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Original article

Metformin is associated with a lower risk of colorectal cancer in Taiwanese patients with type 2 diabetes: A retrospective cohort analysis

C.-H. Tseng [a,b,c,*]

[a] Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan
[b] Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Division of Environmental Health and Occupational Medicine of the National Health Research Institutes, Zhunan, Taiwan

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ABSTRACT

Background. – The association between metformin and colorectal cancer (CRC) has rarely been investigated in Asian populations.
Methods. – This retrospective cohort study included patients with newly diagnosed type 2 diabetes during 1999–2005, recruited from Taiwan's National Health Insurance database. A total of 169,601 patients (original cohort: 153,270 ever-users and 16,331 never-users of metformin) and a subgroup of 1:1 propensity-score-matched pairs of 16,331 ever-users and 16,331 never-users (matched cohort) were followed up to 31 December 2011. Cox regression was constructed with the inverse probability of treatment-weighting, using propensity scores, and was used to estimate hazard ratios (HRs).
Results. – In the original cohort, the incidence of CRC was 242.9 and 480.9 per 100,000 person-years, respectively, in ever- and never-users. The overall HR [0.50, 95% confidence interval (CI): 0.45–0.56] suggested a significantly lower risk in metformin users, while compared with never-users, the HR (95% CI) for the first (<27.1 months), second (27.1–58.1 months) and third (>58.1 months) tertiles of cumulative duration of metformin therapy was 0.86 (0.76–0.98), 0.51 (0.45–0.59) and 0.26 (0.23–0.30), respectively. Analyses in the matched cohort showed similar findings with an overall HR of 0.62 (0.53–0.74), and a tertile analysis HR of 1.02 (0.81–1.28), 0.70 (0.56–0.89) and 0.32 (0.23–0.43), respectively. Re-analyses using more stringent diagnoses of CRC and cumulative duration as a continuous variable have consistently supported a protective effect with metformin use.
Conclusion. – Metformin is associated with a lower frequency of CRC.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and second most common in women [1]. In 2012, it affected around 1.4 million people and caused nearly 700,000 deaths worldwide [1]. Although the highest rates were in Western countries, recent studies suggest that the incidence of CRC is increasing in Western Asia and Eastern Europe [1]. In Taiwan, CRC is also on the rise: it is now ranked as the fourth most common cancer in incidence [2] and the third cause of cancer-related death. Important risk factors include genetic factors, obesity, sedentary lifestyle, smoking, alcohol consumption and a typically Western high-fat, low-fibre diet [3].

Diabetes mellitus significantly increases the incidence [4] and mortality of CRC [5]. However, recent observational studies suggest that metformin, an oral antidiabetic commonly used to treat patients with type 2 diabetes mellitus (T2DM), may reduce the risk of several types of cancer, including thyroid [6], mouth [7], stomach [8], bladder [9], prostate [10], breast [11], endometrial [12], ovarian [13] and cervical [14] cancers. A recent meta-analysis of 15 studies showed that metformin is also associated with an approximately 10% lower risk of CRC [15]. Yet, when examining the individual studies included in the meta-analysis, only five reported a significantly reduced risk, whereas the others reported null associations.

Only two of the 15 studies involved patients of Chinese ethnicity in Taiwan [4,16], while all the others were conducted in Western countries [15]. The two Taiwanese studies used the

* Correspondence to: Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Road, 100 Taipei, Taiwan. Fax: +886 2 2388 3578.
E-mail address: ccktsh@ms6.hinet.net.

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population-based reimbursement database of the National Health Insurance (NHI) system, but failed to find any protective effect of metformin on CRC. However, these two studies were limited by not specifically investigating the effects of metformin on CRC, not fully accounting for potential confounders and not being able to evaluate a dose–response relationship. Furthermore, some of the more commonly encountered problems in pharmacoepidemiological studies, such as prevalent user bias, indication bias and immortal time bias [17,18], were also not addressed.

Thus, the present study has aimed to further elucidate the role of metformin on CRC risk in Taiwanese patients with T2DM while addressing the limitations of the previous studies.

Materials and methods

The NHI system, implemented in Taiwan since March 1995, is a compulsory and nationwide system of healthcare. It covers >99% of Taiwan residents and has contracts with all inpatient hospitals and nearly 93% of all medical settings nationwide. The reimbursement databases of the NHI are handled by the National Health Research Institutes (NHRI), and can be used for academic research after proposal review and approval by an ethics review board. All personal patients' information is de-identified for protection of privacy before the database is released for academic research. The present study was granted approval number 99274.

All diagnoses of diseases are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) in the NHI reimbursement database. The contracted medical settings have to submit all relevant disease codes, medications prescribed and procedures performed to the NHI Bureau for reimbursement purposes. Based on the ICD-9-CM, diabetes was coded 250.XX, and CRC was 153 and 154.

The NHRI released the reimbursement database of a randomly selected cohort of 120,000 patients with newly diagnosed diabetes for each calendar year for the entire nation over a 12-year period (1999–2010). Longitudinal reimbursement records from 1996 to 2011 were also available for academic research upon approval. To become a candidate for inclusion in the 120,000 cohort for each specific calendar year, the patient had to not have had any previous diagnosis of diabetes. Thus, the reimbursement database available for academic research ultimately included 1,440,000 patients with newly diagnosed diabetes for the 12-year period.

The patients included in the present study were derived from these 1,440,000 patients. Fig. 1 is a flowchart of the procedures used to create an unmatched cohort (original cohort) and a cohort of 1:1 matched pairs (matched cohort) of ever-users and never-users of metformin. These diabetes patients were diagnosed between 1999 and 2005, and were followed-up at outpatient clinics and prescribed antidiabetic drugs at least twice to ensure they were genuine cases of diabetes with a certain follow-up duration (n = 423,949). To reduce the potential risk of prevalent user bias [17], only new users of metformin for whom it was their first-ever prescribed antidiabetic drug were defined as ever-users. Patients treated with other antidiabetic drugs before metformin were excluded (n = 183,837). In Taiwan, patients with type 1 diabetes mellitus (T1DM) can be waived of much of their copayment after a certified diagnosis and issuance of a so-called 'severe morbidity card' or 'catastrophic illness certificate'. These patients were excluded because metformin is not indicated for T1DM treatment (n = 2062). In addition, 423 patients were excluded because they were missing the following data: (1) age and/or gender was not identified (n = 65); (2) date of diabetes diagnosis was not confirmed (n = 109); and (3) their region of residence and/or occupation were not recorded (n = 249). Also, patients diagnosed with any cancer at either the outpatient clinics or during hospitalization before the date of entry, or within 6 months of diabetes diagnosis (n = 26,610), were excluded to ensure the accuracy of metformin exposure and outcome. To restrict the age at entry, those aged <25 years (n = 9268) or >75 years (n = 27,328) were excluded. To reduce the potential impact of

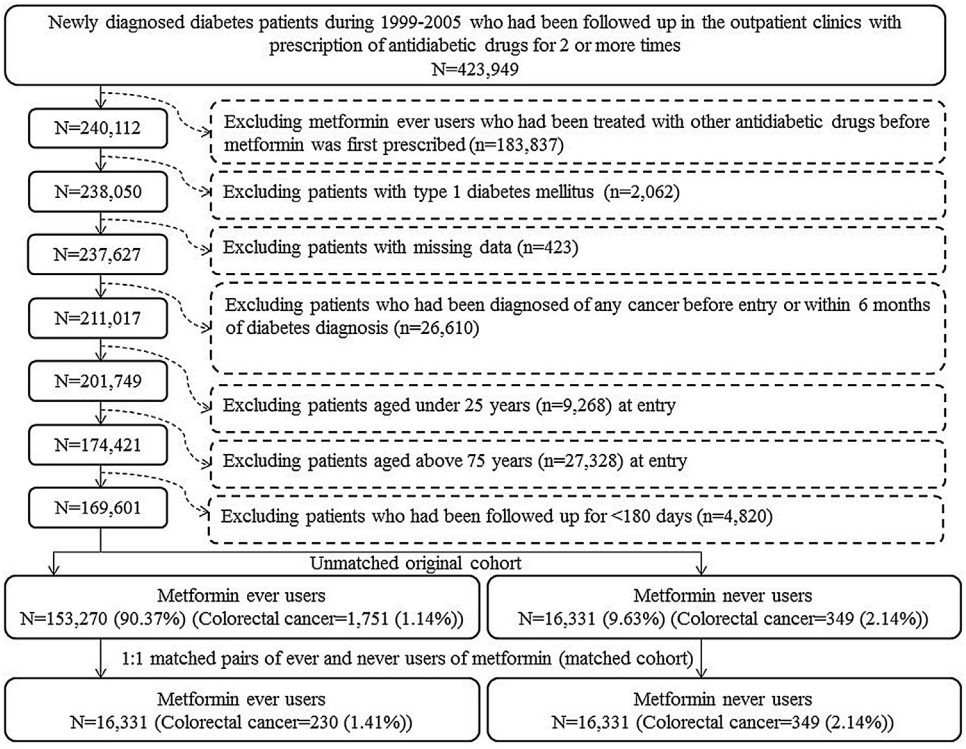

Fig. 1. Flowchart of procedures followed to create the unmatched original cohort and cohort of 1:1 matched pairs of metformin ever- and never-users from the National Health Insurance reimbursement database.

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