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Low-Dose Aspirin Reduces Breast Cancer Risk in Women with Diabetes: A Nationwide Retrospective Cohort Study in Taiwan

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ABSTRACT

Purpose: Low-dose aspirin is commonly used for preventing cardiovascular disease in people with diabetes, but its association with cancer remains controversial. This study used a nationwide population-based reimbursement database to investigate the relationship between low-dose aspirin use and breast cancer incidence in women with diabetes.

Methods: This retrospective cohort study was conducted using data retrieved from the National Health Insurance Research Database in Taiwan from January 1, 1998 to December 31, 2011. Women

diagnosed as having diabetes with low-dose aspirin use (75–165 mg daily) were identified as the study population, whereas those without low-dose aspirin use were selected as the comparison group.

Results: We analyzed 148,739 patients with diabetes. Their mean age (standard deviation) was 63.3 (12.8) years. A total of 27,378 patients were taking aspirin. Overall, the use of aspirin in patients with diabetes reduced the risk of breast cancer by 18% (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.94) after adjustment for potential confounders, namely age and comorbidities. Specifically, a cumulative dose of aspirin exceeding 88,900 mg was observed to reduce the risk of breast cancer by 47% (HR, 0.53, 95% CI, 0.43–0.67); however, low (<8,600 mg) and medium (8,600–88,900 mg) cumulative doses of aspirin did not reduce the risk of breast cancer.

Conclusions: Our findings suggest that a cumulative aspirin dosage of more than 88,900 mg daily was associated with a reduced risk of breast cancer in women with diabetes. However, additional studies are necessary to confirm these findings.

breast cancer
diabetes
aspirin
nationwide cohort study

Introduction

Cancer has a major effect on *global* health; it is the *leading cause of death worldwide, and has been in Taiwan as well since 1982*.[1,2] Breast cancer is the third most common cancer and the fourth major cause of cancer-related deaths worldwide. Its incidence is continuously increasing, and it is currently the fourth most common cancer in Taiwan.[3,4] Among the Asian population, the incidence of type 2 diabetes mellitus has also rapidly increased because of lifestyle changes.[5] Moreover, type 2 diabetes has been found to increase the risk of many types of cancer, including breast cancer.[6,7] An international study investigated the effects of diabetes on the incidence of breast cancer and reported that postmenopausal women with diabetes had an increased risk of breast cancer (odds ratio [OR] = 1.35; 95% confidence interval [CI] = 0.99–1.85).[8] Another population-based cohort study estimated a significant increase of 14% in the incidence of breast cancer in patients with diabetes.[9] Aspirin, at a low dosage, is frequently used as an antiplatelet agent for preventing cardiovascular disease (CVD). Aspirin significantly reduced the risk of breast cancer in one previous case–control study[10]; however, most studies have also indicated that aspirin cannot prevent breast cancer.[11] Overall, prospective studies have yielded mixed results; aspirin has been reported to have no association with,[12–14] reduce the risk of,[15,16] and increase the risk[17] of breast cancer. Most of these studies have focused on the general population, and no study focused exclusively on diabetes. Diabetes is equivalent to CVD, and the prescription rate for aspirin in the secondary prevention of CVD is ~90%.[18] Thus, it is important to determine the relationship between low-dose aspirin and breast cancer incidence in women with diabetes. In response, this study investigated whether low-dose aspirin reduces the risk of breast cancer in women with diabetes by using a population-based reimbursement database.

Methods

Established on March 1, 1995, the National Health Insurance program of Taiwan is a nationwide compulsory health insurance program; by 2005, ~99% of Taiwan's population was enrolled. This data set contains detailed information about patients' disease diagnoses, medical prescriptions and expenses, hospital admissions, and discharges. A detailed description of the patient recruitment and sampling procedure is available on the Website of Taiwan's National Health Insurance Research Database.[19] This database is maintained by the Bureau of National Health Insurance, which collects monthly claims data from all of the medical care units in Taiwan and provides these data to the National Health Research Institutes for research purposes. Notably, the patient data are encrypted before being released to researchers. This study was reviewed and approved by the Institutional Review Board of Chung Shan Medical University Hospital in Taichung, Taiwan.

The Longitudinal Health Insurance Database 2005 was obtained from the National Health Insurance program. This data set comprises a random selection of 1 million people, representing 4% of the total population of Taiwan (23 million people), whose data were entered between January 1 and December 31, 2005. To preserve anonymity, the national identity numbers of the individuals were removed. Sex and age distributions of the sampled individuals in the Longitudinal Health Insurance Database 2005 did not significantly differ from those in the original National Health Insurance Research Database. The present population-based retrospective cohort study was conducted using data retrieved from the Longitudinal Health Insurance Database 2005 from January 1, 1998 to December 31, 2011. The diseases were coded according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study population and endpoint definitions

Patients with diabetes mellitus newly diagnosed from 1999 to 2001 were included in this study; these patients were defined as those who had used antidiabetic agents, including oral antidiabetic agents. Patients taking aspirin were defined as those who were prescribed low-dose aspirin (75–165 mg) within 2 years of their diabetes diagnosis. Finally, patients with breast cancer were defined as those with any hospitalization or outpatient diagnosis codes (ICD-9-CM 174) or catastrophic illness codes. The first hospitalization or an outpatient visit was defined as the time of breast cancer incidence. Patients who had taken aspirin before initiating treatment with antidiabetic agents and those with diabetes who had breast cancer before beginning to take aspirin and antidiabetic agents were excluded.

Aspirin is included in the prescription coverage of the National Health Insurance program. We determined the number of days the prescription would last if a patient took the tablets as directed by the prescribing clinician; thus, a prescription of 28 tablets with directions to take one tablet daily would have a coverage of 28 days. The cumulative dose was calculated from the prescription day to the endpoint event day. Patients were followed from the day of aspirin prescription until the diagnosis of breast cancer, until death resulting from any cause, or until the end of follow-up (December, 2011).

Propensity score matching was performed to include a comparison group according to baseline characteristics, namely age and disease comorbidities (Charlson comorbidity index [CCI]),[20] to minimize the selection bias, thereby allowing a more accurate evaluation of aspirin use in patients with diabetes. Each comorbidity was analyzed as a dichotomous variable (yes or no). We also recorded information about the use of related drugs according to the Anatomical Therapeutic Chemical classification system. The codes for the related drugs are as follows: antihypertensive agents (C02, C03, C07, C08, and C09), HMG-CoA reductase inhibitors (C10AA), other lipid-modifying agents (C10AB and C10BA), antidiabetic agents (A10A and A10B), aspirin (B01AC06), and hormone replacement therapy (G03A, G03C G03D, and G03F). Each related drug used was analyzed as a dichotomous variable (yes or no).

Statistical analyses

Descriptive analysis was used to compare the basic characteristics between aspirin users and nonusers. Unpaired Student *t* and χ^2 tests were used to compare the parametric, continuous, and categorical data between the two groups. The hazard ratio (HR) and Cox proportional hazards model with 95% CI were used to analyze the data and determine the association between aspirin use and breast cancer incidence. Cumulative hazard curves for the time to breast cancer incidence were plotted using the Kaplan–Meier method. A two-sided *p* value of <0.05 indicated statistical significance, and all statistical analyses were performed using SPSS Statistical Package, version 18 (SPSS, Inc.).

Results

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† shows the patient selection flowchart. In total, 148,739 patients with diabetes were recruited; their baseline demographic characteristics, according to those who did and did not use aspirin, are presented in †. Specifically, 27,378 and 74,251 patients were aspirin users and nonusers, respectively, and after an age-matched *comparison,* 24,101 aspirin users and 24,101 aspirin nonusers were recruited for this study. † indicates the results of the time-varying Cox regression model method, used to determine the association between aspirin use and the HR for breast cancer. The risk of breast cancer was first found to be lower in aspirin users (HR, 0.77; 95% CI, 0.68–0.89; $p < 0.01$) in the unadjusted model. After adjustment for age, CCI, hypertension, and hyperlipidemia, Model 2 was modified based on Model 1 (with the addition of antidiabetic agents), and the risk of breast cancer was still found to be lower in aspirin users (HR, 0.78 and 0.81; $p < 0.01$ for Model 1 and Model 2, respectively). † reveals the association between the HRs for breast cancer and aspirin use according to the cumulative dose of aspirin. Specifically, only a high cumulative dose of aspirin (>88,900 mg) for a mean period of 8.5 years was found to reduce the risk of breast cancer (HR, 0.53; 95% CI, 0.43–0.67; $p < 0.01$). The Kaplan–Meier curves of aspirin users and nonusers are depicted in †. Notably, the incidence of breast cancer seemed to reduce after 1 year of aspirin use, with a continued divergence of the cumulative curves throughout the follow-up period.

View larger version (54K)

FIG. 1. Flow diagram of assessment for eligibility. PSM, propensity score matching; CCI, Charlson comorbidity index; DM, diabetes mellitus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHIRD, National Health Insurance Research Database.

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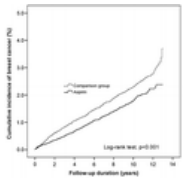

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FIG. 2. Kaplan–Meier analysis of aspirin users and nonaspirin users in patients with diabetes.

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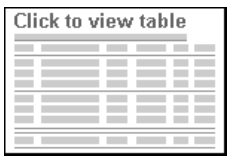
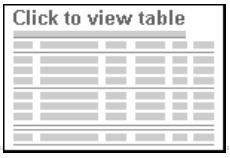


TABLE 1. BASELINE DEMOGRAPHIC DATA OF STUDY POPULATION

TABLE 2. COX PROPORTIONAL HAZARD MODEL TO EVALUATE THE RISK OF BREAST CANCER IN ASPIRIN USE DIABETIC PATIENTS



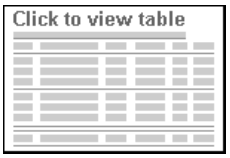


Table 3. Cox Proportional Hazard Model Analysis According to Cumulative Dose of Aspirin Diabetic Patients

Discussion

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The present large population-based cohort study revealed that a high cumulative dose of aspirin reduced the risk of breast cancer in patients with diabetes, whereas low and medium cumulative doses of aspirin did not reduce this risk. Previous studies investigating the association between aspirin use and breast cancer risk in the general population have yielded inconsistent results. For example, epidemiological studies and a recent meta-analysis have reported that aspirin reduces the relative risk of breast cancer by an average of 20%–25%, noting that aspirin exerts similar effects in preventing hormone receptor-positive breast cancer.[21–23] However, the dose, time, and frequency of aspirin use among the subgroup of responsive patients have not been clearly established. Other studies have indicated that aspirin cannot prevent breast cancer incidence.[11,12] Notably, all these studies were conducted in the general population, and none of them focused on patients with diabetes. Thus, this study is the first to discuss whether aspirin reduces the risk of breast cancer in patients with diabetes, a critical topic to address because patients with type 2 diabetes have an increased risk of cancers, including breast cancer, and cancer mortality.[24,25] Hsieh reported that Taiwanese patients with type 2 diabetes are at a higher risk of breast cancer than are their nondiabetic counterparts (adjusted OR, 1.11).[26] The possible relationship between type 2 diabetes and cancer is complex, involving hyperinsulinemia, insulin resistance, and elevated levels of insulin-like growth factor-1 in tumor cell growth.[27]

Aspirin has been proposed to display anticancer activity through many different mechanisms. First, the inhibition of cyclooxygenase,[28] which subsequently reduces the formation of downstream tissue-specific signaling lipids known as prostanoids, has been suggested. Prostanoids play an important role in carcinogenesis by affecting cellular apoptosis, proliferation, and angiogenesis.[29] Moreover, aspirin is an inhibitor of metastasis; it alleviates the production of maspin and regulates maspin through the stimulation of nitric oxide synthesis.[30] Another proposed antimetastatic activity is mediation by platelets, suggesting that aspirin delays the invasion of cancer cells to other tissues.[31]

In addition to its familiar role in the prevention of CVD, aspirin appears to be a promising candidate for preventing cancer, particularly in patients with diabetes. Diabetes is an independent risk factor for several types of CVD, and aspirin is an antiplatelet agent that is commonly prescribed to patients with a high risk of CVD as a primary prevention agent for type 2 diabetes. Thus, patients with diabetes have a higher rate of aspirin use. Recent large clinical trials have focused on cardiovascular outcomes in type 2 diabetes, and an average of 70% of the study population was using aspirin.[32,33] This study determined whether aspirin reduces breast cancer risk in fewer years because patients with diabetes have a higher incidence of breast cancer. The findings revealed that a cumulative dose of aspirin exceeding 88,900 mg reduced the risk of breast cancer. However, low (<8,600 mg) and medium (8,600–88,900 mg) cumulative doses of aspirin were not shown to reduce the aforementioned risk in patients with diabetes. This indicates a reduced risk of breast cancer in patients who must continue their daily low-dose aspirin use for 2.5 years or longer.

Our findings are partially consistent with recent evidence from the general population regarding the chemopreventive effects of aspirin, suggesting that it is likely to reduce breast cancer risk when administered at dosages exceeding 100 mg daily for 3 years or more. This is consistent with a study by Lin et al., which reported aspirin use in patients with diabetes and its association with colon cancer, and demonstrated the highest risk reduction at the highest frequency and after a long duration of aspirin use (HR, 0.32).[34] Thus, a higher accumulation of aspirin decreased the risk of breast cancer.[34] The aforementioned studies highlight the favorable effects of low-dose aspirin over a longer duration. However, considering its clinical use, higher dosages of aspirin are associated with more number of side effects, which may reduce the frequency or duration of aspirin use. Additional studies are required to record data on daily aspirin dosages sufficient to prevent the incidence of breast cancer.

The strengths of this study include the use of a nationwide population-based data set, representative of the entire population of Taiwan. In addition, because patients with cancer in this country can apply for a "catastrophic illness card" through the National Health Insurance program, we were able to minimize the recall bias. Medical treatment is free for most patients when they visit outpatient departments or are admitted to a hospital, and we used a comprehensive prescription and information database rather than self-reported records in the study.

However, there are some limitations. First, we neither have information on the family history of patients with breast cancer nor the information on the patients' risk factors for diabetes or their lifestyle. Laboratory or pathology data were also not evaluated because of the lack of any pathological

information in the database; thus, patients' adherence to prescribed dosages could not be evaluated. We also presumed that patients with diabetes have a higher risk of CVD. Therefore, the prescription patterns of aspirin are expected to be more continuous. The lack of information on over-the-counter medication use is another notable limitation. However, because most prescription drugs are covered by the National Health Insurance program, we assumed that over-the-counter drug use is rare in Taiwan, and the long-term use of aspirin is primarily managed through prescriptions.

In conclusion, our findings suggest that the cumulative aspirin dosage of more than 88,900 mg daily was associated with a reduced risk of breast cancer in patients with diabetes after adjustments for potential confounders, namely age and underlying comorbidities. Nevertheless, additional studies are necessary to confirm these findings.

Acknowledgments

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Author Disclosure Statement

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No competing financial interests exist.

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