Gynecologic Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Metformin and endometrial cancer risk in Chinese women with type 2 diabetes mellitus in Taiwan

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HIGHLIGHTS

- This study evaluated the effects of metformin use on endometrial cancer risk.
- The overall hazard ratio adjusted for propensity score was 0.675 (0.614–0.742).
- An inverse dose–response relationship was also observed.

ARTICLE INFO

Article history:
Received 5 February 2015
Accepted 8 March 2015
Available online xxxx

Keywords:
Diabetes
Dose–response
Epidemiology
Metformin
Endometrial cancer
Taiwan

ABSTRACT

Objective. To evaluate metformin effects on endometrial cancer risk in Chinese female patients with type 2 diabetes mellitus (T2DM) in Taiwan.

Methods. This is a retrospective cohort analysis using the National Health Insurance database of Taiwan. Female patients with newly diagnosed T2DM and without endometrial cancer in 1998–2002 were followed to end of 2009 ($n = 478{,}921$). Among them, 285,916 were never-users and 193,005 were ever-users of metformin. A time-dependent approach was used to calculate endometrial cancer incidence and estimate hazard ratios by Cox regression for ever-users, never-users, and subgroups of metformin exposure (tertiles of cumulative duration and cumulative dose). Sensitivity analyses were conducted in various subgroups.

Results. During follow-up, 728 metformin ever-users and 2157 never-users developed endometrial cancer, representing an incidence of 60.00 and 121.69 per 100,000 person-years, respectively. The overall hazard ratio (95% confidence intervals) for ever- versus never-users after adjustment for propensity score (PS) was 0.675 (0.614–0.742). The PS-adjusted hazard ratios for the first, second, and third tertiles of cumulative duration of metformin therapy were 1.089 (0.966–1.228), 0.707 (0.616–0.812) and 0.313 (0.262–0.374), respectively (P-trend < 0.0001); and 1.062 (0.942–1.197), 0.620 (0.538–0.715) and 0.376 (0.317–0.447), respectively (P-trend < 0.0001), for cumulative dose of metformin. The dose–response relationship was demonstrated in various models and an overall reduced risk was consistently supported by sensitivity analyses.

Conclusions. The use of metformin in women with T2DM was associated with an overall significantly lower risk of endometrial cancer with dose–response relationship.

1. Introduction

The incidence of endometrial cancer is increasing worldwide [1,2], but it is more common in developed countries than in less developed countries, with respective age-standardized incidence of 12.9 and 5.9 per 100,000 population in 2008 [1].

Age and obesity are well recognized risk factors for endometrial cancer; while late menarche, early age at first birth, parity, the use of oral contraceptive and cigarette smoking are associated with a lower risk [3,4]. Studies suggest an increasing epidemic of obesity worldwide [5] and there is a linear relationship between body mass index and endometrial cancer risk [6]. Therefore the increasing epidemic of obesity may be responsible for the increasing incidence of endometrial cancer [4].

Whether metformin may reduce endometrial cancer risk in humans has rarely been studied. In a recent meta-analysis [7], the odds ratio (95% confidence interval) for endometrial cancer associated with metformin use was 0.90 (0.80–1.20) in one observational study [8] and was 0.87 (0.36–2.14) derived from two randomized controlled trials [9]. A case–control study using the UK-based General Practice

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http://dx.doi.org/10.1016/j.ygyno.2015.03.059
0090-8258/

Research Database suggested that ever- versus never-users of metformin had a lower but non-significant risk of endometrial cancer (odds ratio 0.86, 95% confidence interval = 0.63–1.18) [10]. Another recent retrospective cohort analysis using the US healthcare claims of the Truven Health Analytics' MarketScan® and Medicare supplemental databases showed a crude hazard ratio of 0.81 (95% confidence interval = 0.67–0.97) and an adjusted hazard ratio of 1.09 (95% confidence interval = 0.88–1.35) [11]. Therefore, the risk of endometrial cancer associated with metformin use is inconclusive.

The present study aimed at evaluating whether metformin use in the Chinese women with type 2 diabetes mellitus (T2DM) in Taiwan would affect the risk of endometrial cancer. Specifically, the reimbursement database of the National Health Insurance (NHI) was used and a new-user design and time-dependent approach for metformin use in data analyses were applied to minimize the potential "prevalent user bias" [12] and "immortal time bias" [13,14]. "Prevalent user bias" results from the inclusion of prevalent drug users, which may lead to biased estimates because prevalent users are survivors of early pharmacotherapy but risk may vary with time [12]. "Immortal time" refers to a period of follow-up during which the outcome could not occur [13,14]. This may result when the exposure is misclassified such that the person-times in the exposed and unexposed are miscalculated leading to biased estimates [13,14].

2. Methods

The planned analysis of the reimbursement database of all patients with a diagnosis of T2DM during the period from 1996 to 2009 was approved by the ethic review board of the National Health Research Institutes (approval number: 99274).

According to local regulations, the NHI database can be used for academic research after the approval by an ethic review board. For the protection of personal privacy, the identification information of the individuals was scrambled before the release of the database. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) has been used during the study period and diabetes was coded as 250.XX and endometrial cancer as 182.

In Taiwan, physicians always follow the recommendation of the American Diabetes Association for the diagnosis of diabetes mellitus. Because major changes in the diagnostic criteria have been recommended in 1997 [15], the recruitment of patients into the study started after 1998 to minimize the impact of changes in diagnostic criteria. According to the 1997 recommendations, diabetes is diagnosed based on one of the following criteria: 1) symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL; 2) fasting plasma glucose ≥126 mg/dL; or 3) 2-hour plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test [15].

Fig. 1 shows the procedures in creating a cohort of female patients with newly-onset T2DM at entry during 1998–2002 for the study. Male patients and patients with a diagnosis of diabetes at outpatient clinics during 1996 and 1997 were first excluded. This yielded 494,481 female patients. After further excluding patients with type 1 diabetes mellitus (n = 1189), those with a diagnosis of endometrial cancer before the diagnosis of diabetes (n = 1669), those with a duplicated identification number (n = 35), unclear information on date of birth or sex (n = 7366), or a follow-up duration of less than 180 days (n = 11,095), 478,921 patients with a diagnosis of newly-onset T2DM during 1998–2002 were identified.

The age-standardized (to the 2000 World Health Organization population) incidence of endometrial cancer among the diabetic

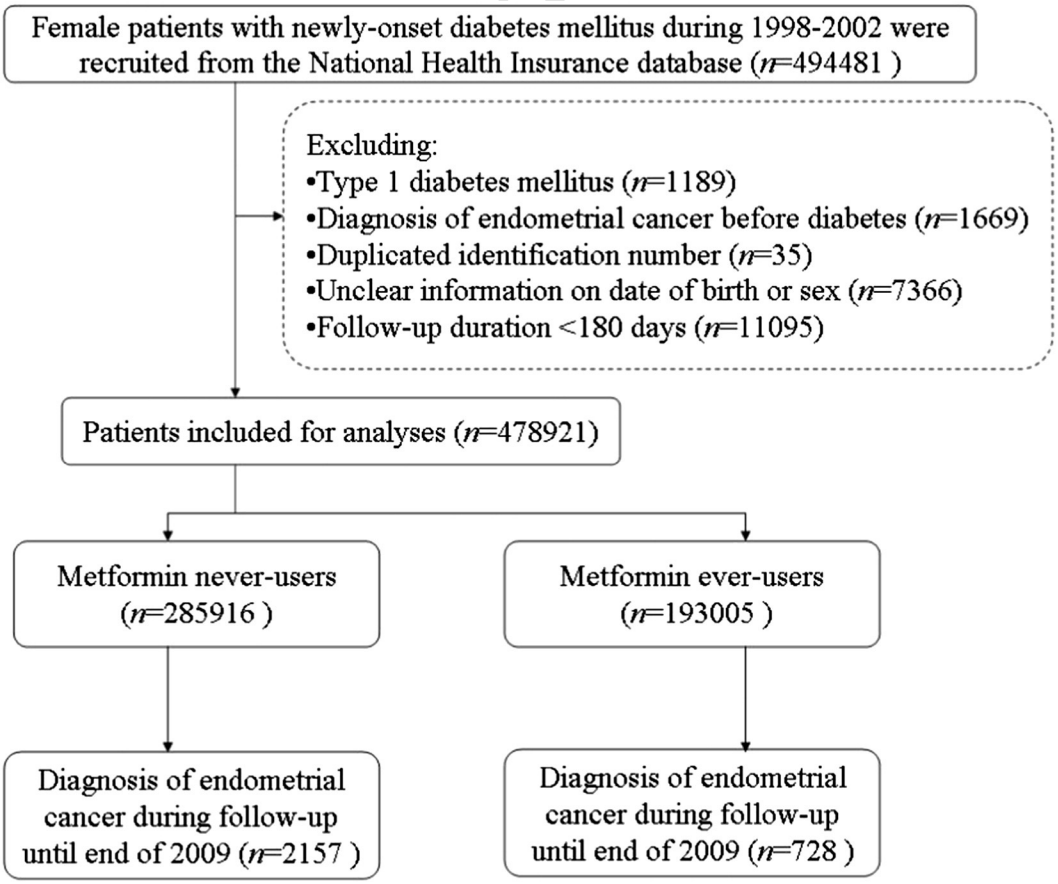

Fig. 1. Flowchart showing the procedures followed in creating a cohort of female patients with newly-onset type 2 diabetes mellitus during 1998–2002.

Please cite this article as: Tseng C-H, Metformin and endometrial cancer risk in Chinese women with type 2 diabetes mellitus in Taiwan, Gynecol Oncol (2015), http://dx.doi.org/10.1016/j.ygyno.2015.03.059