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EPIDEMIOLOGY

Metformin may reduce breast cancer risk in Taiwanese women with type 2 diabetes

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Abstract Whether metformin therapy affects breast cancer risk in Asian patients with type 2 diabetes mellitus (T2DM) has not been investigated. The reimbursement databases of Taiwanese female patients with a new diagnosis of T2DM between 1998 and 2002 ($n = 476,282$) were retrieved from the National Health Insurance for follow-up of breast cancer until the end of 2009. Metformin was treated as a time-dependent variable; and of these patients, 285,087 were never-users and 191,195 were ever-users. A time-dependent approach was used to calculate breast 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). During follow-up, 2,412 (1.26 %) metformin ever-users and 9,322 (2.10 %) never-users developed breast cancer, representing an incidence of 201.08 and 535.88 per 100,000 person-years, respectively. The overall multivariable-adjusted hazard ratio (95 % confidence intervals) for ever- versus never-users was 0.630 (0.597–0.665). The multivariable-adjusted hazard ratios for the first, second, and third tertiles of cumulative duration of metformin therapy were 1.122 (1.043–1.207), 0.754 (0.692–0.820), and 0.280 (0.253–0.310), respectively, (P-trend <0.0001); and 1.099 (1.021–1.182), 0.664 (0.611–0.723), and 0.311 (0.281–0.344), respectively, (P-trend <0.0001), for cumulative dose of metformin. Metformin use is associated with a decreased risk of breast cancer.

Keywords Breast cancer · Diabetes · Epidemiology · Metformin · Taiwan

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Introduction

Breast cancer is the most common type of cancer in females, representing 23 % of total cancer cases and 14 % of cancer deaths in females over the world [1]. Incidence rates are higher in western countries than in Asia, but it was estimated that about half of the incident cases and 60 % of the related deaths occurred in economically developing countries [1]. Reproductive and hormonal factors are important determinants for its occurrence, but availability of early detection services is crucially related to prognosis [1]. Physical inactivity, obesity, and alcohol have also been identified as important risk factors for breast cancer [1, 2]. Although the incidence and mortality rates of breast cancers are both decreasing in North America and some European countries, they have been increasing in Asian countries [1].

In Taiwan, the age-standardized incidence rates of female breast cancer have been increasing steadily over the past few decades, from 12.8 per 100,000 population during 1890–1984 to 44.5 per 100,000 population during 2000–2006 [3]. A female breast screening program with the use of mammography every 2 years has been recommended for females aged 50–69 years in Taiwan since 2002, but the screening rate remained as low as 12 % in 2008 [3]. Intraductal carcinoma represents approximately

90.4 % of all female breast cancers in Taiwan [4]; and the percentages of stages 0, 1, 2, 3, and 4 at diagnosis were 9.7, 27.4, 40.5, 17.7, and 4.7 %, respectively [3]. A recent follow-up study including 1,016 female patients with breast cancer in Taiwan showed that approximately 85 % of the patients survived for 5 years after diagnosis and the mean overall survival was 62.5 months [5].

Metformin may exert anticancer effects in in vitro and animal studies via AMP-activated protein kinase (AMPK) dependent or independent pathways [6, 7]. However, whether metformin use for glycemic control in patients with type 2 diabetes mellitus (T2DM) may reduce the risk of breast cancer is not conclusive. A recent systematic review and meta-analysis did not find any significant association between metformin use and breast cancer in patients with T2DM in either the clinical trials ($n = 3$) or the observational studies ($n = 9$) [7]. The estimated pooled odds ratios (95 % confidence interval) were 1.49 (0.74–2.98) and 0.97 (0.88–1.08), respectively [7]. It is worth to point out that none of the studies included in the meta-analysis was conducted in the Asian population.

Because no information is available for the Asian populations, the purpose of the present study was to evaluate whether metformin use in the Taiwanese women with T2DM would affect the risk of breast cancer. Specifically, the reimbursement databases of the National Health Insurance (NHI) were used and a new-user design and time-dependent approach for metformin use in data analyses were applied in order to minimize the potential "prevalent user bias" [8–10] and "immortal time bias" [11, 12].

Materials and methods

The planned analysis of the reimbursement databases 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 (registered approval number: 99274).

Since March 1995 a compulsory and universal system of NHI was implemented in Taiwan. According to this system, all contracted medical institutes must submit computerized and standard claim documents for reimbursement. More than 99 % of citizens are enrolled in the NHI, and over 98 % of the hospitals nationwide are under the contract with the NHI. The databases contain detailed records of every visit for each patient, including outpatient visits, emergency department visits, and hospital admission. The identification information of the individuals was scrambled for the protection of privacy. Diabetes was coded as 250.1–250.9 and breast cancer as 174, based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

To create a cohort of female patients newly diagnosed with T2DM within the period of 1998–2002, male patients and patients with a diagnosis of diabetes at outpatient clinics during 1996 and 1997 in the available NHI databases were first excluded. The data of all female patients across the country who were newly diagnosed with diabetes and/or were under treatment with either oral antidiabetic agents or insulin at outpatient clinics during the period of 1998–2002 were recruited ($n = 491{,}857$). After excluding patients with type 1 diabetes ($n = 1{,}189$), those with a diagnosis of breast cancer before the diagnosis of diabetes ($n = 4{,}429$), those with a duplicated identification number ($n = 35$), unclear information on date of birth or sex ($n = 7{,}366$), or a follow-up duration of less than 6 months ($n = 11{,}095$), a total of 476,282 patients with a diagnosis of newly onset T2DM during 1998–2002 were identified.

Patients who had ever been prescribed metformin after entry were defined as ever-users ($n = 191{,}195$, 40.1 %); never-users ($n = 285{,}087$, 59.9 %) were defined as those who had never been prescribed metformin. Cumulative duration (months) and cumulative dose (mg) of metformin use were calculated from the reimbursement databases. To evaluate a potential dose–response relationship between metformin and breast cancer, tertiles of cumulative metformin duration and dose were used for analyses. Exposure to other oral antidiabetic drugs (sulfonylurea, acarbose, pioglitazone, and rosiglitazone) and insulin was also similarly defined.

A number of comorbidities and covariates were determined as a status/diagnosis at the time of entry. These have been described in detail previously [13–16] and included nephropathy, hypertension, chronic obstructive pulmonary disease (a surrogate for smoking), stroke, ischemic heart disease, peripheral arterial disease, eye disease, obesity, dyslipidemia, urinary tract disease, and other cancers. Other medications included statins, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, aspirin, ticlopidine, clopidogrel, dipyridamole, and nonsteroidal anti-inflammatory drugs.

Follow-up started on the first day of diabetes diagnosis and ended on 31 December 2009, at the time of a new diagnosis of breast cancer, or at the date of the last reimbursement record. Exposure to metformin was treated as a time-dependent variable. Therefore, the metformin ever-users contributed person-years to the nonmetformin group until they started using metformin, and after starting metformin, to the metformin group.

The baseline characteristics of metformin never-users and ever-users were compared by Chi square test. The crude incidence density of breast cancer was calculated for metformin ever-users and never-users and for the different exposure subgroups. The numerator for the incidence was the number of patients with incident breast cancer during

follow-up, and the denominator was the person-years of follow-up. Time-dependent Cox proportional hazards regression was performed to estimate the hazard ratios for breast cancer among metformin ever-users versus never-users, and for the various dose–response parameter subgroups. The following models were created: (1) adjusted for age; and (2) adjusted for all variables compared previously as baseline characteristics between ever-users and never-users (fully adjusted). Age was treated as a continuous variable in the models.

Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

Results

Table 1 summarizes the baseline characteristics between metformin ever-users ($n = 191195$) and never-users ($n = 285{,}087$). With the exception of rates of ticlopidine and clopidogrel use, all baseline characteristics differed significantly between the two groups.

Table 2 lists breast cancer incidence in metformin ever-users and never-users, and among the different tertiles of the dose–response parameters. A smaller proportion of metformin ever-users versus never-users developed breast cancer during follow-up (1.26 vs. 2.10 %). The incidences of breast cancer in metformin ever-users and never-users were 201.08 and 535.88 per 100,000 person-years, respectively. With longer cumulative duration and higher cumulative dose, the incidence decreased correspondingly.

Table 3 shows the age-adjusted and fully adjusted hazard ratios for breast cancer with regards to metformin exposure. For the overall hazard ratios comparing ever-users versus never-users, there was a significantly lower risk of breast cancer associated with metformin use in either model. In the dose–response analyses adjusted for age, all categories of exposure to metformin were associated with a significantly reduced risk, with significant *P*-trends. In the fully adjusted models, although a significantly reducing risk was observed with increasing cumulative duration and cumulative dose, the first tertiles of the dose–response parameters showed a significantly higher risk associated with metformin use.

Table 1 Baseline characteristics between never-users and ever-users of metformin

Variables	Metformin				*P*
	Never-users		Ever-users		
	n	%	*n*	%	
$n = 476{,}282$	285,087		191,195		
Age (years)	54.93	16.69	56.54	12.31	<0.0001
Hypertension	34,457	12.09	34,151	17.86	<0.0001
Chronic obstructive pulmonary disease	7,533	2.64	3,718	1.94	<0.0001
Stroke	8,017	2.81	4,493	2.35	<0.0001
Nephropathy	12,865	4.51	3,342	1.75	<0.0001
Ischemic heart disease	8,532	2.99	6,059	3.17	0.0005
Peripheral arterial disease	3,407	1.20	2,140	1.12	0.0168
Eye disease	745	0.26	691	0.36	<0.0001
Obesity	1,055	0.37	1,080	0.56	<0.0001
Dyslipidemia	41,922	14.70	23,623	12.36	<0.0001
Urinary tract disease	14,359	5.04	10,970	5.74	<0.0001
Other cancers	16,735	5.87	6,774	3.54	<0.0001
Statin	2,669	0.94	3,781	1.98	<0.0001
Fibrate	2,370	0.83	5,434	2.84	<0.0001
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker	10,479	3.68	14,845	7.76	<0.0001
Calcium channel blocker	11,763	4.13	12,289	6.43	<0.0001
Sulfonylurea	32,051	11.24	172,385	90.16	<0.0001
Insulin	5,299	1.86	43,998	23.01	<0.0001
Acarbose	3,338	1.17	56,485	29.54	<0.0001
Pioglitazone	961	0.34	35,527	18.58	<0.0001
Rosiglitazone	1,349	0.47	38,276	20.02	<0.0001
Aspirin	6,101	2.14	6,432	3.36	<0.0001
Ticlopidine	314	0.11	194	0.10	0.3686
Clopidogrel	25	0.01	19	0.01	0.6809
Dipyridamole	5,967	2.09	5,112	2.67	<0.0001
Nonsteroidal anti-inflammatory drugs (excluding aspirin)	49,704	17.43	32,083	16.78	<0.0001

Discussion

The present study is the first to show an inverse association between metformin use and breast cancer risk in female patients with T2DM in an Asian population. The dose–response relationship was well demonstrated using the parameters of cumulative duration and cumulative dose (Tables 2 and 3).

While most studies conducted in western countries did not suggest a lower risk of breast cancer associated with metformin use in patients with T2DM [7], this is the first observational study conducted in an Asian population showing an overall lower risk with significant dose–response relationship (Tables 2, 3). The discrepant findings between the present study and studies conducted in western

Table 2 Incidence of breast cancer by metformin exposure

Metformin use	Case number observed	Incident cases of breast cancer	%	Person-years	Incidence rate (per 100,000 person-years)
Never-users	443,847	9,322	2.10	1,739,582.21	535.88
Ever-users	191,195	2,412	1.26	1,199,503.76	201.08
Cumulative duration (months)					
Never-users	443,847	9,322	2.10	1,739,582.21	535.88
<14.60	63,067	1,221	1.94	273,808.16	445.93
14.60–46.20	63,102	770	1.22	378,986.08	203.17
>46.20	65,026	421	0.65	546,709.52	77.01
Cumulative dose (mg)					
Never-users	443,847	9,322	2.10	1,739,582.21	535.88
<405,350	63,094	1,202	1.91	273,496.63	439.49
405,350–1,525,500	63,090	760	1.20	383,685.80	198.08
>1,525,500	65,011	450	0.69	542,321.34	82.98

Table 3 Metformin exposure and hazard ratios for breast cancer

Metformin use	Age-adjusted			Fully adjusted[a]		
	HR	95 % CI	*P*	HR	95 % CI	*P*
Ever-users	0.335	(0.318–0.352)	<0.0001	0.630	(0.597–0.665)	<0.0001
Cumulative duration (months)						
<14.60	0.834	(0.776–0.896)	<0.0001	1.122	(1.043–1.207)	0.0019
14.60–46.20	0.406	(0.374–0.440)	<0.0001	0.754	(0.692–0.820)	<0.0001
>46.20	0.137	(0.124–0.151)	<0.0001	0.280	(0.253–0.310)	<0.0001
P-trend			<0.0001			<0.0001
Cumulative dose (mg)						
<405,350	0.845	(0.786–0.908)	<0.0001	1.099	(1.021–1.182)	0.0118
405,350–1,525,500	0.396	(0.365–0.430)	<0.0001	0.664	(0.611–0.723)	<0.0001
>1,525,500	0.143	(0.130–0.157)	<0.0001	0.311	(0.281–0.344)	<0.0001
P-trend			<0.0001			<0.0001

Referent group: never-users of metformin

HR hazard ratio, *CI* confidence intervals

[a] Adjusted for all variables in Table 1

countries [7] remain to be explored. It is not known whether such discrepancies could be due to the different ethnicities included into the studies. It is worthy to point out that the numbers of breast cancer in either the treatment groups or the control groups were relatively small in the studies included in the meta-analysis by Franciosi et al. [7] ranging from 15 to 297 among the nine observational studies and from 0 to 8 among the three clinical trials.

The present study has merits of recruiting more than thousands of incident cases of breast cancer in either the never-users or ever-users of metformin, enabling dose–response analyses with sufficient statistical power (Table 2). Because the databases were derived from the whole population without a sampling procedure and they spanned the whole period from the earliest available databases of the NHI since 1996, there was no concern of potential selection bias related to sampling error. Although misclassification of breast cancer might occur, such a probability was low because labeled diagnoses should be printed on all prescriptions handed to the patients. Mislabeling of a cancer diagnosis would undoubtedly be unacceptable to patients, and thus would be promptly corrected.

Obesity is an important risk factor for breast cancer [1, 2]. A slightly but significantly higher risk in the first tertiles of the cumulative duration and cumulative dose of metformin in models adjusted for all covariates (Table 3) could be resulted from a residual confounding by obesity, because metformin is always prescribed for patients with obesity and users in the present study did show a higher prevalence of obesity diagnosis (Table 1). In clinical practice, we do not usually label a patient with the diagnosis of obesity unless he or she is rather obese (probably when the body mass index is >30 kg/m^2). Therefore, patients who used metformin with less obesity would not be labeled with a diagnosis of obesity, rendering a chance of residual confounding by obesity associated with

metformin use. If such a residual confounding did exist, the estimated hazard ratios associated with metformin use (Table 3) would have been underestimated.

Metformin may show anticancer effects in various cancer cell types including the breast, glial cells, stomach, colon, and pancreas [17]. With regards to breast cancer, an early animal study suggested that chronic treatment of female mice with metformin at 100 mg/kg in drinking water significantly decreased the incidence and size of mammary adenocarcinomas [18]. Metformin has also been shown to inhibit aromatase expression in human breast adipose stromal cells via stimulation of AMPK by increasing the expression of LKB1 protein [19]. Inhibition of breast cancer cell proliferation by metformin can also be associated with cell cycle arrest within G0/G1 phase in cultured cell lines, which is induced by activating AMPK with a resulting loss of cyclin D1 [20]. Furthermore, metformin inhibits hepatic glucose output and improves insulin sensitivity with lowering of circulating levels of insulin and glucose, reduces insulin-like growth factors (IGFs), decreases Akt phosphorylation, and inhibits the crosstalk between receptors of insulin/IGF1 and G protein-coupled receptor signaling pathways [21]. It is also possible that metformin may reduce the development of breast cancer through its inhibition on insulin-mediated effects [22].

This study has several strengths. The databases included all claim records on outpatient visits, emergency department visits, and hospital admission. We derived the diagnoses of breast cancer from all these sources. Cancer is considered a severe morbidity by the NHI and most medical co-payments can be waived. Furthermore, there is a low drug cost-sharing required by the NHI and patients from a low-income household, veterans, or patients with prescription refills for chronic disease are exempted from the drug cost-sharing. Therefore, the detection rate of breast cancer would tend not to differ among different social classes. The use of medical records also reduced the potential bias related to self-reporting.

The study limitations included a lack of actual measurement data for confounders such as family history, physical activity, lifestyle, diet, and genetic parameters. In addition, we could not consider the potential impact of biochemical data such as levels of glucose, insulin, C-peptide, and IGFs. Another limitation is the lack of information on the pathology, grading, and staging of breast cancer. Finally, it is worth to stress that the interpretations of the findings of the present study should be cautious because it is an observational study and bias or residual confounding may not be completely excluded.

In summary, the present study suggests that metformin use is associated with a decreased risk of breast cancer in female patients with T2DM.

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Conflict of interest None.

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