The chemo-preventive effect of metformin deserves further study.

1. Introduction

Lung cancer is one of the most common cancers and the leading causes of death worldwide [1–4]. It accounts for about 20% of cancer-related death in Taiwan and has been the most common cause of cancer death for more than 10 years [1]. Various molecular markers and many clinical epidemiologic factors, such as cigarette smoking, air pollution, pulmonary tuberculosis, exposure to carcinogens, and family history of lung cancer, have been identified [5–12]. Lung cancer is usually diagnosed at advanced stage, so the therapeutic outcome remains unsatisfying although much improvement has been made in the anticancer treatment. Developing preventive strategies to reduce incidence of lung cancer is therefore more important than treating lung cancer [4].

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Increasing epidemiological evidences suggest the association between diabetes mellitus (DM) and various cancers [13–15], and the mortality after incident cancer is also higher in patients with type 2 DM [16]. The biological basis of this association has not been well studied yet, whereas the possible underlying mechanisms may include increased cell survival and proliferation related to insulin and insulin-like growth factor, cancer cell growth driven by hyperglycemia, and alterations in inflammatory cytokines with suppression of anticancer immunity [13]. Although the link between DM and lung cancer has been quite elusive, recent studies revealed higher risk of lung cancer in patients with type 2 DM [4,14,15,17].

Studies assessing the impact of metformin on lung cancer incidence in DM patients have yielded conflicting results. Some observational studies have shown a reduced risk of lung cancer in DM patients taking metformin, but a dose–response relationship has never been reported [4,6,14,18]. Furthermore, few studies, especially those using the United Kingdom General Practice Research Database (UK-GPRD), showed no significant difference in the risk of lung cancer between metformin users and non-users [19,20]. We therefore conducted a nationwide population-based study using Taiwan National Health Insurance (NHI) database with a different study design to demonstrate the effect of metformin on lung cancer incidence in patients with type 2 DM.

2. Materials and methods

2.1. Data sources

The Taiwan National Health Insurance (NHI) has covered ambulatory care, hospital inpatient care, dental services, and prescription drugs, and the NHI medical reimbursement claims database is managed by the National Health Research Institutes (NHRI) in Taiwan since 1996 [21,22]. The NHI coverage rate was 96.16% of the whole population of 23 million in 2000 and rose to 99% by the end of 2004. The dataset used for this study is a cohort of 1 million subjects randomly sampled from individuals enrolled in the NHI system in 2005, and includes information on ambulatory care claims, inpatient care claims, prescriptions, and registration entries. Patient identification numbers has been already scrambled for protection of confidentiality, and hence the researchers are blinded to patient identities. Using the scrambled personal identifier for each study subject, the researchers are able to link the files to obtain socio-demographic information, such as sex, birthday, occupation types, income levels, and longitudinal medical histories [6,14,15]. The study protocol was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUH-IRB-EXEMPT-20130056).

2.2. Diabetic cohort

From the dataset, a total of 47,356 subjects were identified by the algorithm (Fig. 1). In brief, patients with diabetes diagnosis, in the ambulatory claim database or in the inpatient claim database, between January 1, 1996 and December 31, 2008, were identified initially. The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code of 250.xx or A code of A181 was used for diabetes diagnosis whereas codes suggesting type 1 DM (ICD-9-CM code of 250.x1 and 250.x3) were excluded. Patients had at least two claims at ambulatory or one inpatient claim were selected. Subjects with their first diabetes diagnosis before January 1, 1997 were excluded ($n = 18,039$) to ensure newly diagnosed DM; patients with their first diabetes diagnosis after December 31, 2007 were also excluded ($n = 4803$) to ensure enough follow-up periods. Subjects with diagnosis of any neoplasm (ICD-9-CM 140-239 or A-code A08x–A14x) before their first diagnosis of diabetes were excluded ($n = 14,133$). Besides, we also excluded subjects taking metformin before their diabetes diagnosis, patients with diagnosis of polycystic ovarian syndrome (ICD-9-CM 256.4), and subjects who were less than 15 years old at their first DM diagnosis.

2.3. Criteria and definitions of variables

The subjects who had ever used metformin for more than a month (30 days) were considered as metformin users, while the rest of the subjects in the cohort were considered as metformin nonusers because the usual prescription of oral hypoglycemic agents in Taiwan is 28-day or 30-day supply. The endpoint of this study was the development of lung cancer, defined by the appearance of lung cancer diagnosis (ICD-9-CM of 162.xx) in at least twice in the ambulatory claim database or at least once in the inpatient claim database, which was further confirmed with the Catastrophic Illness Registry. Pathological confirmation is generally required for reporting a cancer diagnosis to the Catastrophic Illness Registry. The index date was defined as the date of the earliest DM diagnosis for each patient. The subjects were followed from the date of their initial DM diagnosis, defined as the index date, to either the development of lung cancer, end of the study period, or termination of the record because of death or withdrawal from the insurance program, whichever came first. To minimize immortal time bias, the follow-up time used for Cox regression analyses was calculated from a year after the index date.

The modified Charlson Comorbidity Index (mCCI) score was calculated by subtracting two diabetic conditions from the original Charlson Comorbidity Index score [23]. The defined daily dose of metformin is 2 g [24]. The cumulative dose of metformin use was calculated as cumulative defined daily dose (cDDD). The intensity of metformin use during the treatment period was calculated with dividing cDDD by the period of metformin use.

2.4. Statistical analysis

First, the age, gender, lung cancer incidence, and mCCI score were compared between metformin users and metformin nonusers. The subjects were further classified with the development of lung cancer, and the demographic data, mCCI score, follow-up time, and duration, cumulative dose, and intensity of metformin use were compared. Categorical variables and continuous variables were compared using χ^2 test and Student's t-test, respectively.

To further confirm the association between lung cancer incidence and metformin use, Kaplan–Meier survival analyses and multivariable Cox regression analyses were performed with adjustment of age, gender and mCCI score. Three models were developed using different ways to estimate utilization of metformin, including period of metformin use (Model 1), cumulative defined daily dose (cDDD) of metformin use (Model 2), and intensity of metformin use during the treatment period (dividing cDDD by the period of metformin use) (Model 3). In addition, stratified analyses, which included only either male or female patients, were performed to further confirm our findings.

Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, Wash) was used for data linkage, processing and sampling. All statistical analyses were performed using IBM SPSS statistical software (version 19.0 for Windows; IBM Corporation, New York, NY). The statistical significance level was set at a p value of <0.05.