

Antidepressant medication use and nasopharyngeal cancer risk: a nationwide population-based study

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Background: The association between antidepressant exposure and nasopharyngeal cancer (NPC) has not been previously explored. The purpose of this study was to investigate the association between antidepressant prescription, including novel antidepressants, and the risk of NPC in a population-based study.

Materials and methods: Data for the analysis were derived from National Health Insurance Research Database. We identified 16,957 cases with a diagnosis of NPC and 83,231 matched controls by using a nested case-control design. A conditional logistic regression model was used, with adjustments for potentially confounding variables (eg, comorbid physical diseases, comorbid psychiatric diseases, and other medications).

Results: We report no association between NPC incidence and antidepressant prescription. For all classes of antidepressants, antidepressant exposure, regardless of cumulative dose, had no significant effect on NPC incidence (adjusted odds ratio of cumulative selective serotonin reuptake inhibitor exposure ≥ 336 defined daily dose was 1.18 [95% CI: 0.90–1.53]; tricyclic antidepressant exposure ≥ 336 defined daily dose was 1.18 [95% CI: 0.80–1.74]).

Conclusion: There was no association between antidepressant prescription and incident NPC.

Keywords: nasopharyngeal cancer, antidepressants, Taiwan national insurance

Introduction

Antidepressants are the first line of treatment for major depressive disorder¹ and a number of other psychiatric disorders, including anxiety disorders and obsessive compulsive disorder.² They can also be prescribed for the treatment of insomnia, chronic pain, and inflammatory disorders, such as irritable bowel syndrome.³ The increase in prescription of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), was reported from 1999 to 2012.⁴

Procarcinogenic effects of some antidepressants have been reported in non-Asian populations. Amerio et al reviewed the US Food and Drug Administration preclinical in vivo evidence comparing the carcinogenic risk of various psychotropic drugs. Among antidepressants, 63.6% (7/11) of examined agents were associated with carcinogenicity.⁵ However, epidemiologic evidence of a relationship between antidepressant use and cancer risk remains inconclusive. Results from a meta-analysis suggested that there is a modest increase in the risk of breast and ovarian cancers with the use of antidepressants, with a pooled odds ratio (ORs) of 1.11 (95% CI: 1.03–1.20). Another nested case-control study indicated that SSRIs, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs, eg, duloxetine and venlafaxine) did not significantly increase gastric cancer risk in the overall group, including those with a history of peptic ulcers.⁶ Similarly, Chan et al reported no association between the classes of antidepressants and invasive cervical cancer.⁷ In contrast, a separate

population-based case-control study found that antidepressant use may actually reduce the risk of colorectal cancer.⁸ Other study also showed that use of TCAs and SSRIs was associated with lower risk of hepatocellular carcinoma.⁹ The main cancer types investigated in previous studies include breast, ovarian, and colorectal. To our knowledge, no epidemiological study has assessed the association between antidepressant use and nasopharyngeal cancer (NPC).

NPC is a prevalent cancer in several specific populations, including natives of south China, Southeast Asia, and North Africa. In these regions, the age-standardized incidence rate of NPC is >20 per 100,000 person-years.¹⁰ However, it is rare in most parts of the world, where the age-standardized incidence rate is <1 per 100,000 person-years.¹¹ Evidence strongly suggests that Epstein-Barr virus (EBV) infection and genetic susceptibility are important etiologic factors for NPC.¹² Several epidemiological studies showed an association of NPC with early childhood EBV infection and with chronic ear, nose, and sinus conditions.¹³ Nonviral environmental contributors to NPC development include smoking, preserved food, and exposure to formaldehyde.¹⁴ In most cases, NPC is regarded to be squamous in origin.¹⁵ Kinjo et al proposed that TCAs inhibit the growth of squamous cell carcinoma cell line.¹⁶ However, little is known about the relationship between antidepressant medication use and incident NPC.

Accordingly, the purpose of the present study was to assess the association between the prescription of antidepressants and the diagnosis of NPC. Toward addressing our primary purpose, we used a nationwide population-based registry database from Taiwan, taking into consideration the effects of several potentially confounding factors.

Materials and methods

Source population

The National Health Insurance (NHI) program was launched by the Taiwan government on March 1, 1995. In the 15 years that followed, it covered over 23 million residents, ~99% of Taiwan's population. The National Health Insurance Research Database (NHIRD), derived from the original claims data of the NHI program, includes patients' socio-demographic information, diagnostic codes, and records of medical procedures, ambulatory care, hospital inpatient care, and prescription claims. Cases and controls were selected from the NHIRD between January 1, 1997 and December 31, 2008. NHIRD does not contain identifying patient information. This study was approved by the Institutional Review Board of Chiayi Chang Gung Memorial Hospital.

In Taiwan, patients with definitive cancer diagnoses register with the Catastrophic Illness Registry and apply for a Catastrophic Illness Certificate. Issuance of the Certificate requires a diagnosis made by a physician and a formal panel review by the Bureau of National Health Insurance. A diagnosis of cancer must be confirmed by tissue pathology.

The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) was used to define cases: NPC was coded as 147.xx, and a diagnosis of cancer was confirmed with the Catastrophic Illness Registry Dataset. Cases were defined as people with newly diagnosed NPC between January 1, 1999, and December 31, 2008. Individuals with NPC who had any previous cancer diagnoses in the dataset between January 1, 1997, and December 31, 2008, were excluded. Index date was the date of the first NPC claim. Using an incidence density sampling method,¹⁷ we randomly selected five matched controls for each case. To be included in the control population, individuals were required to have been without a cancer diagnosis before the index date. Controls were individually matched to the case by birth year.

Exposure assessment

The pharmacological coding system we used is based on the Anatomical Therapeutic Chemical classification system. Antidepressants were identified as N06A. In the present study, antidepressants were classified as SSRIs (ie, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (eg, duloxetine and venlafaxine), TCAs (eg, amitriptyline, clomipramine, dothiepin, doxepin, imipramine, maprotiline, and melitracen), reversible inhibitor of monoamine oxidase A (eg, moclobemide), noradrenergic and specific serotonergic antidepressant (eg, mirtazapine), serotonin antagonist and reuptake inhibitors (eg, trazodone), and norepinephrine-dopamine reuptake inhibitors (ie, bupropion). Information on exposure to antidepressants for all participants was confirmed with the prescription claims in the NHIRD. Antidepressants prescribed within the 365 days preceding the index date were selected as the unit of analysis. All antidepressant exposures after the index date were excluded from the analysis.

Each patient's exposure to an antidepressant was determined using the cumulative dose of antidepressants, which is quantified by a defined daily dose (DDD), defined by World Health Organization.¹⁸ The cumulative doses were divided into four exposure dose levels as follows: ≥ 28 DDD, ≥ 84 DDD, ≥ 168 DDD, and ≥ 336 DDD.

The use of potentially confounding drug (metformin) prescribed before the index date was also confirmed in cases and controls. Confounding medical conditions (eg, depressive disorder, type 2 diabetes mellitus [T2DM], hypertension, hypercholesterolemia, EBV infection, alcohol-related disorders, COPD, and tobacco use disorder) were also identified.

Statistical analyses

Descriptive statistics of cancer cases and controls were reported for sociodemographic data (eg, age, income, and urbanization), comorbid disorders, and medication use. To assess the association between antidepressant use and NPC risk, we used SAS version 9.2 (SAS Institute, Cary, NC, USA) to carry out conditional logistic regression models. The different classes of antidepressants and four cumulative dose levels were assessed separately. Corrected ORs were calculated after adjusting for demographic data and confounding factors. The statistical significance of associations was assessed by a *P*-value <0.05 or a 95% CI.

Results

The study population consisted of 16,957 cases with a diagnosis of NPC and 83,231 controls identified between January 1, 1997 and December 31, 2008. Descriptive demographic data are shown in Table 1. Males had higher risk of NPC (male: 73.09%; female: 26.91% in cases group). Table 2 shows

Table 1 Demographic data of cases and controls

	Cases (n=16,957)		Controls (n=83,231)		P-value
Age (years)					0.99
≤40	5,566	32.82%	27,196	32.68%	
41–50	5,311	31.32%	26,148	31.42%	
51–60	3,099	18.28%	15,298	18.38%	
61–70	2,104	12.41%	10,317	12.40%	
71–80	808	4.76%	3,932	4.72%	
≥80	69	0.41%	340	0.41%	
Sex, female	4,563	26.91%	22,475	27.00%	0.80
Income (NTD) ^a					<0.0001
0	2,167	12.78%	10,382	12.47%	
1–25,000	2,859	16.86%	14,025	16.85%	
25,001–40,000	7,515	44.32%	35,063	42.13%	
≥40,001	4,416	26.04%	23,761	28.55%	
Urbanization ^b					<0.0001
Very high	4,797	28.29%	25,289	30.38%	
High	8,162	48.14%	39,601	47.59%	
Moderate	2,752	16.23%	12,690	15.25%	
Low	1,246	7.35%	5,650	6.79%	

Notes: ^a1 US \$=32.3 NTD in year 2008. ^bQuartiles by human development index.

Abbreviation: NTD, New Taiwan Dollars.

Table 2 Medical diseases and drugs used with cases and controls

	Cases (n=16,957)		Controls (n=83,231)		P-value
Medical diseases					
Depressive disorders	339	2.00%	1,669	2.01%	0.96
T2DM	1,252	7.38%	6,007	7.22%	0.45
Hypertension	2,426	14.31%	10,030	12.05%	<0.0001
Hypercholesterolemia	1,141	6.73%	5,692	6.84%	0.60
EBV infection	0	0%	2	0%	0.52
Alcohol-related disorders and diseases	63	0.37%	309	0.37%	0.99
COPD	1,271	7.50%	5,575	6.70%	0.0002
Tobacco use disorder	26	0.15%	108	0.13%	0.44
Medications					
Metformin	696	4.10%	3,376	4.06%	0.77

Abbreviations: EBV, Epstein–Barr virus; T2DM, type 2 diabetes mellitus.

descriptive information related to comorbid mental and physical disorders and medication use. The incidence rates of hypertension and COPD were significantly higher in the cancer group than in the control group.

Results of our primary analyses, after adjusting for age, urbanization, income, depressive disorders, T2DM, alcohol-related disorders, tobacco use disorder, and metformin use, can be found in Table 3. The adjusted OR for cumulative SSRI exposure ≥28 DDD was 0.94 (95% CI: 0.81–1.09) and the adjusted OR for cumulative TCA exposure ≥28 DDD was 1.02 (95% CI: 0.89–1.17). For all classes of antidepressants, antidepressant exposure, regardless of cumulative dose, was not significantly associated with the risk of developing NPC (adjusted OR for cumulative SSRI exposure ≥336 DDD was 1.18 [95% CI: 0.90–1.53]; adjusted OR for cumulative TCA exposure ≥336 DDD was 1.18 [95% CI: 0.80–1.74]).

Discussion

To our knowledge, this is the first population-based nested case–control study to evaluate the association between antidepressant use and the risk of NPC. Results of our primary analyses indicate that there is no association between antidepressant use and the risk of NPC. The lack of a significant association remained after adjusting for different cumulative doses and various classes of antidepressants.

NPC is distinct from other types of cancer in terms of its geographical distribution. A preponderance of etiological studies of NPC have hitherto focused on exposure to EBV, as well as environmental factors and genetic components.^{13,14} Relatively few studies have evaluated the potential iatrogenic contribution to NPC incidence. Di Maso et al conducted a hospital-based case–control study in Italy, enrolling 198 Caucasian patients with NPC. They reported an inverse

Table 3 Associations of antidepressants use and nasopharyngeal cancer

Antidepressants	Cases (n=16,957)		Controls (n=83,231)		OR	
	N	%	N	%	Crude (95% CI)	Adjusted ^a (95% CI)
SSRIs						
≥28 DDD	269	1.59	1,388	1.67	0.94 (0.83–1.07)	0.94 (0.81–1.09)
≥84 DDD	159	0.94	819	0.98	0.94 (0.79–1.12)	0.94 (0.78–1.14)
≥168 DDD	118	0.70	561	0.67	1.02 (0.84–1.25)	1.05 (0.84–1.30)
≥336 DDD	79	0.47	339	0.41	1.13 (0.88–1.45)	1.18 (0.90–1.53)
SNRIs						
≥28 DDD	24	0.14	120	0.14	0.97 (0.62–1.50)	0.98 (0.62–1.53)
≥84 DDD	17	0.10	81	0.10	1.01 (0.60–1.70)	1.02 (0.60–1.73)
≥168 DDD	12	0.07	56	0.07	1.02 (0.54–1.90)	1.03 (0.55–1.95)
≥336 DDD	6	0.04	38	0.05	0.75 (0.32–1.78)	0.76 (0.32–1.80)
TCAs						
≥28 DDD	288	1.70	1,372	1.65	1.02 (0.90–1.16)	1.02 (0.89–1.17)
≥84 DDD	113	0.67	627	0.75	0.86 (0.71–1.06)	0.86 (0.70–1.05)
≥168 DDD	63	0.37	310	0.37	0.97 (0.74–1.28)	0.97 (0.74–1.28)
≥336 DDD	32	0.19	128	0.15	1.18 (0.80–1.74)	1.18 (0.80–1.74)
RIMAs						
≥28 DDD	49	0.29	315	0.38	0.76 (0.56–1.02)	0.75 (0.55–1.03)
≥84 DDD	24	0.14	157	0.19	0.74 (0.48–1.14)	0.74 (0.48–1.15)
≥168 DDD	14	0.08	95	0.11	0.71 (0.41–1.25)	0.72 (0.41–1.27)
≥336 DDD	4	0.02	45	0.05	0.42 (0.15–1.18)	0.43 (0.15–1.19)
NaSSA						
≥28 DDD	10	0.06	46	0.06	1.02 (0.51–2.02)	1.03 (0.51–2.06)
≥84 DDD	8	0.05	20	0.02	1.85 (0.81–4.20)	1.90 (0.83–4.35)
≥168 DDD	6	0.04	14	0.02	1.97 (0.76–5.13)	2.00 (0.76–5.24)
≥336 DDD	2	0.01	4	0.00	2.41 (0.44–13.2)	2.42 (0.44–13.3)
SARI						
≥28 DDD	110	0.65	560	0.67	0.96 (0.78–1.17)	0.96 (0.77–1.19)
≥84 DDD	45	0.27	253	0.30	0.86 (0.63–1.19)	0.87 (0.63–1.20)
≥168 DDD	16	0.09	115	0.14	0.68 (0.40–1.14)	0.67 (0.40–1.14)
≥336 DDD	5	0.03	45	0.05	0.53 (0.21–1.34)	0.53 (0.21–1.34)
NDRI						
≥28 DDD	5	0.03	28	0.03	0.86 (0.33–2.22)	0.85 (0.33–2.21)
≥84 DDD	2	0.01	17	0.02	0.55 (0.13–2.42)	0.55 (0.13–2.41)
≥168 DDD	2	0.01	6	0.01	1.62 (0.33–8.03)	1.69 (0.34–8.40)
≥336 DDD	2	0.01	2	0.00	4.73 (0.67–33.6)	4.97 (0.70–35.4)

Note: ^aAdjusting with age, urbanization, income, depressive disorders, T2DM, hypertension, hypercholesterolemia, EBV infection, alcohol-related disorders, tobacco use disorder, and metformin.

Abbreviations: DDD, defined daily dose; EBV, Epstein–Barr virus; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine–dopamine reuptake inhibitor; OR, odds ratio; RIMAs, reversible monoamine oxidase inhibitors; SARI, serotonin antagonist and reuptake inhibitor; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; T2DM, type 2 diabetes mellitus; TCAs, tricyclic antidepressants.

association between aspirin use and NPC risk. However, generalization of their results to a larger population is limited by their small sample size (n=3 cases [1.5%] and 27 controls [4.5%] reported regular aspirin use [OR=0.24; 95% CI: 0.07–0.87]).¹⁹

It was proposed that antidepressants use is associated with increased risk of cancer, with breast, ovarian, and colon cancers being the most studied malignancies. Moorman et al reported long-term use of SSRIs could increase the risk of breast cancer. However, further studies demonstrated that

breast cancer risk was not a concern for female patients who require long-term antidepressant use.^{20,21} Harlow and Cramer first reported that antidepressants could be associated with an increased risk of ovarian cancer.²² However, later studies indicated that there was no association between risk of ovarian cancer and use of antidepressant drugs.^{23,24} In colon cancer, Haukka et al reported a bias in the association of antidepressants with increased risk of colon cancer.²⁵ Azmitia reported that serotonin acted as a carcinogen in the development of colorectal cancer due to its role in stimulating cell

division.²⁶ However, some other studies have found either no effect on cancer growth or even an antineoplastic effect.^{23,27,28} Taken together, the results from experimental studies can be summarized as providing inconsistent findings.

Several *in vivo* studies have investigated the relationship between antidepressant use and oral cancer cells. One study reported that SSRIs (ie, paroxetine and sertraline) induced a dose-dependent inhibition of cell viability and proliferation in two cell lines.²⁹ Similarly, another study reported that in human oral cancer cells, paroxetine induced cytosolic-free Ca^{2+} concentrations rise by causing phospholipase C-independent Ca^{2+} release from the endoplasmic reticulum and Ca^{2+} influx via store-operated Ca^{2+} channels in a manner regulated by protein kinase C and phospholipase A2. Paroxetine (up to 50 μM) induced human oral cancer cell death in a Ca^{2+} -independent manner.³⁰

The study herein is strengthened by our population-based nested case-control design, utilizing a large, representative database. The information regarding sociodemographic data, diagnostic codes, and medical prescriptions was extracted from NHIRD, reducing the opportunity for selection bias and recall bias. Moreover, confounding factors such as income, urbanization, other medication (ie, metformin) prescribed before the index date, and comorbid medical conditions (ie, depressive disorder, T2DM, hypertension, hypercholesterolemia, EBV infection, alcohol-related disorders, COPD, and tobacco use disorder) were adjusted for in our analyses. Moreover, medical diagnoses were established by a physician using standardized codes of the ICD-9-CM. Finally, we explored the temporal relationship between all classes of antidepressants and NPC, and the cumulative dose effect of antidepressants on the risk of NPC.

Limitations

Notwithstanding the foregoing methodological strengths, interpretation of our study findings needs to take into consideration several methodological limitations. First, several confounding factors such as lifestyle, diet, and smoking were not included in our database. Diet, such as consuming nitrosamine-containing preserved foods, is an important nonviral environmental risk factor for NPC.¹⁴ Hsu et al also reported a relationship between smoking and NPC: the longer and heavier the cigarette smoking habit, the higher is the NPC risk.³¹ Second, using prescription records might overestimate cumulative doses of antidepressant use because drug adherence could not be determined. Further studies analyzing the relationship between antidepressant use, lifestyle factors, and risk of NPC are needed.

Conclusion

Our results indicate that there is no association between prescription of antidepressant drugs and the risk of NPC. Antidepressants are widely prescribed for the treatment of psychiatric and medical disorders, with increasing utilization in some jurisdictions. Moreover, prescription renewal, a proxy of longer-term antidepressant exposure, has been increasing, as has the coprescription of multiple antidepressants. The foregoing pharmacoepidemiological observations provide further impetus for scrutiny of possible tolerability and/or safety concerns associated with greater antidepressant exposure. We did not find any association between variable antidepressant exposure and incident NPC.

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Disclosure

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