Original Study

Sitagliptin May Reduce Breast Cancer Risk in Women With Type 2 Diabetes

Chin-Hsiao Tseng[1,2,3]

Abstract

Breast cancer risk associated with sitagliptin use was evaluated in female patients with diabetes. The overall hazard ratio was 0.718 (95% confidence interval, 0.573-0.901). When evaluated by the tertiles of cumulative duration and cumulative dose, a significant risk reduction was noted in the third tertiles (ie, > 12.73 months and > 33,800 mg, respectively). The findings supported a reduced risk after prolonged use of sitagliptin.

Background: Whether sitagliptin may affect breast cancer risk remains to be answered. This study evaluated such an association in Taiwanese female patients with type 2 diabetes. **Methods:** A retrospective cohort of female patients with newly diagnosed type 2 diabetes at an age ≥ 25 years between 1999 and 2010 was recruited from the National Health Insurance database. A total of 32,457 ever-users and 396,021 never-users of sitagliptin were followed until December 31, 2011. The treatment effect was estimated by Cox regression incorporated with the inverse probability of treatment weighting using propensity score. Sensitivity analyses were conducted in a matched cohort. **Results:** During follow-up, 78 ever-users and 2204 never-users were diagnosed with breast cancer, representing an incidence of 150.44 and 215.87 per 100,000 person-years, respectively. The hazard ratio (95% confidence intervals [CIs]) for ever- versus never-users was 0.718 (95% CI, 0.573-0.901). The hazard ratio for the first, second, and third tertile of cumulative duration < 5.73, 5.73-12.73, and > 12.73 months was 0.783 (95% CI, 0.523-1.171), 1.021 (95% CI, 0.723-1.441), and 0.455 (95% CI, 0.296-0.700), respectively; and was 0.823 (95% CI, 0.554-1.222), 0.918 (95% CI, 0.639-1.317), and 0.499 (95% CI, 0.331-0.753) for cumulative dose < 14,400, 14,400-33,800, and > 33,800 mg, respectively. Findings were supported by analyses in the matched cohort. **Conclusions:** Sitagliptin may reduce breast cancer risk in female patients with type 2 diabetes mellitus, especially 1 year after its use.

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Introduction

Breast cancer represents 23% of total cancer cases and 14% of cancer deaths in females over the world.[1] It is the most common type of cancer in women, and the incidence is higher in Western countries than in Asian countries. Although the incidence and mortality rates of breast cancer are both decreasing in North American countries and some European countries, they have been increasing in Asian countries.[1]

In Taiwan, the age-standardized incidence (per 100,000 population) of female breast cancer has been increasing steadily, from 12.8 during 1980 to 1984 to 44.5 during 2000 to 2006.[2] Intraductal carcinoma represents approximately 90.4% of all female breast cancers,[3] and the mean overall survival was 62.5 months[4] in Taiwan.

When compared with the nondiabetes population, the incidence of[5] and mortality from[6] breast cancer in female patients with type 2 diabetes mellitus (T2DM) are both significantly increased. The use of antidiabetic drugs may affect the risk of breast cancer in patients with T2DM. For example, metformin use was associated with a significantly lower risk of breast cancer.[7] On the other hand, long-term use or high dose of insulin glargine,[8] human insulin,[9,10] and sulfonylureas[11] may significantly increase the risk of breast cancer.

Incretin-based therapies by using dipeptidyl peptidase-4 (DPP4) inhibitors or glucagon-like peptide-1 receptor (GLP-1R) agonists have become a mainstay in the treatment of T2DM in the recent decade. However, the cancer risk associated with these drugs remains to be clarified.[12] Sitagliptin was the first DPP4 inhibitor

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approved for clinical use in 2006, and it was approved for reimbursement by the National Health Insurance (NHI) on March 1, 2009 in Taiwan. Sitagliptin is probably the most commonly used incretin-based therapy, but its association with breast cancer has not been extensively explored. A pooled analysis of 25 clinical studies including 7726 sitagliptin users and 6885 non–sitagliptin-treated patients with study durations ranging from 12 weeks to 2 years showed that the incidence of breast cancer in patients treated with sitagliptin and the non-sitagliptin group was 0.09 and 0.07 per 100 patient-years, respectively.[13] However, because of the small numbers of incident cancer, statistical analyses could not be reliably performed in the study.

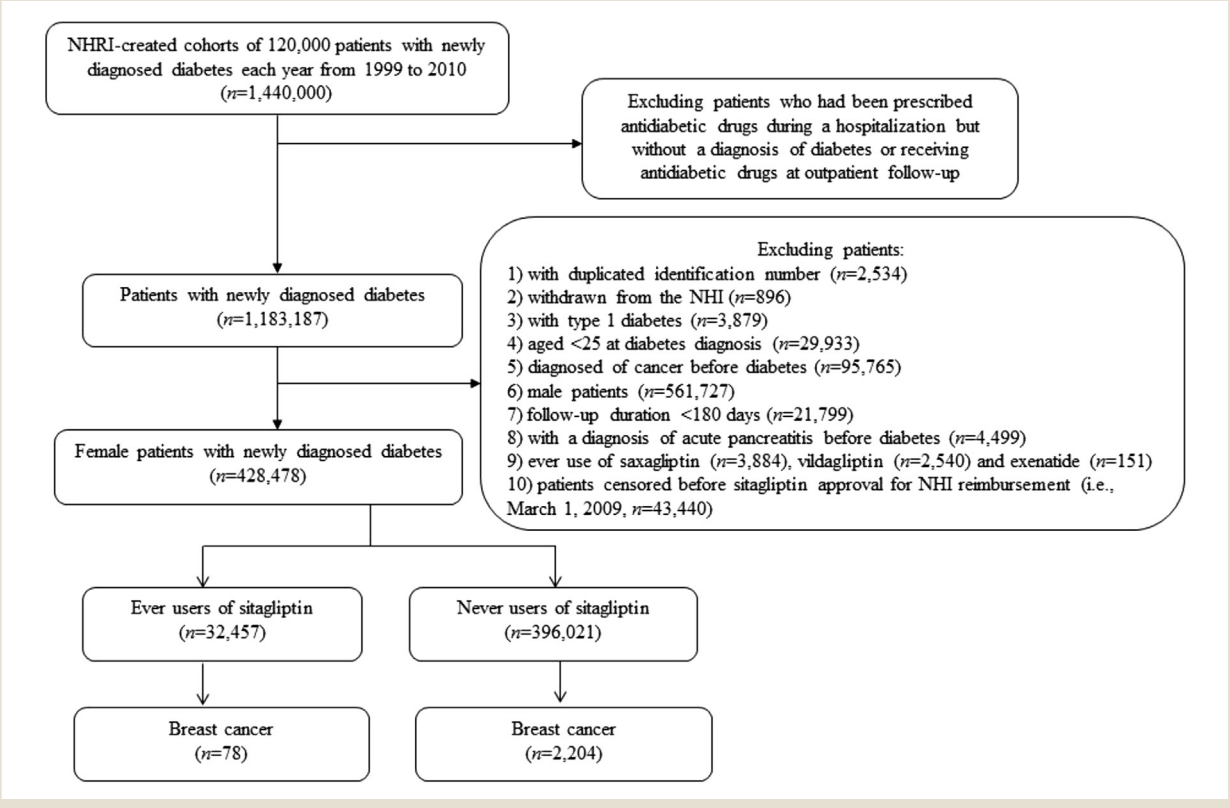
The present study aimed at evaluating whether sitagliptin use in the Taiwanese female patients with T2DM would affect the risk of breast cancer by using the reimbursement database of the NHI. Other incretins (ie, saxagliptin, vildagliptin, and linagliptin for DPP4 inhibitors; and exenatide and liraglutide for GLP-1R agonists) currently available in Taiwan were not evaluated because they were not approved a few years after the approval of sitagliptin and had not been used commonly during the study period. To minimize the potential "prevalent user bias"[14] and "immortal time bias" (the initial period of follow-up during which the outcome cannot occur),[15] a new-user design was applied, and patients should have been prescribed antidiabetic drugs at least 2 times, and those who were followed up for a short period of time (ie, < 180 days) were excluded. To address the differences in baseline characteristics associated with treatment allocation in nonrandom observational studies, Cox regression models were created by incorporation with the inverse probability of treatment weighting (IPTW) using propensity score (PS),[16] and analyses were also conducted in a matched cohort.[17]

Materials and Methods

This retrospective cohort analysis was approved by an ethic review board of the National Health Research Institutes (NHRI, approval number 99274). The compulsory and universal health care system of NHI has been implemented since March 1995. It covers more than 99% of the Taiwanese population and has contracts with over 98% of the hospitals nationwide. Detailed medical records are kept in the database, which includes the information of principal and secondary diagnostic codes, prescription orders, and claimed expenses. According to local regulations, written informed consent was not required because the identification information had already been scrambled prior to the release of the NHI database for analysis.

Figure 1 shows the flowchart for the procedures followed in creating the original cohort of newly diagnosed female patients with T2DM with onset age ≥ 25 years for the study. The NHRI created a cohort of 120,000 newly diagnosed patients with diabetes in each

Figure 1 Flowchart Showing the Procedures Followed in Creating the Original Cohort of Female Patients With Newly Diagnosed Type 2 Diabetes Mellitus and Aged ≥ 25 Years at Diabetes Onset From 1999 to 2010 for the Study



Abbreviations: NHI = National Health Insurance; NHRI = National Health Research Institutes.