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Relationship between antidepressant prescription and breast cancer: a population based study in Taiwan

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Abstract

***Objective*: To investigate the association between antidepressant prescription and breast cancer.**

***Methods*: The National Health Research Institute in Taiwan provided a database of 1 000 000 random subjects for this study. We identified 14 737 new antidepressant female users who were more than 15 years old during 1999–2005 with at least 10 prescriptions and one year exposure to an antidepressant. These were matched 1:1 by age and residence to non-antidepressant users from the same database to compare the risk of breast cancer.**

***Results*: In a model adjusted by age, residence, insurance amount, and depressive disorder, antidepressant prescription was not associated with breast cancer risk. This held true for both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants.**

***Conclusions*: There was no evidence for an association between antidepressant prescription and the risk of breast cancer.**

Introduction

Breast cancer is the most common malignancy in women, with 178 480 new cases in the United States each year [1]. More than 1.6 million new diagnoses of breast cancer were found among women worldwide in 2010 [2]. With the improvement of early detection and treatment, survival rates have increased to the extent that 89% of patients survive 5 years beyond diagnosis [1]. Antidepressants (ADs) are increasingly prescribed for other conditions besides depression such as hot flashes, headache, back pain, neuropathy, sleep-related conditions, anxiety spectrum disorders, eating disorders, and fibromyalgia [3]. Some biological evidence has suggested that ADs might be related to cancer risk [4,5], in that certain agents promote mammary tumor growth in mouse models [6]. AD use has also been associated with acute increases in prolactin levels in women [7], and higher serum prolactin levels have been associated with increased breast cancer risk [8]. However, several epidemiologic studies have not supported an association between AD use and breast cancer [9–13].

One earlier systematic review of nine studies investigated the association between ADs with breast cancer [14], concluding that current evidence did not support an association. However, there were mixed results and several methodological flaws noted, including recall bias, lack of statistical power, and underestimated confounding [14]. A recent review [15] of 61 articles concerning associations with breast and ovarian cancer specifically reported that 41 of the studies showed no association or an anti-proliferative effect but 20 studies reported a positive association between ADs and cancer. The pooled odds ratio for the association between AD use and breast/ovarian cancer in the epidemiologic studies was 1.11 (95% CI, 1.03–1.20) [15]. This review also found that researchers with industry affiliations were significantly less likely than researchers without those ties to conclude that ADs increase the risk of breast or ovarian cancer. Because of these inconsistent results, the authors suggested that large scale prospective cohort studies of women using SSRIs were needed in order to determine if ADs cause and/or enhance breast tumor growth [15].

Discrepancies in previous studies have included the type of ADs used, introduction of new medications, the inclusion of minimum duration of use as an exposure, short-versus long-duration AD use, and changes in prescription practices in AD classes [9]. Some studies have utilized pharmacy database records [14,16], while others

have relied on self-report [13,17,18]. Recall bias for antidepressant use is the major limitation for previous case–control studies [9]. Furthermore, most have been carried out in Western Countries.

Despite the inconsistent conclusions, antidepressant use remains common and increasing. This study aimed to use a population-based cohort dataset in Asia to provide further epidemiological evidence on the relationship between breast cancer risk and prior use of selective serotonin reuptake inhibitors, tricyclic antidepressants, and other newer antidepressants.

Methods

National Health Insurance in Taiwan

In 1995, National Health Insurance (NHI), a government-run insurer with a single-payer insurance system, was established in Taiwan and centralized the disbursement of all health-care funds. The characteristics of NHI include: payroll-related premiums shared by employers, employees, and the government, fee-for-service under the global budget, and the requirement of co-payment for ambulatory care, inpatient care, and medicine. In addition, there is mandatory enrollment. By December 2008, there were 22 918 million individuals nationwide enrolled in the program, with a coverage rate of 99.5%, rising from 92% in the launch period in 1995. The Bureau of NHI (BNHI) contracted almost 93.3% of medical institutions nationwide providing the public with comprehensive medical benefit coverage, such as outpatient, hospitalization, day care for the mentally ill, and social rehabilitation. The Bureau of NHI also requires the registration of all cases of serious disabling disease (SDD), including chronic renal failure, myasthenia gravis, and cancer.

Sample

This was a population-based retrospective cohort study. The NHI medical claims database, including ambulatory care, hospital inpatient care, dental services, and prescription drugs, was provided by the National Health Research Institute (NHRI). The NHRI provided a database of 1 000 000 randomly selected registered people for research. The sampling proportion was about 5% of the total Taiwan population. There were no significant differences in age or sex in all enrollees within the NHI. In this study, we were able to define 10 848 female new AD users who were more than 15 years old during 1999–2005 with at least 10 prescriptions and one year's exposure to ADs. From the same dataset non-AD users were identified and matched 1:1 by sex, age, and residence. We also limited the matched non-users to those with no breast cancer diagnosis for more than 12 months prior to the matched case's antidepressant first use.

The diagnosis of breast cancer was identified according to the International Classification of Disease, ninth revision (ICD-9), code 174. Patients with SDD certificates are eligible for exemption from insurance premium and co-payments. Therefore, approval of SDD certificate needs strict evaluation by the BNHI. In this study, all breast cancer subjects were verified by linking the encrypted identification number with the SDD certificate. All study subjects were alive in 2005. The study data did not indicate any identifying information, and therefore Institutional Review Board approval was not required.

Statistical analysis

The association between AD prescription and breast cancer was analyzed by time-dependent survival regression models adjusted for age, residence, insurance amount, and depressive disorder. In the analysis period (1999–2005), patient's antidepressant exposure was time-cumulative. We calculated the cumulative prescriptions for each antidepressant user at each medical record and fitted accumulative prescriptions effect on breast cancer incidence using the time-dependent survival regression model. Age was categorized into 15–24, 25–44, 45–64, and ≥65 year groups. Residence was categorized as rural and urban. The insurance amount was classified into one of four categories: fixed premium and dependent, less than US$640 (NTD20 000), US$640–1280 (NTD20 000–39 999), and US$1281 (NTD40 000) or more. In this respect, 'fixed premium' identifies people receiving social welfare support including those with low income and/or veterans. The 'dependent' category identifies members of a family with no income. The model was tested first for all study patients, then among subgroups according to different classes of antidepressants: tricyclics, SSRIs, and others. SAS version 9.2 was used to analyze the data. In this study, the significance level was set at 0.05.

Results

Because of the matched design, the distribution of age and residence was identical between the AD and non-AD groups. The proxy economic status (insurance amount) for the AD group was slightly lower than the non-AD group ($p < 0.001$). The incidence of breast cancer revealed no significant difference between antidepressant (0.74%) and non-antidepressant groups (0.60%) in our samples. In the total 14 737 new antidepressant users with at least 10 prescriptions and one year exposure to antidepressants during 1999–2005, there were 7761 (52.66%) with 10–19 prescriptions, 2939 (19.94%) with 20–29 prescriptions, 1580 (10.72%) with 30–39 prescriptions, 827 (5.61%) with 40–49 prescriptions, and 528 (3.58%) with more than 50 prescriptions. Depressive disorder was predominately among the antidepressant group ($P < 0.001$) (Table 1). Prescriptions of different antidepressant agents are shown in Table 2.

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Table 1. Demographic and clinical characteristic statistics, 1999–2005

Characteristic	Antidepressant N	Antidepressant %	Non-antidepressant N	Non-antidepressant %	P value
Age group					
15–24	1182	8.02	1211	8.22	0.381
25–44	4974	33.75	5084	34.5	
45–64	5529	37.52	5401	36.65	
65+	3052	20.71	3041	20.64	
Residence					
Rural	3708	25.16	3708	25.16	1.000
Urban	11 029	74.84	11 029	74.84	
Breast cancer					
No	14 628	99.26	14 648	99.4	0.714
Yes	109	0.74	89	0.60	
Insurance amount (NTD [a])					
Fixed premium and dependent	6538	44.36	5898	40.02	<0.001
<20 000 NTD	4857	32.96	4917	33.36	
20 000–39 999 NTD	2507	17.01	2727	18.5	
≥40 000 NTD	835	5.67	1195	8.11	
Antidepressant prescriptions					
0			14 737	100	
10–19	7761	52.66			
20–29	2939	19.94			
30–39	1580	10.72			
40–49	827	5.61			
≥50	528	3.58			
Depressive disorder [b]					
No	5980	40.58	14 000	95.00	<0.001
Yes	8757	59.42	737	5.00	

[a]1 US $ = 32.2 New Taiwan Dollars (NTD) in 2005.
[b]Depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311).

Table 2. Antidepressant prescriptions and patients in 14 737 female cases with age ≥ 15 years old, 1999–2005

Antidepressant class	Antidepressant agent	Prescriptions N	Prescriptions %	Patients	Mean prescriptions
Tricyclics					
	Imipramine	50 929	20.40	7174	21.49
	Amitriptyline	17 793	7.13	2396	7.18
	Doxepin	13 835	5.54	3534	10.58
	Maprotiline	2696	1.08	464	1.39
	Clomipramine	1418	0.57	277	0.83
	Dothiepin	544	0.22	121	0.36
	Viloxazine	0	0	0	0
SSRIs [a]					
	Fluoxetine	28 386	11.37	3374	10.11
	Sertraline	21 676	8.68	2554	7.65
	Paroxetine	19 416	7.78	2246	6.73
	Citalopram	10 356	4.15	1324	3.97
	Fluvoxamine	7069	2.83	843	2.52
	Escitalopram	230	0.09	78	0.23
Others					
	Moclobemide	2288	0.92	345	1.03
	Trazodone	61 982	24.83	6919	20.72
	Venlafaxine	4360	1.75	614	1.84
	Mirtazapine	4898	1.96	778	2.33
	Bupropion	1686	0.68	324	0.97
	Duloxetine	0	0	0	0
	Milnacipran	58	0.02	22	0.07

[a]SSRIs: selective serotonin re-uptake inhibitors.

Results for associations of interest are summarized in Table 3. In the fully adjusted model which included adjustment for age, residence, insurance amount, and depressive disorder, antidepressant prescriptions were not significantly associated with breast cancer. When we focused on different classes of ADs, SSRIs (Table 4), TCAs, and others all showed no significant association with breast cancer.

Discussion

Our study showed no association between AD use and occurrence of breast cancer even after controlling for effects of depression. When stratified with different types of ADs, the results were similar. The finding is consistent with a population-based case–cohort study from the USA. Wernli et al. also reported that the association between AD use and breast cancer risk was null (OR: 0.89, 95% CI 0.78–1.01), and specific analysis of selective-serotonin reuptake inhibitors (SSRIs) resulted in a similar risk [9]. The authors suggested that confounding by depression was unlikely to be an issue. The result was also

Table 3. The risk of antidepressant (n = 14 737) use on breast cancer in Taiwan, 1999–2005[a]

Variable	Un-adjusted odds-ratio Estimate (95% CI[b])	Un-adjusted odds-ratio P value	Adjusted odds-ratio Estimate (95% CI[b])	Adjusted odds-ratio P value
Antidepressant prescriptions				
0	1.00		1.00	
10–19	0.92 (0.64–1.33)	0.657	0.93 (0.62–1.38)	0.705
20–29	0.79 (0.45–1.39)	0.417	0.77 (0.42–1.43)	0.407
30–39	0.84 (0.41–1.74)	0.643	0.85 (0.39–1.83)	0.673
40–49	1.01 (0.41–2.48)	0.985	1.04 (0.41–2.69)	0.929
50+	0.94 (0.30–2.98)	0.921	0.97 (0.30–3.18)	0.957
Age group				
15–44	1.00		1.00	
45–64	3.99 (2.64–6.02)	<0.001	4.12 (2.72–6.23)	<0.001
≥65	2.47 (1.51–4.04)	<0.001	2.92 (1.74 –4.89)	<0.001
Residence				
Rural	1.00		1.00	
Urban	1.30 (0.89–1.89)	0.177	1.27 (0.85–1.89)	0.250
Insurance amount (NTD[c])				
Fixed premium and dependent	1.00		1.00	
<20 000 NTD	0.75 (0.51–1.10)	0.144	0.84 (0.57–1.26)	0.405
20 000–39 999 NTD	1.14 (0.76–1.71)	0.538	1.19 (0.77–1.82)	0.432
≥40 000 NTD	1.56 (0.93–2.61)	0.095	1.83 (1.07–3.12)	0.027
Depressive disorder[d]				
No	1.00		1.00	
Yes	0.84 (0.60–1.18)	0.312	1.01 (0.67–1.54)	0.948

[a]Time-dependent covariate survival analysis, antidepressant prescription as time-dependent covariate.
[b]CI: confidence interval.
[c]1 US $ = 32.2 New Taiwan Dollars (NTD) in 2005.
[d]Depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311).

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Table 4. The risk of selective serotonin re-uptake inhibitors (SSRIs) antidepressant (AD) use on breast cancer in Taiwan, 1999–2005 (N = 1271)[a]

	Un-adjusted hazard ratio		Adjusted hazard ratio	
Variable	Estimate (95% CI[b])	P value	Estimate (95% CI[b])	P value
Antidepressant prescriptions				
0	1.00		1.00	
10–19	1.20 (0.52–2.74)	0.668	1.26 (0.46–3.45)	0.656
20–29	1.19 (0.29–4.82)	0.811	1.11 (0.24–5.07)	0.894
30+	3.17 (1.00–10.02)	0.049	2.96 (0.80–10.90)	0.104
Age group				
15–44	1.00		1.00	
45–64	6.28 (3.46–11.38)	<0.001	6.75 (3.70–12.31)	<0.001
≥65	3.80 (1.91–7.54)	<0.001	4.92 (2.39–10.11)	<0.001
Residence				
Rural	1.00		1.00	
Urban	1.31 (0.80–2.13)	0.285	1.17 (0.70–1.97)	0.546
Insurance amount (NTD[c])				
Fixed premium and dependent	1.00		1.00	
<20 000 NTD	0.61 (0.36–1.03)	0.066	0.66 (0.38–1.15)	0.142
20 000–39 999 NTD	1.24 (0.75–2.05)	0.403	1.36 (0.80–2.31)	0.261
≥40 000 NTD	1.51 (0.81–2.81)	0.195	1.86 (0.97–3.55)	0.060
Depressive disorder[d]				
No	1.00		1.00	
Yes	1.58 (0.94–2.66)	0.086	1.44 (0.7–2.93)	0.318

[a]Time-dependent covariate survival analysis, antidepressant prescription as time-dependent covariate.
[b]CI: confidence interval.
[c]1 US $ = 32.2 New Taiwan Dollars (NTD) in 2005.
[d]Depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311).

consistent with the report from a large nested case–control study in the UK. The breast cancer cases were identified and reviewed through the medical record system, and the exposure was assessed using a drug database. Among 3708 breast cancer cases and 20 000 controls, the use of SSRIs was not associated with breast cancer risk (OR: 0.98, 95% CI 0.81–1.19) [13].

There were several strengths in this study, which utilized a large and nationally representative sample. We also explored different classes of AD on breast cancer risk. The cohort study design of our research avoided the problem of recall bias in some previous studies. Confounding factors such as depression and socioeconomic status (insurance amount) were also adjusted in the analysis. This study was not sponsored by any pharmaceutical company.

Despite these advantages, there were several limitations. The information was extracted from the dataset with a limited follow-up period of 6 years, so the results cannot be generalized to longer term effects. A problem with newer ADs is also the lack of experience regarding long-term use, and future studies to examine antidepressant use and breast cancer over a longer follow-up period are needed. We did not have information on past use of ADs before the emergence of the national insurance databank, and the information from NHRI did not permit the differentiation of former and current users. Of relevance, one previous study did suggest different effects of former and current AD use, with a reduced risk of breast cancer associated with former use of fluoxetine hydrochloride and reduced breast cancer risk associated with current use of paroxetine hydrochloride [9]. The NHRI data did not include information of all risk factors for breast cancer, such as BMI, family history, and smoking, and the effect of obesity on breast cancer risk was not reported. Women who were not overweight (BMI < 25) have been reported to have a 27% reduction in breast cancer risk among ever users of ADs compared to never users in previous research (OR: 0.73, 95% CI 0.60–0.90) [9]. Cronin-Fenton et al. also found a slight difference between genotoxic and non-genotoxic TCAs on colorectal cancer risk [19], but we did not explore such differences in TCA types on breast cancer. A nationwide, population-based study of cancer patients in Denmark showed the risk for depression after a cancer diagnosis was increased [20]. The treatment of depression, including antidepressants, after cancer diagnosis emerges as an important issue. The present study revealed the influences of antidepressants before cancer diagnosis, but did not provide the related information after cancer diagnosis, and further studies are warranted to investigate this.

In conclusion, the present study did not find any association between ADs and onset of breast cancer. The finding can lessen the worry for many women with depression regarding the use of ADs.

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Conflict of interests

RS has received research funding from Pfizer, Janssen, Lundbeck, and Roche. The authors otherwise declare that they have no conflict of interest.

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