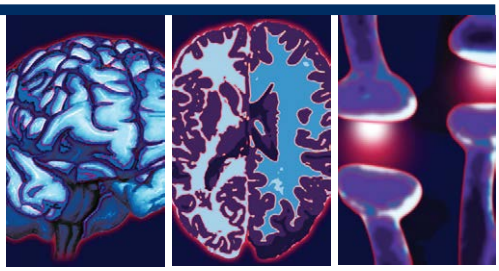

Risperidone Exposure and Breast Cancer Risk: A Cohort Study Using the Taiwan National Health Insurance Research Database

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ABSTRACT

Background

Conventional (typical) antipsychotics are thought to be associated with the development of breast cancer (BC) due to their dopamine-antagonistic effects that lead to increased circulating prolactin. Atypical antipsychotics, particularly risperidone and paliperidone may also increase prolactin secretion. We investigated whether risperidone use was associated with an increased BC risk by estimating the incidence of BC in users of risperidone, other atypical antipsychotics, and conventional antipsychotics.

Methods

This retrospective cohort study used data from Taiwan's Nation Health Insurance Research Database (NHIRD) which captures claims from mandatory universal health insurance in Taiwan. All women aged ≥18 years who initiated treatment with any antipsychotic between July 2000-December 2011 were identified in the database. BC was identified from the NHIRD Registry of Catastrophic Illness and Taiwan Cancer Registry. Cox proportional hazards models were used to adjust for potential confounders and compare BC incidence among the three antipsychotic exposure groups.

Results

There were 233,237 women included in the total cohort analysis. The mean follow-up period was 3.34-5.56 years. Crude incidence rates of BC were 123.1 per 100,000 person-years in the risperidone group, 135.7 per 100,000 person-years in the other atypical group and 149.8 per 100,000 person-years in the typical group. The adjusted hazard ratio was 1.13 (95%CI 0.98-1.29) and 1.07 (95%CI 0.95-1.22) comparing the other atypical and the typical groups, respectively with the risperidone group.

Conclusion

There is no evidence of an increased risk of BC associated with risperidone compared to other atypical or conventional antipsychotics.

Keywords

Risperidone, Taiwan National Health Insurance Database (NHIRD), Breast Cancer, Conventional (Typical) Antipsychotics, Atypical Antipsychotics

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Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women and accounts for approximately 25% of all female cancers [1]. In Taiwan, BC is also one of the most common cancers and the fourth leading cause of cancer death in women [2]. Between 1997 and 2013, the incidence of BC in Taiwan increased from 52.3 to 93.0 per 100,000 person-years, and the median age at diagnosis was 52.6 years [3].

More than 95% of BC display overexpression of the prolactin receptor, and genes that are activated by this receptor are associated with tumorigenesis and cancer cell proliferation. Nevertheless, while some epidemiological studies suggest a possible link between circulating prolactin levels and increased BC risk [4-9], such results have not been consistently observed and the link between prolactin and the pathogenesis of BC remains controversial [10].

Antipsychotic drugs are the most common cause of pharmacologically-induced hyperprolactinemia. Most antipsychotic drugs are dopamine type 2 receptor antagonists which may result in raised circulating prolactin levels [11]. Retrospective cohort studies exploring the effect of antipsychotic drugs on BC risk have produced disparate results. Studies conducted in Sweden and the United Kingdom (UK) showed no increased risk of BC in women using risperidone compared to other antipsychotics [12,13], whereas a study in the United States (US) showed a 16% increase in BC in users compared to non-users of dopamine antagonists including antipsychotics, with a dose-response relationship between larger cumulative dosages and greater risk [14]. Risperidone is known to elevate prolactin more often and to a greater degree than other atypical antipsychotic drugs [15,16]. We applied the same research protocol employed by Reutfors et al. [13] in Sweden to study long-term risperidone exposure and the risk of BC in Taiwan.

Methods

Data source

The NHIRD is a large, representative, population-based claims database provided by the Taiwan National Health Research Institute [17]. The National Health Insurance program was implemented in March 1995, and provides mandatory universal health insurance for approximately 99% of >23 million people in Taiwan. The NHIRD offers a comprehensive set of patient and clinical information, including demographic data, diagnostic codes, dates and types and procedures, dispensed prescription drugs, of expenditures. The National Health Insurance Bureau of Taiwan randomly reviews the charts of one per 100 ambulatory, and one per 20 inpatient claim cases, and interviews patients to verify the accuracy of the diagnosis [17-19]. All personally identifiable information is encrypted to protect patient privacy. A separate subset of the NHIRD is the Registry of Catastrophic Illness (NHIRD-RCI). Insured patients who suffer from certain major diseases can apply for a catastrophic illness certificate which grants exemption from all co-payments. Cancers are statutorily included in the catastrophic illness category. To apply for a cancer catastrophic illness certificate, cytological or pathological reports or evidence supporting the diagnosis of malignancy is required. Records from this database were used to identify cancer diagnoses.

Study population

Individuals with exposure to an antipsychotic between July 2000 and December 2011 were identified by the presence of an antipsychotic prescription/dispensing record in the NHIRD classified as risperidone, any other atypical antipsychotic (except paliperidone), or a conventional antipsychotic using the Anatomical Therapeutic Chemical classification (Appendix). Exposure index date was defined as the first (i.e. the earliest) prescription followed by at least another prescription of the same antipsychotic drug within 90 days, and with no other antipsychotics between the two dispensings. The date of the second dispensing among the earliest pair of consecutive prescriptions in the databases was set as the exposure index date. Eligible study subjects were women ≤ 18 years of age on the exposure index date. Study follow-up started 365 days after the exposure index date. To exclude prevalent BC cases, patients with a diagnosis of BC prior to the exposure index date or within 365 days after the exposure index date were excluded from the study population. Additional inclusion criteria were having lived or immigrated to Taiwan for at least 6 months prior to the start of exposure (i.e. the first dispensing of the qualifying antipsychotic pair), and having remained in the database for at least 365 days after the exposure index date. Individuals were excluded if they had a record of malignancy (other than non-melanoma skin cancer) any

time prior to the start of follow-up (365 days after the exposure index date), or if they had ever received a prescription for paliperidone.

■ Exposure group assignment

We divided exposed subjects into risperidone, other atypical and typical antipsychotic drug groups. The exposure groups were assigned in the following hierarchical order: women with risperidone prescriptions were assessed for eligibility to be included in the risperidone cohort; if not eligible (due to no records of risperidone prescriptions or due to failing other eligibility criteria), women with any other atypical antipsychotic drug prescriptions were assessed for eligibility for the other atypical antipsychotic cohort. If not eligible, remaining women were assessed for eligibility for inclusion in the typical antipsychotic cohort. Exposed individuals had no previous prescription record for the specified antipsychotic prior to the first dispensation.

■ Breast cancer case ascertainment

The Taiwan NHIRD-RCI and the Taiwan Cancer Registry (TCR) are considered accurate and specific for cancer diagnosis given that both sources require pathologic/histology verification. The primary study endpoint was a BC diagnosis (the earliest date of record) identified from the TCR annual report, and/or the NHIRD-RCI.

■ Study follow-up

All women included in the study were followed over time for the occurrence of incident BC. There were two follow-up approaches: the total cohort follow-up period extended from 365 days following the exposure index date until occurrence of BC, emigration, death, or end of the study period (31st December 2012), whichever occurred first. The active treatment follow-up time extended from 365 days following the exposure index date until discontinuation of the initial treatment regimen + 365 days, occurrence of BC, disenrollment from the database, or end of the study period, whichever occurred first. A gap of 1 year or more was considered as discontinuation of a treatment regimen, with the actual date of treatment discontinuation defined as the date of the last received prescription plus days of drug supply.

■ Comorbidity profile

The presence of comorbidities prior to the exposure index date was investigated based on all available history records in the NHIRD using International Classification of Diseases, 9th Revision Clinical Modification and 10th Revision codes (ICD-9-CM/ICD-10). The prevalence of benign breast disorders as well as the following potentially prolactin-elevating somatic conditions (within 6 months prior to exposure index date) was also assessed: acromegaly, pituitary hyperfunction (including drug-induced hyperprolactinemia), hypothyroidism, sarcoidosis, liver cirrhosis, chronic renal failure, Cushing's disease, and polycystic ovary syndrome.

■ Statistical analyses

BC incidence rates were estimated using person-time of the total cohort follow-up, as well as the person-time of active treatment exposure follow-up, for each of the three antipsychotic drug exposure cohorts. Incidence rates were reported as number of cases per 100,000 person-years. BC incidence rates were compared between other atypical antipsychotics and risperidone groups or conventional antipsychotics and risperidone groups using Cox proportional hazards regression models. Covariates (including age, index year, psychiatric diagnosis, medical service use situation, BC-associated physical illnesses, prolactin-elevating medications, mammography) were only retained in the final Cox regression model if their inclusion in a model containing the single covariate and the antipsychotic exposure variable changed the hazard ratio (HR) for the antipsychotic exposure variable by 10% or more, relative to the unadjusted HR for antipsychotic exposure (i.e., adjusted HR/unadjusted HR is either >1.10 or <0.90) [20].

To account for cases of BC possibly missed in either the TCR or NHIRD-RCI, we conducted a sensitivity analysis to additionally include BC diagnosed from NHIRD inpatient records. That is, the sensitivity analysis identified BC cases from any one or more of the following three sources: TCR, NHIRD-RCI, or NHIRD inpatient diagnoses.

We also estimated BC incidence rates for newly treated patients, defined as those patients having no prescription record for any antipsychotic in the six months prior to the first identified index treatment of each exposure group.

Data management and analyses were conducted using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

■ Characteristics of study subjects

There were approximately 9.3 million women aged ≥ 18 years in Taiwan over the study period [21]. During the 11.5-year study period, 233,237 women were included in the total study cohort: there were 72,561 (0.8%) eligible women included in the risperidone group, 84,668 (0.9%) included in the other atypical antipsychotics group, and 76,008 (0.8%) included in the typical antipsychotics group (**Figure 1**). The mean age of women was 54.4 years in the risperidone group, 57.0 years in the other atypical group, and 53.0 years in the typical group (**Table 1**). The risperidone group appeared to have a higher proportion of younger women (30.4% were aged 18-39 years versus 26.4% and 27.1% in the other atypical and typical groups, respectively), whereas the other atypical group appeared to have a higher proportion of older women (36.9% were aged ≥ 70 years versus 31.9% in the risperidone group and 23.7% in the typical group).

'Neurotic stress related or somatoform disorder' was the most common psychiatric diagnosis for all three groups (65%-75%) based on all available history in the database (**Table 1**). The second most common diagnoses were 'schizophrenia' for the risperidone group (48.4% of women), and 'major depression' for the other atypical and typical groups (39.7% and 16.7%, respectively).

The highest proportion of women who had received inpatient psychiatric care within 180 days prior to the first prescription was in the risperidone group (16.0% versus 8.1% in the other atypical group and 3.4% in the typical group) (**Table 2**). The other atypical group had the highest proportion of women who had received inpatient care for somatic symptoms within 180 days prior to the first prescription (25.1% *vs.* 19.2% in the risperidone group and 17.1% in the typical group. Most of the risperidone and other atypical subjects had a psychiatric diagnosis (92.2% and 89.9% respectively), compared with 48.9% of those in the typical group. Higher rates of benign breast neoplasm were observed in the other atypical and typical groups (0.7% in each cohort) than the risperidone group (0.4%). Although medical and medication use 180 days prior to the index exposure differed between the three groups, most of these variables were not confounders for BC risk. Of the covariates tested, all factors except age were excluded from the Cox regression model using the 10% change-in-estimate rule of confounder screening.

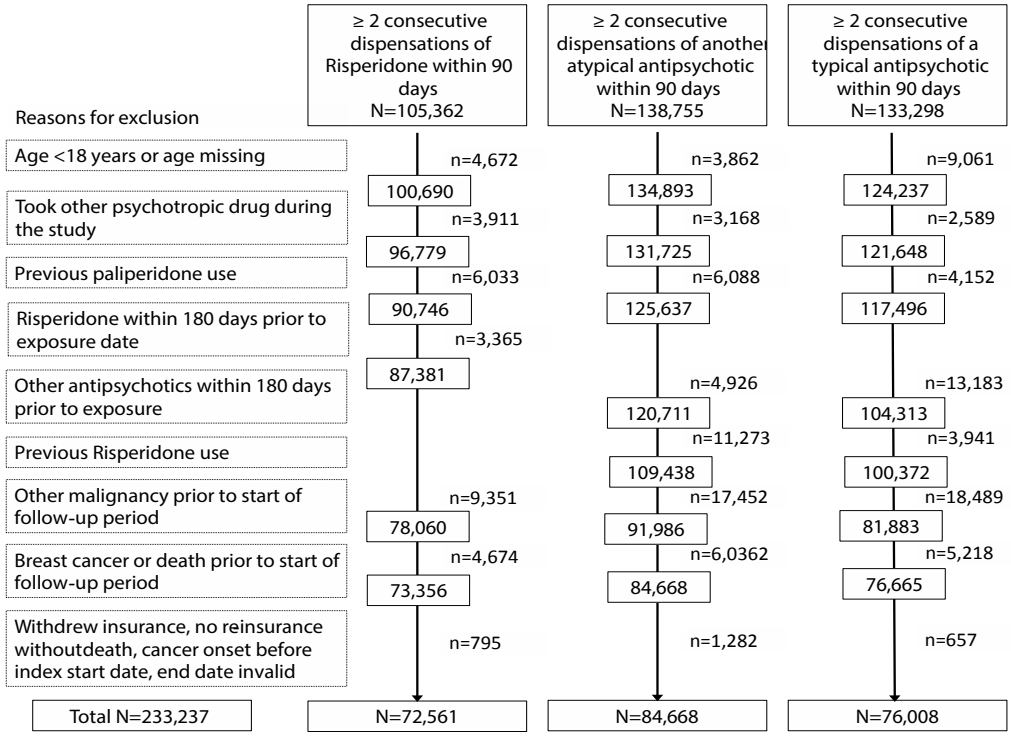

Figure 1: Cohort creation flowchart.

N= Total number in each exposure group n = number excluded

Table 1: Demographic data of included women by index antipsychotic drug exposure (N= 233,237)

	Risperidone		Other atypical		Typical	
Total number included	72,561		84,668		76,008	
	n	%	n	%	n	%
Age at inclusion						
Mean (SD)	54.4	(21.2)	57.0	(21.2)	53.0	(18.7)
Age group						
18-39	22,031	30.4	22,387	26.4	20,623	27.1
40-49	10,905	15.0	12,258	14.5	14,000	18.4
50-59	8,852	12.2	10,172	12.0	13,061	17.2
60-69	7,663	10.6	8,635	10.2	10,334	13.6
≥ 70	23,110	31.9	31,216	36.9	17,990	23.7
Index year						
2000	1,480	2.0	413	0.5	4,777	6.3
2001	5,474	7.5	1,584	1.9	10,198	13.4
2002	6,309	8.7	2,450	2.9	7,945	10.5
2003	7,535	10.4	4,265	5.0	7,557	9.9
2004	7,555	10.4	5,548	6.6	7,434	9.8
2005	6,519	9.0	6,910	8.2	6,463	8.5
2006	6,857	9.5	7,401	8.7	5,216	6.9
2007	7,040	9.7	7,975	9.4	4,800	6.3
2008	6,494	9.0	9,617	11.4	4,598	6.1
2009	5,918	8.2	11,208	13.2	5,854	7.7
2010	5,811	8.0	13,034	15.4	5,444	7.2
2011	5,569	7.7	14,263	16.9	5,722	7.5
Psychiatric diagnosis						
Any psychiatric diagnosis, ICD: 290-319	71,951	99.2	83,295	98.4	62,393	82.1
Schizophrenia	35,084	48.4	13,892	16.4	7,931	10.4
Bipolar disorder	15,365	21.2	20,946	24.7	6,292	8.3
Dementia	23,901	32.9	27,728	32.8	10,313	13.6
Major depression	19,173	26.4	33,649	39.7	12,686	16.7
Other organic psychiatric disorder	21,299	29.4	20,802	24.7	8,204	10.8
Alcohol use disorder	2,201	3.0	4,740	5.6	2,618	3.4
Other substance use disorder	2,980	4.1	5,449	6.4	2,448	3.2
Other psychosis	23,073	31.8	13,968	16.5	6,255	8.2
Neurotic stress related or somatoform disorder	47,445	65.4	64,470	76.1	51,364	67.6
Personality disorder	3,419	4.7	5,958	7.0	1,924	2.5
Mental retardation and autism	3,754	5.2	1,837	2.2	1,126	1.5
Suicide attempt	815	1.1	1,621	1.9	728	1.0
Psychiatric conditions, other than the above	340	0.5	1,003	1.2	2,182	2.9
No psychiatric diagnosis	610	0.8	1,373	1.6	13,615	17.9

n% = number/percentage of women.
Index year: the year of the exposure index date (the earliest prescription followed by at least another prescription of the same antipsychotic drug within 90 days).

Women in the typical group were more likely to have index antipsychotic drug exposure in the early years of the study (mean total cohort follow-up period of 5.56 years), whereas women in the other atypical cohort were more likely to be included in the final years of the study (mean total cohort follow-up of 3.34 years) (Tables 1 and 3).

■ BC incidence and risk estimates

During the total cohort follow-up period, there were a total of 1,449 cases of BC identified in the study cohort from the TCR annual report and/or NHIRD-RCI (Table 3). The rate of incident BC (total cohort follow-up period) was 123.1 per 100,000 person-years in the risperidone group, 135.7 per 100,000 person-years in the other atypical group and 149.8 per 100,000 person-years in the typical group (Table 4). From the crude (i.e., unadjusted) Cox regression model, the typical group had a significantly higher BC

Table 2: Medical history and use of medications of the study cohort.						
	Risperidone		Other atypical		Typical	
	n	%	n	%	n	%
Psychiatric inpatient care within 180 days prior to the first prescription (of the index exposure)						
Yes	11,586	16.0	6,870	8.1	2,563	3.4
Somatic inpatient care within180 days prior to the index exposure						
Yes	13,961	19.2	21,237	25.1	12,978	17.1
Inpatient and outpatient diagnosis within 180 days prior to the index exposure						
Psychiatric diagnosis, ICD: 290-319	66,877	92.2	76,084	89.9	37,149	48.9
Schizophrenia	24,959	34.4	7,886	9.3	4,939	6.5
Bipolar disorder	7,310	10.1	10,303	12.2	2,356	3.10
Dementia	16,215	22.4	18,540	21.9	4,164	5.5
Major depression	8,847	12.2	20,634	24.4	5,049	6.6
Other organic psychiatric disorder	8,859	12.2	8,770	10.4	2,601	3.4
Alcohol use disorder	631	0.9	1,533	1.8	824	1.1
Other substance use disorder	770	1.1	1,535	1.8	729	1.0
Other psychosis	12,033	16.6	6,209	7.3	2,656	3.5
Neurotic stress related or somatoform disorder	16,720	23.0	29,310	34.6	19,553	25.7
Personality disorder	1,008	1.4	2,129	2.5	584	0.8
Mental retardation and autism	1,906	2.6	978	1.2	492	0.7
Suicide attempt	113	0.2	244	0.3	87	0.1
Autism	87	0.1	39	0.1	18	0.0
Disruptive behavior	25	0.0	19	0.0	9	0.0
Psychiatric conditions, other than the above	2,230	3.1	6,494	7.7	3,944	5.2
None of the above	5,684	7.8	8,584	10.1	38,859	51.1
Patients with no psychiatric diagnosis recorded						
Autoimmune disorders	72	0.1	119	0.1	53	0.1
Seizures	2,082	2.9	1,899	2.2	1,228	1.6
Herpes zoster	535	0.7	808	1.0	693	0.9
Polycystic ovary syndrome	116	0.2	200	0.2	97	0.1
Pseudocyesis	70	0.1	95	0.1	58	0.1
Renal dysfunction	1,806	2.5	3,100	3.7	1,670	2.2
Inpatient and outpatient diagnosis (prolactin related) within 180 days prior to the index exposure						
Benign neoplasm of female breast	296	0.4	586	0.7	527	0.7
Hyperprolactinemia	208	0.3	276	0.3	117	0.2
Hypothyroidism	644	0.9	995	1.2	493	0.7
Liver cirrhosis	40	0.1	56	0.1	61	0.1
Chronic renal failure	317	0.4	377	0.5	319	0.4
Cushing's disease	86	0.1	153	0.2	114	0.2
Empty sella syndrome	44	0.1	60	0.1	31	0.0
Lymphoid hypophysis	19	0.0	23	0.0	14	0.0
Chest wall trauma	20	0.0	32	0.0	22	0.0
Cirrhosis	368	0.5	494	0.6	434	0.6
Chronic liver disease and cirrhosis	2,803	3.9	4,167	4.9	4,299	5.7
Alcoholic cirrhosis of liver	40	0.1	56	0.1	61	0.1
Cirrhosis of liver without mention of alcohol	344	0.5	458	0.5	406	0.5
Biliary cirrhosis	3	0.0	17	0.0	7	0.0
Prolactin-elevating medications (common)						
Gastrointestinal medications	18,559	25.6	28,412	33.6	28,542	37.6
Methyldopa	39	0.1	74	0.1	56	0.1
Prolactin-elevating medications (possible)						
Selective serotonin reuptake inhibitors	16,647	22.9	30,583	36.1	8,500	11.2
Opiates	16,221	22.4	25,145	29.7	22,042	29.0
Prolactin-elevating medications (rare)						
Antihypertensive medications	1,692	2.3	2,090	2.5	3,510	4.6
Tricyclic and tetracyclic antidepressants	4,697	6.5	8,031	9.5	6,116	8.1
Other psychotropics	17,005	23.4	29,577	34.9	16,505	21.7

Estrogens	2,623	3.6	3,593	4.2	4,516	5.9
Mammogram exams						
Within 1 year prior to index drug exposure	624	0.9	1,211	1.4	1,142	1.5
Within 1 year after index drug exposure	524	0.7	1,015	1.2	1,109	1.5
Ultrasound breast exams						
Within 1 year prior to index drug exposure	802	1.1	2,143	2.5	1,266	1.7
Within 1 year after index drug exposure	962	1.3	2,069	2.4	1,455	1.9
n% = number/percentage of women.						

Table 3: Demographic data of patients with breast cancer identified from the Taiwan Cancer Registry annual report and/or NHIRD Registry of Catastrophic Illness.

	Risperidone	Other atypical	Typical
Total number	72,561	84,668	76,008
Number Censored			
End of follow-up			
Death	15,356	14,303	12,875
Emigration	1,336	1,315	1,424
Number of breast cancer cases			
Total cohort follow-up	432	384	633
Active treatment follow-up	151	161	110
Person-years of follow-up			
Total cohort follow-up (person-years)	351,012	282,902	422,554
mean (SD) (years)	4.84 (3.14)	3.34 (2.64)	5.56 (3.48)
Active treatment follow-up (person-years)	114,315	116,169	66,603
Mean (SD) (years)	1.58 (2.22)	1.37 (1.87)	0.88 (1.63)
SD: Standard Deviation			

incidence rate than the risperidone group (HR 1.19, 95% confidence interval [95% CI] 1.06-1.35). The crude HR for development of BC was 1.14, 95% CI (0.99-1.31) for the other atypical group compared with the risperidone group.

After adjustment for age, the HR comparing the typical antipsychotic group to the risperidone group was no longer significant (HR 1.07, 95% CI =0.95-1.22). The adjusted HR for the other atypical antipsychotic group versus the risperidone group was 1.13, (95% CI=0.98-1.29).

Results from the active treatment cohort follow-up period (time on drug) were similar to those of the total cohort follow-up (Table 4). In the active treatment analysis, the rate of incident BC was 121.0 per 10,000 person-years in the risperidone group, 117.0 per 100,000 person-years in the other atypical group, and 157.3 per 10,000 person-years in the typical group. There were no significant differences among the three groups based on the HR estimates after adjustment for age.

■ Sensitivity analyses

Among the subgroup of women who were newly treated with antipsychotic drugs (i.e., no prescriptions for any antipsychotic during the 6 months prior to index exposure), the rates of incident BC were 123.2 per 100,000 person-years, 135.5 per 100,000 person-years, and 153.1 per 100,000 person-years, for the risperidone, other atypical and typical groups, respectively. There were no significant differences among the three groups based on the HR estimates after adjustment for age (Table 4).

The results adjusted for age remained similar when we included BC cases identified by inpatient diagnosis (n=1526) in addition to the 1,449 cases identified by the TCR and/or NHIRD-RCI (Table 4).

Discussion

Using a population-based retrospective cohort approach, we found no increased risk of BC among women using risperidone compared to women using other antipsychotic drugs in Taiwan. While the unadjusted rate of incident BC was observed to be higher in women using typical antipsychotics, there was no statistically significant increased risk after adjustment for age. The consistency of the results across the different sensitivity analyses confirms the robustness of the study results.

Age is a well-recognized risk factor for BC [22], and we observed differences in the age

Table 4: Breast cancer incidence rates (breast cancer cases identified by Taiwan Cancer Registry annual report and/or NHIRD Registry of Catastrophic Illness).

	PYR	Number of cases	Cases/ 100,000 PYR	Crude HR	Crude 95% CI	Adjusted* HR	Adjusted* 95% CI
Total cohort follow-up							
Risperidone	351,012	432	123.1	Ref=1	-	Ref=1	-
Other atypical	282,902	384	135.7	1.14	(0.99-1.31)	1.13	(0.98-1.29)
Typical	422,554	633	149.8	1.19	(1.06-1.35)	1.07	(0.95-1.22)
Active treatment follow-up							
Risperidone	124,822	151	121.0	Ref=1	-	Ref=1	-
Other atypical	137,562	161	117.0	1.09	(0.87-1.36)	1.10	(0.88-1.38)
Typical	69,912	110	157.3	1.30	(1.02-1.67)	1.19	(0.93-1.52)
Sensitivity analyses							
Including additional 1,526 BC cases from inpatient records.							
Risperidone	350,955	453	12.91	Ref=1	--	Ref=1	-
Other atypical	282,858	415	14.67	1.17	(1.02-1.34)	1.15	(1.01-1.32)
Typical	422483	658	15.57	1.18	(1.05-1.34)	1.07	(0.95-1.21)
Treatment-naïve total cohort follow-up							
Risperidone	225,568	278	123.2	Ref=1	-	Ref=1	-
Other atypical	220,594	299	135.5	1.13	(0.96-1.33)	1.11	(0.94-1.31)
Typical	1,357,727	2,079	153.1	1.19	(1.05-1.35)	1.11	(0.98-1.26)

PYR: person-years of follow-up, HR: Hazard Ratio, 95% CI: 95% Confidence Interval
* Adjusted by age group

distribution of women included in each of the three groups, with almost half of all women in the typical group (49.20%) aged between 40-69 years, versus 37.79% and 36.69% in the risperidone and other atypical groups. In Taiwan, BC incidence rates increase markedly after 49 years of age [3], and the disparity in age distribution between groups may have caused the difference in BC incidence rates in the crude analysis.

A higher percentage of women in the risperidone group had a recent mammogram and a diagnosis of schizophrenia, which may be associated with a lower risk of cancer [23], and a lower proportion had benign breast neoplasms, baseline hyperprolactinemia, or were taking prolactin-elevating medications: all of which may have influenced the risk of BC in this group. However, none of these factors were retained in the Cox regression model for BC risk based on the 10% change-in-estimate rule of confounder screening.

Risperidone has been marketed in Taiwan since 2000, other atypical antipsychotics since 2008, whereas typical antipsychotic drugs have been available for decades. In our study, the typical group had the longest total person-years of follow-up time, but the shortest active treatment follow-up time. This may reflect the higher percentage of women in this group who had no psychiatric diagnosis, reflecting widespread use of sulpiride, an antipsychotic commonly used to treat gastrointestinal conditions in Taiwan. Alternatively, patients who were initiated on typical antipsychotics may have been more likely to have had their medication changed during the study. By contrast, the risperidone group had the longest active treatment follow-up time, possibly reflecting a positive benefit and more acceptable side-effect profile than other antipsychotics.

In 2013, the estimated incidence of BC in Taiwan was 93 per 100,000 person-years [3]. Our study found that the incidence of BC among women having antipsychotics was 30%-70% higher than that reported in the general population. This finding should be interpreted with caution given that patients exposed to antipsychotics receive more healthcare services and BC is more likely to be detected earlier than in the general population. This detection bias may contribute to the higher incidence rate of BC; however, a similar trend was observed in a large retrospective US study which found a 16% increase in BC among users of antipsychotics [14]. On the other hand, there have been numerous studies that have not shown associations between BC risk and antipsychotic use, and no causal association has been identified [10].

Consistent with our results, cohort studies conducted in the UK and Sweden observed no increased BC risk in risperidone users, and an apparent increased risk associated with typical

antipsychotic use that was no longer present after adjustment for age [12,13]. Our study had a longer follow-up period compared to the Swedish study that used the same protocol (2.4-2.8 years versus 3.3-5.6 years), and we were able to include a substantially larger sample size compared to either the UK or Swedish studies. Our results build on these previous studies and provide additional evidence supporting that risperidone use is not associated with an increased risk of BC.

Strengths of the study include the use of large, nationally-representative data from the NHIRD, in which more than 98% of Taiwan's population is enrolled. While previous studies comparing the risk of BC between users versus non-users of antipsychotics may have been confounded by the presence of underlying disease, the NHIRD made it possible to compare the BC risk accounting for other medical conditions or medications that are associated with elevated prolactin.

A potential study limitation is that women who were included in one exposure group may have switched their antipsychotic drug during the follow-up period. We accounted for possible changes in treatment by evaluating the active treatment follow-up period as well as the total follow-up period. Similar results in both analyses suggest that changes to antipsychotic treatment had little impact on the results, and support the robustness of the conclusion.

Another study limitation is that several BC risk factors, such as excessive alcohol use, obesity, the presence of non-alcoholic fatty liver disease, and smoking status, were not included in this study, and potential differences between the study groups in terms of these risk factors may have influenced cancer risk. Finally, we did not assess the impact of dose or exposure time on BC risk, although previous studies of potential dose-relationships between antipsychotic use and BC risk have given conflicting results [12,14].

Conclusion

In this large retrospective cohort study, we found no evidence for an increased risk of BC among women using risperidone versus other antipsychotics. These results are consistent with the findings of previous studies, and provide reassurance for women requiring antipsychotic medication and prescribers of these drugs.

Ethics Approval

The study was approved by the Ethics Review Board of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital (KSPH-2013-34).

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Declaration of Competing Interests

The authors declare the following conflicts of interest:

FHCC, KYT and SPS received grants from Janssen Research & Development for the submitted work.

HCW and YMC declare no conflicts of interest. HQ, YW and HP are employees of Janssen Research & Development LLC which manufactures and markets risperidone. HP reports stock ownership in Johnson & Johnson Pte Ltd. The contents do not represent the views of the Kaohsiung Municipal Kai-Syuan Psychiatric Hospital or the Taiwan Government.

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