Psycho-Oncology
Psycho-Oncology **24:** 579–584 (2015)
Published online 21 October 2014 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3700

Ovarian cancer and antidepressants

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Received: 28 April 2014
Revised: 4 August 2014
Accepted: 10 September 2014

Abstract

***Background*: The association between antidepressant use and ovarian cancer remains unclear. This study aimed to assess the ovarian cancer risk with antidepressant use in the general population.**

***Methods*: Taiwan's National Health Insurance Research Database was used to identify 957 patients with ovarian cancer and 9570 controls. We used a conditional logistic regression model for data analysis, excluding a 1-year latent period before the diagnosis of ovarian cancer to account for the quantification of treatment duration.**

***Results*: We found no increased risk of developing ovarian cancer among antidepressant users. Neither the duration of antidepressant use nor the average dose had a significant effect on the risk of ovarian cancer. In addition, timing of antidepressant use was not linked to ovarian cancer risk. However, we found the estimate of ovarian cancer risk increased slightly among subjects under 50 years (adjusted OR = 2.03, 95% CI [0.82, 5.02]), although this association was still statistically insignificant ($p = 0.12$).**

***Conclusions*: There was no association between risk of ovarian cancer and use of antidepressant drugs. Whether or not there is possible risk of using antidepressant whose mechanism of action involves dopamine and norepinephrine warrants further investigation.**

Introduction

Antidepressants are widely prescribed to treat depression and anxiety disorders that may become chronic and need long-term medication. There is some evidence suggesting that antidepressant use is associated with increased risk of cancer, with reproductive system and gastrointestinal cancers being the most studied malignancies. However, the results from both epidemiological and experimental studies are inconclusive [1–3].

It has been hypothesized that antidepressants may have a growth-promoting effect on cancer, including melanoma, fibrosarcoma, mammary tumors [2], and colon cancer [4]. It has also been suggested that some antidepressants suppress immune function and increase the risk of cancer [1]. *In vitro* and *in vivo* tests showed that antidepressants may cause genotoxicity and carcinogenicity [5] in animal models. Antidepressants may affect levels of dopamine or norepinephrine, leading to increased levels of gonadotropins and thus the risk of ovarian cancer [6]. However, the results of experimental studies are not entirely consistent, and some studies have found either no effect on cancer growth or even an antineoplastic effect [7–9].

Ovarian cancer is the second most frequently occurring female genital cancer and causes more deaths than any other type of female reproductive cancer [10]. Harlow and Cramer were the first to report the association of self-reported use of antidepressants and risk of ovarian cancer, particularly with use before the age of 50 [11]. In their second study [6], they showed an increased risk of ovarian cancer with drugs affecting dopamine and/or norepinephrine but not with those affecting serotonin. The follow-on studies did not find an increased risk of onset of ovarian cancer among antidepressant users [12–14]. A meta-analysis study recently reported that there may be a modest increase in the risk of breast/ovarian cancer with the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) [7]. The possibility that antidepressants may exhibit a biphasic effect, characterized by 'low-dose stimulation and high-dose inhibition' of neoplastic cell proliferation, has been suggested [7].

There are some limitations to the previous studies. For example, few studies have reported on SSRIs and the association with ovarian cancer risk. No study in the past has investigated the novel antidepressants, such as norepinephrine-dopamine reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor. Most previous studies had relatively small sample sizes.

In the present study, we aimed to explore the associations between the use of antidepressants and diagnosis of ovarian

cancer under conditions of controlled socio-demographic factors, comorbid mental disorders and physical disorders using a nationwide population-based registry dataset.

Methods

Data source

Taiwan's government launched the single-payer National Health Insurance (NHI) program on March 1, 1995. By December 2008, 22.9 million individuals nationwide, 99.5% of the Taiwanese population, were enrolled in the NHI program. The National Health Insurance Research Database (NHIRD), derived from the original claims data of the NHI program, includes ambulatory care, hospital inpatient care, and prescription claims data. The database has been used for pharmacoepidemiological studies and various cancer research studies [15].

The Longitudinal Health Insurance Database 2005, one of the NHIRD subsets, including all original claims data from 1997 to 2011, was used in the study. A total of 1,000,000 individuals, roughly 5% of the total population, were randomly sampled from the NHI registry for beneficiaries 2005. The random sample was representative of the original NHIRD. The study dataset included no identification of the subjects, so institutional review board approval was unnecessary.

Study cohort

We assembled a cohort of NHI participants to conduct a nested case-control study. All individuals who aged ≥15 and had been participants in the NHI program since January 1, 1998 were identified. We followed up the cohort from this entry date until [1] the end of the study period (December 31, 2011) [2] dropping out of the NHI program [3] undergoing of bilateral oophorectomy or [4] development of ovarian cancer. To ensure complete ascertainment of prior medication exposure and clinical diagnoses, subjects were excluded if they had less than a 1-year screening period before 1998. In addition, we excluded patients who were diagnosed with cancer except non-melanoma skin cancer before 1998. In order to have at least 1 year of observation, participants who developed ovarian cancer in 1998 were also excluded.

Cases of ovarian cancer and controls

The study outcome was the incidence of ovarian cancer. The diagnosis was defined as two or more outpatient diagnoses or one inpatient diagnosis of ovarian cancer based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code: 183. The date of the first ovarian cancer claim was defined as the index date.

For each ovarian cancer case, we used an incidence density sampling method [16] and randomly selected 10 controls without ovarian cancer at the time of the case's diagnosis of ovarian cancer. The control was individually matched with the case by year of birth. For the controls, the sampled date was assigned as the index date, which was also the diagnosis date of the matched ovarian cancer case. To be included in the nested case-control analysis, an individual must have been free of any cancer except non-melanoma skin cancer before the index date, and still participated before the assigned index date.

Antidepressants' exposure

We identified antidepressants (N06A) based on the Anatomical Therapeutic Chemical classification system [17]. Antidepressants were classified into tricyclic antidepressants (TCAs; amitriptyline, clomipramine, dothiepin, doxepin, imipramine, maprotiline, and melitracen), SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), or other antidepressants (bupropion, duloxetine, milnacipran, mirtazapine, moclobemide, trazodone, and venlafaxine) [18]. In addition, we considered the antidepressants based on their primary action on the neurotransmitter and grouped them as antidepressants that act via dopamine and/or norepinephrine (bupropion and maprotiline) or those that act via serotonin (amitriptyline, citalopram, clomipramine, dothiepin, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, melitracen, milnacipran, mirtazapine, moclobemide, paroxetine, sertraline, trazodone, and venlafaxine).

In order to avoid protopathic bias, all drug exposure in the year immediately prior to the index date was excluded [19]. Exposure to an antidepressant was classified as non-used or ever-used. 'Ever-used' indicated that a participant had received a prescription for any antidepressant between 1 and 13 years before the index date. In order to explore the dose-response relationship between ovarian cancer and antidepressant use, we calculated the overall duration of use by summing up the day supply of each prescription and classifying it into one of four categories: 0, ≤90, 91–360, and >360 days. To assess the effect of average dose on the risk, we calculated the median daily dose of each antidepressant during the study period. We dichotomized antidepressant users into low daily dose users (<the median daily dose) or high daily dose users (≥the median daily dose). The calculated median dose were 25 mg for amitriptyline, 150 mg for bupropion, 20 mg for citalopram, 75 mg for clomipramine, 75 mg for dothiepin, 10 mg for doxepin, 30 mg for duloxetine, 10 mg for escitalopram, 20 mg for fluoxetine, 25 mg for imipramine, 50 mg for maprotiline, 25 mg for milnacipran, 10 mg for milnacipran/0.5 mg for flupentixol, 50 mg for fluvoxamine, 30 mg for mirtazapine, 300 mg for moclobemide, 20 mg for paroxetine, 50 mg for trazodone, and 75 mg for venlafaxine.

Patient characteristics and potential confounding factors

Patient characteristics included age on the index date and gender. The confounding variables included comorbid

DOI: 10.1002/pon

medical and psychiatric illnesses, which were assessed using inpatient and outpatient claims records before the index date. Comorbid obstetric and gynecologic conditions included polycystic ovary syndrome, infertility, endometriosis, menopause, unilateral oophorectomy, and long-term use of estrogen or progesterone (≥12 months). Psychiatric disorders included depressive disorders, anxiety disorders, sleep disorders, dementia psychotic disorders, and alcoholism. Concomitant use of psychotropic agents included antipsychotics, mood stabilizer, and benzodiazepine. Smoking status and body mass index were not available in the NHIRD; therefore, we used proxy measures including chronic pulmonary disease, cerebrovascular disease, congestive heart failure, chronic renal failure, diabetes mellitus, hyperlipidemia, and hypertension. General health status was measured by the Charlson comorbid index score [20]. Health care system utilization was assessed by the average number of outpatient visits and hospitalizations per year during the 1–13 years before the index date.

Statistical analysis

Descriptive statistics of the ovarian cancer cases and controls were reported in terms of their demographic characteristics, comorbid disorders, and health care system utilization.

To estimate the effect of antidepressants on ovarian cancer risk, we used the PHREG procedure in SAS (version 9.2) to carry out conditional logistic regression models. In order to explore the effect of various characteristics of antidepressants, we examined separate models to explore the ovarian cancer risk of antidepressant use based on antidepressant exposure status, overall duration, cumulative dosage, and antidepressant classes, respectively. In addition, because the exposure history in this cohort was long and heterogeneous, we divided it into four successive periods (1–3, 4–6, 7–9, and 10–13 years prior to the index date) to assess the effect of timing of antidepressant exposure on the risk of ovarian cancer. In this analysis, we included only those patients who were followed up more than 10 years ($N = 3454$).

Because the case number was small, we conducted a stepwise selection for all the previously mentioned potential confounders. We considered that a variable could be entered at the 0.25 level, while a variable should be at the 0.15 level to remain in the model. Using these criteria, we included chronic renal failure, endometriosis, infertility, and mean number of hospitalization per year in the final model.

In order to examine the antidepressant effect modified by the demographic and clinical characteristics of the study subjects, we performed subgroup analyses by stratifying age (15–49 or ≥50 years), mood disorders (presence or absence), concomitant use of antipsychotics (yes or no), menopause status (yes or no), and Charlson comorbid index score (0, 1–2, ≥3). Because the cases and controls were not matched by clinical characteristics, unconditional logistic regression models with adjustment of age and selected confounders were used to evaluate the influence of clinical variation among the study subjects.

The statistical significance of relationships was assessed by using a 95% confidence interval (CI) or p value less than 0.05. All of the analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

In this study, we identified 957 cases with a diagnosis of ovarian cancer and 9570 matched controls between 1999 and 2011. The mean age and corresponding standard deviation of the cases and controls at the first-time ovarian cancer diagnosis was 49.7 ± 15.1 years. The average follow-up period was 7.8 ± 3.8 years. The distributions of demographic characteristics, comorbid medical and psychiatric disorders, and health system utilization are provided in Table 1.

The exposure rate of overall antidepressant use among the cases was not significantly different from that among the controls, yielding crude OR of 1.08 (95% CI, 0.91–1.27) (Table 2). After adjustment for confounding factors, the risk of ovarian cancer among antidepressant users was 1.00 (95% CI, 0.84–1.18). Longer duration of use or higher average dose of antidepressant did not lead to a higher risk of developing ovarian cancer. In addition, timing of antidepressant use was not associated with ovarian cancer risk. There was no significant difference in risk of ovarian cancer across TCAs, SSRIs, and other antidepressants. In addition, we found a statistically insignificantly increased risk of ovarian cancer among antidepressants that act via dopamine and/or norepinephrine (adjusted OR = 1.38, 95% CI, 0.65–2.94).

We found that there were no significant differences in the subgroups by age or other clinical features (refer to Table 3). However, if we focused on antidepressants that acted via dopamine/norepinephrine in those aged <50, the estimate of ovarian cancer risk increased slightly (adjusted OR = 2.03, 95% CI [0.83, 5.02]), although this association was still statistically insignificant ($p = 0.12$) (Supplement Table 3).

Discussion

We found no increased risk of developing ovarian cancer among antidepressant users. The duration or cumulative dose of antidepressant use did not have a significant influence on the risk of ovarian cancer. In addition, timing of antidepressant use was not linked to ovarian cancer risk. No effect of age or other clinical features was found.

The overall lack of an association between antidepressants and ovarian cancer is consistent with the findings reported by Coogan *et al.* [12] in a hospital-based, case-control study involving 748 ovarian cancer cases. Dublin *et al.* [13] demonstrated similar findings in a case-control

DOI: 10.1002/pon

Table 1. Demographic and clinical characteristics of study sample 1999–2011

	Cases (*N* = 957)		Controls (*N* = 9570)			
	N	%	*N*	%	X^2	*p*-value
Age at cohort entry, year					.00	1.00
15–49	712	74.4	7120	74.4		
≧50	245	25.6	2450	25.6		
Charlson comoribid index score					9.01	.0111
0	495	51.7	5486	57.3		
1–2	311	32.5	2788	29.1		
≧3	151	15.8	1296	13.5		
Medical conditions						
Chronic pulmonary disease	131	13.7	1175	12.3	1.59	.207
Cerebrovascular disease	42	4.4	457	4.8	.29	.592
Congestive heart failure	55	5.7	445	4.6	2.32	.128
Chronic renal failure	35	3.7	227	2.4	5.92	.015
Diabetes mellitus	103	10.8	908	9.5	1.63	.202
Hyperlipidemia	138	14.4	1292	13.5	.63	.429
Hypertension	205	21.4	1958	20.5	.49	.483
Endometriosis	71	7.4	295	3.1	48.75	<.001
Infertility	29	3.0	154	1.6	10.29	.001
Menopause	458	47.9	4524	47.3	.12	.730
Polycystic ovary syndrome	5	0.5	38	0.4	.34	.562
Unilateral oophorectomy	10	1.0	54	0.6	3.33	.068
Long-term use of estrogen or progesterone	89	9.3	900	9.4	.01	.916
Psychiatric comorbidity						
Depressive disorders	58	6.1	529	5.5	.47	.493
Anxiety disorders	147	15.4	1461	15.3	.01	.939
Sleep	183	19.1	1802	18.8	.05	.825
Dementia	9	0.9	119	1.2	.67	.415
Psychotic disorders	12	1.3	112	1.2	.05	.819
Alcoholism	5	0.5	32	0.3	.88	.349
Concomitant psychotropic agent						
Antipsychotics	227	23.7	2261	23.6	.00	.948
Mood stabilizer	601	62.8	6103	63.8	.36	.551
Benzodiazepine	47	4.9	433	4.5	.30	.585
Health system utilization	Mean ± SD		Mean ± SD		*t*	*p*-value
Number of hospitalization	0.11 ± 0.29		0.09 ± 0.20		−2.24	.025
Number of outpatient visits	14.0 ± 11.2		13.8 ± 11.5		−.48	.630

study conducted within a health maintenance organization with 314 cases. Of note, Moorman *et al.* [14] found no association between ovarian cancer risk and agents that worked through serotonin or serotonin/norepinephrine pathways in a population-based study with 593 cases identified from the North Carolina Central Cancer Registry. These pathways were the main mechanism of action of the SSRIs, as well as some TCAs. Given that the majority of antidepressant use in our study population was TCAs and SSRIs, the lack of association that we observed was consistent with the findings reported by Moorman *et al.* [14].

Harlow *et al.* [6] reported that an increased risk of ovarian cancer with dopamine/norepinephrine reuptake inhibitors, especially in those with a first use of an antidepressant before menopause. The authors suggested that antidepressants that act via dopamine and/or norepinephrine might induce gonadotropin secretion and consequently increase the ovarian cancer risk. In this study, the risk of ovarian cancer risk with antidepressant via dopamine and/or norepinephrine did not increase statistically significantly. However, among subjects under 50 years old, we found that the adjusted OR with antidepressants that act via dopamine and/or norepinephrine was 2.03 (95% CI = 0.82–5.02; $p = 0.12$). Of note, the case number was small; therefore, the CI was quite wide. The potential association between dopamine and/or norepinephrine and ovarian cancer needs further investigation.

Several epidemiological studies have investigated the possibility that there may be an association between depression and an increased risk of cancer incidence and progression [21–24]. A study specifically identified an association between depression and hormonally mediated types of cancer [25]. Considering that severely depressed patients are more likely to be treated with antidepressants, they might just be a surrogate marker for depression-related ovarian cancer incidence.

DOI: 10.1002/pon

Table 2. Ovarian cancer risk by exposure status of antidepressant use

	Cases (*N* = 957)		Controls (*N* = 9570)		Crude OR	(95% CI)	Adjusted OR	(95% CI)
Exposure status								
None	738	(77.1)	7490	(78.3)	1.00		1.00	
Ever	219	(22.9)	2080	(21.7)	1.08	(0.91, 1.27)	1.00	(0.84, 1.18)
Duration (day)								
≤90	151	(15.8)	1487	(15.5)	1.04	(0.86, 1.25)	0.97	(0.81, 1.18)
91–360	39	(4.1)	305	(3.2)	1.31	(0.93, 1.85)	1.18	(0.83, 1.67)
>360	29	(3.0)	288	(3.0)	1.31	(0.93, 1.85)	0.95	(0.63, 1.42)
Duration (day), by average dose								
≤90, low	61	(6.4)	552	(5.8)	1.13	(0.86, 1.49)	1.06	(0.80, 1.41)
≤90, median/high	90	(9.4)	930	(9.7)	0.99	(0.78, 1.25)	0.93	(0.73, 1.18)
91–360, low	15	(1.6)	136	(1.4)	1.13	(0.66, 1.94)	1.05	(0.61, 1.82)
91–360, median/high	24	(2.5)	169	(1.8)	1.45	(0.94, 2.25)	1.27	(0.82, 1.98)
>360, low	11	(1.1)	115	(1.2)	0.98	(0.52, 1.84)	0.93	(0.50, 1.76)
>360, median/high	18	(1.9)	173	(1.8)	1.07	(0.65, 1.75)	0.95	(0.57, 1.59)
Classes of antidepressant								
Tricyclic antidepressant	161	(16.8)	1581	(17.5)	1.01	(0.83, 1.22)	0.94	(0.78, 1.14)
SSRIs	66	(6.9)	535	(5.9)	1.32	(0.99, 1.77)	1.30	(0.97, 1.74)
Other	67	(7.0)	690	(7.6)	0.88	(0.66, 1.17)	0.84	(0.63, 1.13)
Classes of antidepressant								
Dopamine or norepinephrine	8	(0.8)	54	(0.6)	1.44	(0.68, 3.04)	1.38	(0.65, 2.94)
Serotonin	217	(22.7)	2070	(21.6)	1.06	(0.90, 1.25)	0.99	(0.83, 1.17)
Exposure period before the index date (*N* = 3674)								
1–3 years	45	(13.5)	435	(13.0)	1.06	(0.74, 1.53)	1.05	(0.73, 1.50)
4–6 years	42	(12.6)	456	(13.7)	0.85	(0.58, 1.23)	0.82	(0.56, 1.19)
7–9 years	47	(14.1)	402	(12.0)	1.27	(0.89, 1.82)	1.24	(0.87, 1.78)
10–13 years	35	(10.5)	355	(10.6)	0.93	(0.62, 1.38)	0.95	(0.64, 1.41)

Table 3. Ovarian cancer risk with antidepressant use, stratification analysis by patient characteristics

	Case		Control					
	User	Non-user	User	Non-user	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Age								
15–49 (*N* = 7832)	138	574	1271	5849	1.11	(0.91, 1.36)	1.03	(0.84, 1.26)
≥50 (*N* = 2695)	81	164	809	1641	1.00	(0.75, 1.34)	0.95	(0.71, 1.28)
Mood disorder								
Yes (*N* = 587)	52	6	477	52	0.95	(0.39, 2.31)	0.87	(0.35, 2.14)
No (*N* = 9940)	167	732	1603	7438	1.06	(0.89, 1.26)	0.97	(0.80, 1.16)
Concomitant use of antipsychotics								
Yes (*N* = 2488)	90	137	915	1346	0.97	(0.73, 1.28)	0.90	(0.67, 1.20)
No (*N* = 8039)	129	601	1165	6144	1.13	(0.93, 1.38)	1.05	(0.85, 1.29)
Menopause								
Yes (*N* = 4982)	144	314	1396	3128	1.03	(0.84, 1.26)	0.97	(0.78, 1.20)
No (*N* = 5545)	75	424	684	4362	1.13	(0.87, 1.46)	0.99	(0.76, 1.30)
Charlson comorbid index score								
0 (*N* = 5981)	54	441	613	4873	0.97	(0.73, 1.31)	0.91	(0.68, 1.23)
1–2 (*N* = 3099)	89	222	819	1969	0.96	(0.74, 1.25)	0.93	(0.71, 1.20)
≥3 (*N* = 1477)	76	75	648	648	1.01	(0.72, 1.42)	0.99	(0.70, 1.40)

Limitations and strengths

There were several methodological advantages to the present study. The use of the Taiwan's NHI claims database reduced the likelihood of selection bias and recall bias. It also allowed us to select representative controls from the underlying population. A longitudinal study ensures temporal association between antidepressant use and ovarian cancer. Using physician diagnoses to confirm ovarian cancer rather than questionnaires can eliminate information bias. Controlling for comorbid medical and psychiatric illness can avoid confounding factors. We also explored the association between antidepressants and ovarian cancer extending to newer classes of drugs.

DOI: 10.1002/pon

Nonetheless, there are also some limitations to this article, including the lack of data on other confounding factors such as smoking, estrogen level, oral contraceptive use and family history of ovarian cancer. In addition, ovarian cancer includes several classes, such as epithelial ovarian cancer, germ cell tumors, sex cord cell tumors, etc. Using claims records based on the ICD9-CM, the subclasses could not be specified. Thus, we could not explore the effect of antidepressants on different classes of ovarian cancer. Furthermore, we have used prescription records to reduce the likelihood of individual recall bias; however, misclassification of exposure status might still occur. Some women might have used antidepressants before the dataset was established. Patients might also not take the prescribed antidepressant. If incorrect classification from these sources would occur similarly in both the case and control groups, and thus bias, the risk estimates toward the null. The follow-up period was another limitation, and drug compliance could not be determined by the registry database alone. Finally, the prevalence of antidepressant users was relatively low, and the duration of antidepressant treatment was short in Taiwan [26,27]. Therefore, the case number of patients exposed to specific antidepressants such as newer antidepressants is very small. The results regarding ovarian cancer risk of using antidepressants that act via dopamine or norepinephrine pathways must be interpreted cautiously.

Conclusions

Generally, there was no association between risk of ovarian cancer and use of antidepressant drugs. Whether or not there is possible risk of using antidepressant whose mechanism of action involves dopamine and norepinephrine warrants further investigation.

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