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Invasive Cervical Cancer and Antidepressants

A Nationwide Population-Based Study

Hsiang-Lin Chan, MD, Yi-Hsuan Hsieh, MD, Chiao-Fan Lin, MD, Hsin-Yi Liang, MD, Kuo-You Huang, PhD, Wei-Che Chiu, MD, PhD, Yena Lee, Roger S. McIntyre, MD, PhD, and Vincent Chin-Hung Chen, MD, PhD

Abstract: To our knowledge, no prior population-based study has been published wherein the primary aim was to evaluate whether an association between psychotropic drug prescription and cervical cancer exists. Herein we have conducted the first study that primarily aimed to determine the association between antidepressants use and risk of invasive cervical cancer in the general population.

This is a population-based study utilizing Taiwan's National Health Insurance Research Database. We identified 26,262 cases with invasive cervical cancer and 129,490 controls. We adopted the conditional logistic regression model as the statistical method and adjusted for potential confounding factors.

The prescription of selective serotonin reuptake inhibitors (SSRIs) (adjusted OR = 0.93, 95% CI = 0.84–1.04), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine and bupropion, adjusting for cumulative dose, was not associated with an increased, or decreased, risk for invasive cervical cancer. An association between trazodone prescription and invasive cervical cancer was observed (adjusted OR = 1.22, 95% CI = 1.03–1.43).

An association between the major classes of antidepressants and invasive cervical cancer was not observed herein. Our preliminary finding regarding a possible association between trazodone and cervical cancer requires replication.

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Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, DDD = defined daily dose, DM = diabetes mellitus, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, MAOIs = monoamine oxidase inhibitors, NaSSA = noradrenergic and specific serotonergic antidepressant, NDRI = norepinephrine dopamine reuptake inhibitor, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, OR = odds ratio, RR = relative risk, SARI = serotonin antagonist and reuptake inhibitor, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, STD = sexual transmitted diseases, TCAs = tricyclic antidepressants, WHO = World Health Organization.

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From the Department of Child Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan (HLC, YHH, CFL, HYL); Department of Psychiatry, Chang Gung University, Taoyuan, Taiwan (HLC, YHH, CFL, HYL, VCHC); Department of Speech, Language Pathology and Audiology, Chung Shan Medical University, Taichung, Taiwan (KYH); Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan (WCC); School of Medicine, Fu Jen Catholic University, Taipei, Taiwan (WCC); Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, Canada (YL, RSM); Department of Psychiatry, University of Toronto, Toronto, Canada (RSM); and Department of Psychiatry, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan (VCHC).

Corresponding: Vincent Chin-Hung Chen, Department of Psychiatry, Chang Gung Memorial Hospital Chiayi Branch, Puzi City, Chiayi County, Taiwan (e-mail: hjcch@yahoo.com.tw).

W-CC and H-LC equally contributed to this study.
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INTRODUCTION

Antidepressants are prescribed widely to treat common and chronic disorders including but not limited to depressive disorders, anxiety disorders, pain disorder, smoking cessation, and alcohol use disorders.[1,2] Total expenditures on the antidepressant acquisition per year are estimated at ~1 to 2 billion in United States.[2] The trajectory for antidepressant prescription in North America has been increasing steadily during the past 2 decades. For example, between 1981 and 2000, total prescriptions of antidepressants increased from 3.2 to 14.5 million in Canada.[3] Moreover, it is also reported that ~10% of adults in the United States are prescribed an antidepressant with a significant increase in the number of adults in recent years prescribed multiple antidepressants for a period of time >6 months.[4]

Frequently prescribed classes of antidepressants include the selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The effects of antidepressants on cancer growth had been investigated in previous experimental and epidemiological studies, and important mechanisms of the effects were hypothesized to be related to serotonin,[5] damage to DNA,[6,7] cell cycle modulation,[7,8] and immune regulation.[8,9]

Some experimental studies[10] reported that antidepressants could promote the growth of some cancers. For example, fluoxetine and amitriptyline were found to promote fibrosarcomas, melanomas, and mammary carcinogenesis in rodent models.[11] Moreover, desipramine was reported to exacerbate experimental carcinogenesis in the rat colon.[12] Notwithstanding the foregoing studies, there are other studies with results that are not directionally consistent with the notion that antidepressants are carcinogenic. For example, antidepressants were noted to be associated with decreased incidence of pituitary adenomas, mammary adenomas, fibroadenomas,[13] and to exert inhibitory effects on colon cancer,[14] colorectal cancer,[15] melanoma,[16] prostate cancer,[17] and lymphoma[18] in animal models.

According to the World Health Organization (WHO), cervical cancer is the second most common cancer in women living in less developed regions in the world in 2012. There have been reports of possible association between antidepressant exposure and cervical cancer.[19,20] The notion that antidepressants could lower cervical cancer was supported by an in vitro study that reported the cytotoxic effect of fluoxetine on cervical cancer cells.[19] A separate in vitro study reported that serotonin application to HeLa cells (Human cervical cancer cells) did not increase the cellular survival.[20] To our knowledge, only one epidemiological study investigated the effect of antidepressants on cervical cancer in clinical populations with HIV. When included as an AIDS-related cancer, invasive cervical cancer was not associated with antidepressant use.[21]

In Taiwan, cervical cancer is the seventh most common cause of death from cancer in women in 2013.[22] In the present study, we aimed to explore the associations between the use of antidepressants and diagnosis of invasive cervical cancer with control of potential confounding factors (eg, socio-demographic factors, comorbid mental disorders, and physical disorders utilizing a nationwide population-based registry dataset).

METHODOLOGY

The National Health Insurance (NHI) program has been conducted by the Taiwanese government since March 1, 1995. It has been determined that 99.5% (till December 2008) of Taiwanese residents are represented in the NHI program, providing for a unique, inclusive, cross-national perspective.[23] The National Health Insurance Research Database (NHIRD) included details about ambulatory care, inpatient care, prescription data, medical procedures, and diagnostic coding data. The data of population we used in this study was derived from NHIRD between January 1, 1997, and December 31, 2008.

We conducted a population-based nested case-control study to assess the association between antidepressant use and the incidence of invasive cervical cancer. The diagnosis of invasive cervical cancer was established using the diagnostic code from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 180, and traced to the Catastrophic Illness Claim Dataset to assure the accuracy of the cancer diagnosis. The date of invasive cervical cancer claim was defined as the index date.

Each case with invasive cervical cancer was matched to 5 female controls using incidence density sampling at the time of the cancer case diagnosed as invasive cervical cancer. Each control was free of cancer before the index date and matched to each cancer case by year of birth. For the control group, the sampled date was assigned as the index date. To ensure the same exposure time between the matched control cases, the control subjects who were dead or discontinued insurance before the index date were excluded.

We identified antidepressants (N06A) according to the Anatomical Therapeutic Chemical classification system[24] and retrieve prescription data from NHI files. Antidepressants were divided into different classes according to their mechanism of action including TCAs (ie, amitriptyline, clomipramine, dothiepin, doxepin, imipramine, maprotiline, and melitracen), MAOIs (ie, moclobemide, clorgyline, tranylcypromine, isocarboxacid, phenelzine, and selegiline), SSRIs (ie, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (ie, duloxetine, venlafaxine), SARI (trazodone), NaSSA (mirtazapine), and NDRI (bupropion).

The statistical measure used in this study for the amount of TCAs, MAOIs, SSRIs, SNRIs, SARI, NaSSa, and NDRI exposure was defined daily dose (DDD) defined by WHO.[24] The cumulative doses were divided into 4 exposure dose levels as below, equal to and greater than 28 DDD ($\geqq$28 DDD), equal to and greater than 84 DDD ($\geqq$84 DDD), equal to and greater than 168 DDD ($\geqq$168 DDD), and equal to and greater than 336 DDD ($\geqq$336 DDD). Under consideration to minimize protopathic effect, we excluded antidepressants exposure in the year directly before the index date.[25]

Sociodemographic variables including age at the index date, income, and residential area were retrieved from the NHI files. Potential confounding factors were comorbid mental disorders, comorbid physical disorders, procedures, and other medication use were recognized in outpatient and inpatient claim records before the index date. Comorbid mental disorders included depressive disorders, whereas comorbid physical disorders included type 2 diabetes mellitus (DM), HIV infection, and sexual transmitted diseases (STD). Smoking status was not recorded in NHI files; consequently, we used smoking-related diseases (eg, chronic obstructive pulmonary disease [COPD] and asthma) to proxy smoking status. Frequency of Pap smear was taken into consideration since more frequent use of Pap smear may result in a higher frequency of detection of cervical cancer. The use of aspirin was also controlled as a variable.

Statistical Analysis

Descriptive statistics of invasive cervical cancer cases and controls were presented in terms of their demographic characteristics, comorbid disorders, medical procedure, and other medication use.

The conditional logistic regression model was used to evaluate the effect of antidepressant on invasive cervical cancer. To understand variable aspects that antidepressant may affect the incidence of invasive cervical cancer, we examined the association between risk of invasive cervical cancer and 7 classes of antidepressants. In each class of antidepressant class, the crude odds ratio (OR) and the adjusted OR were calculated in 4 cumulative dosages ($\geqq$28 DDD, $\geqq$84 DDD, $\geqq$168 DDD, and $\geqq$336 DDD).

Corrected odds ratio are calculated after adjusted by demographic data and all confounding factors including depressive disorders, type 2 DM, COPD, asthma, HIV infection, STD, aspirin, and Pap smear frequency. The statistical significance of associations was assessed by using P value <0.05 or a 95% confidence interval (CI). All of the analyses were performed using SAS version 9.2.

Ethics Statement

The study was approved by the Institutional Review Board of Chiayi Chang Gung Memorial Hospital.

RESULTS

We identified 26,262 cases with a diagnosis of invasive cervical cancer and 129,490 matched controls between 1997 and 2008. The mean age of diagnosis of invasive cervical cancer was 55.5 ± 13.2 years old. Sociodemographic variables including age, income, and urbanization were presented in Table 1. After matched to the age of cancer cases, ages of controls recruited were similar to cancer cases. The distribution of income levels and urbanization status between cancer cases and controls showed significantly different ($P < 0.001$).

The percentages of comorbid mental disorders, comorbid physical disorders, medical procedures, and other medication use were presented in Table 2.

TABLE 1. Demographic Data of Cases and Controls

		Cases (n = 26,262)		Controls (n = 129,490)		*P* Value
Age						0.98
	≦40	5616	(21.38%)	27,563	(21.29%)	
	41–50	7623	(29.03%)	37,704	(29.12%)	
	51–60	5377	(20.47%)	26,625	(20.56%)	
	61–70	4881	(18.59%)	24,123	(18.63%)	
	71–80	2324	(8.85%)	11,362	(8.77%)	
	≧80	441	(1.68%)	2113	(1.63%)	
Income (NTD*)						<0.0001
	0	5986	(22.79%)	28,599	(22.09%)	
	1–25,000	4013	(15.28%)	17,491	(13.51%)	
	25,001–40,000	13,802	(52.56%)	65,495	(50.58%)	
	≧40,001	2461	(9.37%)	17,905	(13.83%)	
Urbanization†						<0.0001
	Very high	7242	(27.58%)	40,044	(30.92%)	
	High	12,452	(47.41%)	58,512	(45.19%)	
	Moderate	4548	(17.32%)	20,932	(16.16%)	
	Low	2020	(7.69%)	10,002	(7.72%)	

* 1US $ = 32.3 New Taiwan Dollars (NTD) in year 2008.
† Quartiles by the human development index.

After adjustment for comorbid mental disorders, comorbid physical disorders, frequency of Pap smear and aspirin use, main results of this study were presented in Table 3. Among antidepressants surveyed in this study, a greater percentage of patients had ever used TCAs, MAOIs, and SSRIs; a smaller percentage of patients were prescribed trazodone with smallest percentages of patients were prescribed SNRIs, mirtazapine and bupropion at least one year before the index date.

For TCAs, MAOIs, SSRIs, the overall results showed the frequency of antidepressant exposure was not significantly different between cancer cases and controls regardless of different levels of cumulative dose; the foregoing finding persisted after adjusting for income, urbanization, depressive disorders, type 2 DM, COPD, asthma, HIV infection, STD, Pap smear frequency, and aspirin use. The comparison of the use of non-SSRIs antidepressants (SNRIs, mirtazapine, and bupropion) in cancer cases and controls also did not show a significant

TABLE 2. Medical Diseases and Drugs Used With Cases and Controls

	Cases (n = 26,262)		Controls (n = 129,490)		*P* Value
Medical diseases					
Depressive disorders*	562	(2.14%)	3477	(2.69%)	<0.0001
Type 2 DM	2598	(9.89%)	11,910	(9.20%)	0.0004
COPD	1828	(6.96%)	9451	(7.30%)	0.054
Asthma†	737	(2.81%)	3859	(2.98%)	0.13
HIV infection‡	2	(0.01%)	2	(0.00%)	0.077
STD	634	(2.41%)	3306	(2.55%)	0.19
Procedures					
Pap smear (per year)					<0.0001
<0.2	17030	(64.85%)	82275	(63.54%)	
0.2–0.5	7276	(27.71%)	33738	(26.05%)	
> = 0.5	1956	(6.66%)	13477	(10.41%)	
Medications					
Aspirin	2234	(8.51%)	11588	(8.95%)	0.22

COPD = chronic obstructive pulmonary disease (ICD-9: 490∗-492∗), STD = sexual transmitted diseases (ICD-9: 0541∗, 0781∗, 0788∗, 091∗-099∗, 131∗, 6149∗), Type 2 DM = type 2 diabetic mellitus (ICD-9: 249∗, 250∗, A181).
* Depressive disorder (ICD-9: 296.2, 296.3, 300.4, 311).
† Asthma (ICD-9: 493∗).
‡ HIV infection (ICD-9: 042).

TABLE 3. Associations of Antidepressants Use and Invasive Cervical Cancer Risk

Antidepressants	Cases (n = 8392)		Controls (n = 82,432)		OR	
					Crude (95% CI)	Adjusted* (95% CI)
	N	%	N	%		
TCAs						
≧28DDD	624	2.38	3182	2.46	0.96 (0.88–1.05)	1.00 (0.92–1.10)
≧84DDD	291	1.11	1419	1.10	1.01 (0.89–1.14)	1.06 (0.93–1.21)
≧168DDD	144	0.55	711	0.55	0.99 (0.83–1.19)	1.04 (0.87–1.25)
≧336DDD	49	0.19	292	0.23	0.82 (0.61–1.11)	0.86 (0.64–1.17)
MAOIs						
≧28DDD	599	2.28	2853	2.20	1.03 (0.94–1.12)	0.99 (0.91–1.09)
≧84DDD	292	1.11	1409	1.09	1.01 (0.89–1.14)	0.99 (0.87–1.12)
≧168DDD	152	0.58	770	0.59	0.95 (0.80–1.14)	0.95 (0.80–1.14)
≧336DDD	57	0.22	305	0.24	0.90 (0.68–1.20)	0.91 (0.69–1.22)
SSRIs						
≧28DDD	490	1.87	2862	2.21	0.83 (0.77–0.92)	0.93 (0.84–1.04)
≧84DDD	280	1.07	1626	1.26	0.84 (0.74–0.95)	0.98 (0.85–1.13)
≧168DDD	188	0.72	1067	0.82	0.86 (0.73–1.00)	1.03 (0.87–1.22)
≧336DDD	112	0.43	650	0.50	0.84 (0.69–1.03)	1.03 (0.83–1.27)
SNRIs						
≧28DDD	35	0.13	229	0.18	0.74 (0.52–1.06)	0.92 (0.63–1.32)
≧84DDD	30	0.11	150	0.12	0.96 (0.65–1.43)	1.21 (0.81–1.81)
≧168DDD	19	0.07	113	0.09	0.80 (0.49–1.31)	1.00 (0.61–1.65)
≧336DDD	14	0.05	60	0.05	1.10 (0.61–1.97)	1.41 (0.78–2.55)
SARI(Trazodone)						
≧28DDD	199	0.76	903	0.70	1.08 (0.92–1.26)	1.22 (1.03–1.43)
≧84DDD	82	0.31	362	0.28	1.10 (0.86–1.40)	1.27 (0.99–1.62)
≧168DDD	43	0.16	151	0.12	1.38 (0.99–1.94)	1.61 (1.14–2.28)
≧336DDD	9	0.03	55	0.04	0.80 (0.40–1.62)	0.92 (0.45–1.86)
NaSSA (Mirtazapine)						
≧28DDD	12	0.05	59	0.05	0.94 (0.50–1.76)	1.17 (0.62–2.21)
≧84DDD	6	0.02	27	0.02	0.96 (0.39–2.37)	1.22 (0.49–3.02)
≧168DDD	3	0.01	14	0.01	0.88 (0.25–3.14)	1.26 (0.35–4.56)
≧336DDD	1	0.00	5	0.00 7	0.66 (0.07–6.12)	0.91 (0.09–8.83)
NDRI (Bupropion)						
≧28DDD	2	0.01	30	0.02	0.32 (0.08–1.35)	0.41 (0.10–1.74)
≧84DDD	0	0.00	15	0.01	–	–
≧168DDD	0	0.00	10	0.01	–	–
≧336DDD	0	0.00	5	0.00	–	–

CI = confidence interval, MAOIs = monoamine oxidase inhibitors, NaSSA = noradrenergic and specific serotonergic antidepressant, NDRI = norepinephrine dopamine reuptake inhibitor, SARI = serotonin antagonist and reuptake inhibitor, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

* Adjusted by income, urbanization, depressive disorders, type 2 DM, COPD, asthma, HIV infection, STD, Pap smear frequency, and aspirin use.

association with cervical cancer. An increased rate of cancer cases was associated with trazodone prescription, moderated by DDD, that is, for cumulative doses ≧ 28 DDD, adjusted OR = 1.22, 95% CI = 1.03 to 1.43 and cumulative doses ≧ 168 DDD, adjusted OR = 1.61, 95% CI = 1.14 to 2.28. Notwithstanding the foregoing results, the interpretation of our finding should be taken into consideration that it is not possible to adjust for all possible confounding factors.

DISCUSSION

To our best knowledge, this is the first population-based study to investigate the association between antidepressant use and invasive cervical cancer. The primary finding of our study was that a null association exists between most classes of antidepressants use and incidence of invasive cervical cancer. Our findings persist after adjustment for comorbid mental disorders, comorbid physical disorders, Pap smear frequency, and aspirin use. Trazodone was noted to slightly increase the risk for invasive cervical cancer.

Notwithstanding previous preclinical studies, which have reported possibly carcinogenic effects of antidepressants, our study did not find a significant association between antidepressant exposure and elevated risk for invasive cervical cancer. Moreover, in contradistinction to some published studies, we did not find a lower risk of invasive cervical cancer associated with antidepressant exposure.[19] A derivative of our finding is that prescription of antidepressant medications would not be

expected to exert any direct effect on survival amongst individuals with pre-existing human cervical cancer.[20]

Extant literature has largely confined its focus to the epidemiological association between antidepressant use with breast, ovarian, and colorectal cancer. A recent meta-analysis study concluded that antidepressants may exert a bi-phasic risk effect characterized by ''low-dose stimulation and high-dose inhibition'' and that short-term use and/or low-dose antidepressants may increase the risk of breast and ovarian cancer.[26] Harlow et al reported that pharmacological agents that affect dopamine and/or norepinephrine may increase relative risk for ovarian cancer.[27] Two epidemiology studies reported a decreased risk for colorectal cancer risk with SSRIs use.[28,29] Coogan et al also reported a null association between tricyclic antidepressants and colorectal cancer.[29] Discrepant results, however, appeared in a separate report insofar as exposure to tricyclic antidepressants reduced the incidence of colorectal cancer.[30]

In contradiction to other studies reporting on the antidepressant-gynecological cancer risk (ie, including breast cancer and ovarian cancer),[26] we did not find a bi-phasic effect associated with antidepressants on and invasive cervical cancer risk. Results of a previous study by Harlow et al suggested that pharmacological agents affecting dopamine and/or norepinephrine may increase risk of ovarian cancer via induction of gonadotropins secretion.[27] Lin et al reported that the human cervix contains functional gonadotropins receptors as do other parts of female genital tract.[31] The effect of gonadotropin on risk of cervical cancer had not been investigated. The NDRI (Bupropion), an agent known to engage catecholamines, did not show significant association with risk of invasive cervical cancer (adjusted OR: 0.41, 95% CI = 0.10–1.74).

A recent publication by Amerio et al broadly reviewed the carcinogenicity of psychotropic drugs based on US Food and Drug Administration-required preclinical in vivo studies. A significant association between mechanistically diverse psychotropic agents and carcinogenicity in animal models was reported: that is, antipsychotics (90%), antidepressants (63.6%), benzodiazepines/sedative-hypnotics (70%), amphetamines/stimulants (25%), and anticonvulsants (85.7%). The category of antidepressants used in this study included duloxetine, mirtazapine, and bupropion.[32] Our results, however, failed to replicate this finding as we found no association between either one of the foregoing non-SSRIs antidepressants and invasive cervical cancer. More studies to survey potential carcinogenicity of non-SSRIs antidepressants would be important.

A separate independent study in a large managed care health program reported that trazodone was significantly associated with laryngeal cancer (RR: 2.06, 95% CI = 1.25–3.39) and lung cancer (RR: 1.40, 95% CI = 1.25–1.57).[33] The results of this study are, however, open to variable interpretation several possible confounding factors were not adjusted for. Preliminary evidence with animal studies provided suggestive evidence of carcinogenic effects associated with trazodone.[32]

Fang at al studied mechanisms how mirtazapine acted to inhibit tumor growth. They reported mirtazapine-enhanced immune function and may increase serotonin biosynthesis for cytokines production, and therefore restored the equilibrium between physiological/pathological cytokines levels in the brain.[34] Different kinds of antidepressants including imipramine, venlafaxine, fluoxetine, clomipramine, sertraline, and trazodone had been reported to show negative immunoregulatory effects via reducing the IFN-γ/IL-10 ratio.[8] Trazodone acts predominantly as a serotonin antagonist, which is different from other antidepressants we studied. Trazodone inhibited serotonin reuptake only at higher dose.[35] We proposed a hypothesis that at lower dose, trazodone would break the balance equilibrium between physiological/pathological of cytokines level in the brain to promote tumor growth, and at higher doses, the balance equilibrium would be repaired due to the increase of serotonin level. This hypothesis may help explain our data that increased risk of invasive cervical cancer was found at cumulative doses ≧28 DDD and cumulative doses ≧168 DDD, but not at cumulative doses ≧336 DDD. However, we cannot exclude other possibility that there is no association between trazodone and invasive cervical cancer. The present study only provided preliminary data of possible association of trazodone and invasive cervical cancer.

Limitations and Strengths

The present study had many important methodological advantages. Information collected from population-based database reduces selection and recall biases. We also have the ability to evaluate the temporal relationship regarding antidepressants use and happening of invasive cervical cancer clearly. We were also able to select a representative control population from the underlying population. We attempted to enhance the validity of our findings by adjusting for several confounding covariates. We also took an inclusive approach evaluating the association between not only conventional antidepressants but also older antidepressant categories (eg, TCAs). New generations of antidepressants were also surveyed for the association with risk of invasive cervical cancer.

There are several limitations to our data that may affect interpretations and inferences of our findings. We cannot assure that coding in all cases of cancer was accurate. Other covariate factors including smoking, contraceptives use, HPV infection, and lifestyles (eg, sexual activities) were not available in NHI files. Moreover, we cannot assure that despite antidepressant prescription that they in fact were utilized by patients; existing literature strongly indicates that nonadherence with antidepressants is the rule rather than the exception.

CONCLUSIONS

In conclusion, we did not find any association between the use of antidepressants and the risk for invasive cervical cancer. A notable exception was trazadone, of which our results must be interpreted cautiously.

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