



An association between benzodiazepine use and occurrence of benign brain tumors



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ABSTRACT

Objective: This study was designed to evaluate the impact of long-term benzodiazepine use on the subsequent risk of benign brain tumor (BBT) or malignant brain tumor (MBT) development.

Method: We used data from the National Health Insurance System of Taiwan. For the study cohort, we identified 62,186 patients who had been prescribed benzodiazepine for at least 2 months between January 1, 2000 and December, 31, 2009. For each of the benzodiazepine cases, we randomly selected one insured person from the non-benzodiazepine cohort with frequency matching sex, age, and year of index date. The non-benzodiazepine cohort comprised 62,050 patients. The related hazard ratios (HRs) and 95% confidence intervals (CIs) of developing brain tumors were investigated.

Results: The overall BBT incidence rate was 3.33-fold higher in the benzodiazepine cohort than the non-benzodiazepine cohort (46.3 vs 13.9 per 100,000 person-years) with an adjusted HR of 3.15 (95% CI = 2.37–4.20). Similarly, the MBT incidence rate was 84% higher in the benzodiazepine cohort (3.71 vs 2.02 per 1000 person-years), and the adjusted HR of 1.21 (95% CI = 0.52–2.81) was not statistically significant. When compared with the non-benzodiazepine cohort, the adjusted HRs of BBTs increased with benzodiazepine dosage (adjusted HR = 2.12, 95% CI = 1.45–3.10, for 36–150 mg/year; adjusted HR = 7.03, 95% CI = 5.19–9.51, for ≥151 mg/year).

Conclusion: In this population-based study, we found a significant increase in the risk of benign brain tumor development in a cohort of long-term BZD users.

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1. Introduction

Benzodiazepines are a category of drug that is widely used to treat various neurological and psychiatric conditions such as seizures, agitation, insomnia, anxiety, alcohol dependence, and panic. The prevalence of benzodiazepine use ranges from 10% to 43% worldwide among the aged population [1–5]. Meanwhile, benzodiazepines are also known to have some adverse effects, such as nausea, vertigo, amnesia, ataxia, headache, drowsiness, confusion, or even tremor, which imply the possible neuro-toxicity in long-term or high-dose use of benzodiazepines. Previous animal studies have revealed that benzodiazepine might increase the risk of liver and breast cancer [6,7]. A survey conducted in the United States found that the use of sleeping pills (most of which are benzodiazepines) increased the risk of developing cancer [8]. We published similar results from a retrospective cohort study conducted

in Taiwan in 2012 [9]. However, although there is a long history of human beings modulating the central nervous system, the potential link between benzodiazepine use and subsequent brain tumor development remains unclear. This study was conducted using the Taiwan nationwide population-based database.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program was initiated in Taiwan on March 1, 1995. By the end of 2009, approximately 99% of Taiwan's 23.74 million people were enrolled in the National Health Insurance Research Database (NHIRD) [10]. The National Health Research Institute maintains and updates the NHIRD. The data used in this study was obtained from a NHIRD sub-data set, which contains the longitudinal claim data of a cohort of 1,000,000 insurance enrollees randomly selected from all of the insured beneficiaries. The NHIRD is one of the largest insurance databases in the world, and previous studies have shown the accuracy and high validity of ICD-9 codes' diagnoses

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stored in the database [11,12]. We used three data files: the registry of beneficiaries, ambulatory care claims, and inpatient claims. The database provided confidential information such as patient identification number, birthdate, sex, occupation, residential area, medications, and diagnostic codes in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). With approval from NHI and China Medical University, this study was exempted by the Institutional Review Board (CMU-REC-101-012).

2.2. Study participants

For the benzodiazepine cohort, we identified 62,186 patients (mean age = 47.4 years, SD = 14.1 years) who had been prescribed benzodiazepine for at least 2 months between January 1, 2000 and December 31, 2009. We defined the index date as the initial date of benzodiazepine treatment. We excluded patients with a history of benign brain tumors and malignant brain tumors diagnosed before the index date. We also excluded patients for whom we could not determine the sex or age. For each benzodiazepine case, we randomly selected one insured person from the non-benzodiazepine cohort who had no history of benign brain tumors, malignant brain tumors, or benzodiazepine treatment. Moreover, each person selected was of the same sex, age (every 5 years), and index date year. The non-benzodiazepine cohort totaled 62,050 patients (mean age = 45.7 years, SD = 14.3 years).

2.3. Outcome measures

The person-years of follow-up were estimated for the study participants from the index date until the diagnosis of benign brain tumors (BBTs) (ICD-9-CM code 225) or malignant brain tumors (MBTs) (ICD-9-CM codes 191, 192, 194.3 and 194.4) or censored because of death, loss to follow-up, withdrawal from the insurance system, or December 31, 2010.

The baseline comorbidities and treatment that may be associated with BBTs and MBTs were identified before the end dates (the date of BBT or MBT diagnosis, date the patient was lost to follow-up, date of death, date of withdrawal from insurance, or final day of 2010) for the participants in both cohorts. Comorbidities and treatments that were considered in the data analysis included stroke (ICD-9-CM code 430–438), dementia (ICD-9-CM code 290.0–290.4, and 331.0), epilepsy (ICD-9-CM code 345), head injuries (ICD-9-CM 850–854, and 959.01), and brain CT/MRI examinations (ICD-9-OP procedure code 870.3 and 889.1).

For further analysis, we divided the benzodiazepine cohort into 4 groups, according to their disease status, as follows: (1) those with sleep disorders (ICD-9-CM codes 370.4 and 780.5 [except for sleep apnea syndrome: codes 780.51, 780.53, and 780.57]); (2) those with anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 309.81); (3) those with both sleep disorders and anxiety; and (4) those with neither.

2.4. Statistical analysis

Demographic factors, including age, sex, residential status, comorbidities and treatment, were compared between the benzodiazepine cohort and non-benzodiazepine cohort by using the χ^2 test. The incidence densities of BBTs and MBTs in both cohorts were calculated. Poisson regression models were used to evaluate the benzodiazepine cohort to non-benzodiazepine cohort incidence rate ratio (IRR) with 95% confidence intervals (CIs). Univariable and multivariable Cox proportional hazard regression analyses were performed to assess the risk of developing BBTs and MBTs associated with benzodiazepine use, compared with non-benzodiazepine cohort. The multivariate models were simultaneously adjusted for demographic characteristics, comorbidities and brain CT, or MRI examinations. Hazard ratio (HR) and 95% CI were estimated in the Cox model. We further stratified benzodiazepine

according to annual dosage taken to estimate the risk of BBT and MBT development associated with benzodiazepine use. All of the analyses were performed using the SAS statistical package (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA). A two-tailed p-value lower than 0.05 suggests statistical significance.

3. Results

3.1. Characteristics of the study participants

Table 1 lists the characteristics of all of the 124,236 study participants in both the benzodiazepine and non-benzodiazepine cohorts. Approximately 31.9% of the patients were young, between 20 and 39 years of age. There were more women than men in both cohorts (52.8% vs 47.2% and 52.1% vs 47.9%, respectively). In both cohorts, more patients were living in urban areas (59.8% and 61.6%, respectively). Compared to the non-benzodiazepine cohort, the benzodiazepine patients were more likely to have a stroke (2.82% vs 8.28%), dementia (0.49% vs 2.05%), epilepsy (0.35% vs 2.05%), head injury (3.37% vs 8.06%), and brain CT or MRI examinations (2.38% and 7.59%).

3.2. Incidence rate ratios of BBTs and MBTs

The overall incidence of BBTs was 3.33-fold higher in the benzodiazepine cohort than in the non-benzodiazepine cohort (46.3 vs 13.9 per 100,000 person-years, IRR = 3.33, 95% CI = 3.17–3.50) (Table 2). The overall incidence of MBTs was also significantly higher in the benzodiazepine cohort than in the non-benzodiazepine cohort (3.71 vs 2.02 per 1000 person-years, IRR = 1.84, 95% CI = 1.75–1.93). The age-specific analyses showed that BBTs were significantly highest for those aged 50–59 years in the benzodiazepine cohort than the non-benzodiazepine cohort (IRR = 4.30, 95% CI = 3.84–4.81). Age-specific benzodiazepine cohort-to-non-benzodiazepine cohort incidence densities of MBTs increased with age in both cohorts and comparison of benzodiazepine cohort with non-benzodiazepine cohort showed that the IRR of MBTs decreased with age (from IRR = 3.82, 95% CI = 3.44–4.25 in the ≤ 39 -year-old age group to IRR = 1.28, 95% CI = 1.16–1.40 in the ≥ 60 -year-old age group).

Table 1
Baseline characteristics between BZD group and non-BZD group in 2000–2009.

Variables	BZD		non-BZD		p-Value
	No N = 62,050		Yes N = 62,186		
	n	%	n	%	
Age, years					0.91
20–39	19,838	32.0	19,838	31.9	
40–49	15,819	25.5	15,819	25.4	
50–59	12,815	20.7	12,815	20.6	
≥ 60	13,578	21.9	13,714	22.1	
Sex					0.02
Women	32,335	52.1	32,812	52.8	
Men	29,715	47.9	29,374	47.2	
Urban status ^a					<0.0001
Level 1	21,179	32.1	20,947	31.3	
Level 2	19,451	29.5	19,033	28.5	
Level 3	11,968	18.1	11,566	17.3	
Level 4	13,455	20.4	15,323	22.9	
Comorbidity					
Stroke	1747	2.82	5147	8.28	<0.0001
Dementia	307	0.49	1277	2.05	<0.0001
Epilepsy	217	0.35	1277	2.05	<0.0001
Head injury	2089	3.37	5010	8.06	<0.0001
Treatment					
Brain CT or MRI examinations	1478	2.38	4717	7.59	<0.0001

Chi-square test.

^a Level = 1 highest urban area; level 7 = lowest urban areas. Levels 4, 5, 6 and 7 were grouped together because of low populations in these areas.

3.3. Hazard ratios of BBTs and MBTs

After adjusting for age, sex, comorbidities and brain CT, or MRI examinations, benzodiazepine cohort had a 3.15-fold increased risk of developing BBTs compared to the non-benzodiazepine cohort (adjusted HR = 3.15, 95% CI = 2.37–4.20). With an adjusted HR of 3.74 (95% CI = 2.02–6.92), the age-specific relative risk of BBTs was highest for those aged 50–59 in the benzodiazepine cohort, as compared with the non-benzodiazepine cohort. Table 3 shows that the benzodiazepine cohort with anxiety had a 3.76-fold higher risk of BBTs (95% CI = 2.52–5.25). Compared with non-BZD cohort, those in the benzodiazepine cohort with sleep disorders and anxiety had a 3.64-fold higher risk of developing BBTs (95% CI = 2.36–4.62), followed by benzodiazepine cohort without sleep disorders and anxiety (adjusted HR = 3.30, 95% CI = 2.36–4.62) and benzodiazepine cohort with sleep disorders (adjusted HR = 2.23, 95% CI = 2.50–3.31). To examine the dose–response relationship between benzodiazepine use and BBTs/MBTs risk. Table 4 shows that, compared with the non-benzodiazepine cohort, the adjusted HRs of BBTs increased with benzodiazepine dosage (adjusted HR = 2.12, 95% CI = 1.45–3.10, for 36–150 mg/year; adjusted HR = 7.03, 95% CI = 5.19–9.51, for ≥ 151 mg/year).

4. Discussion

The results of the adjusted analysis from the population-based study indicated that benzodiazepine use significantly increases the risk of subsequently developing benign brain tumors. We could not find increases of the risk of developing malignant ones, which is probably due to the small number of patients with malignant brain tumors in this study. Additionally, malignant brain tumors include metastatic as well as primary lesions, which could confound the mechanistic relationship of the results. The most frequently reported benign brain tumor is meningioma (tumors of the meninges, 24.0% of brain tumors), and the most frequently reported malignant tumor is glioblastoma (tumor of the neuroepithelial tissues, 22.6%). This implies that, in most instances, benign and malignant brain tumors are derived from different histologies, and thus have different genetic and molecular expressions [13–15].

The risk of benign brain tumor diagnosis was highest among patients in their sixties who used benzodiazepines for an extended period during their middle-aged years. The risk of developing benign brain tumors also exhibited a dose-dependent trend; if the benzodiazepine dosage was more than 36 mg per year, then there was a higher rate of tumor occurrence in the patients with anxiety, regardless of having a sleep

Table 3

Cox proportional hazard regression analysis for the risk of BZD associated benign brain tumor and malignant brain tumor with interaction of comorbidity.

	N	Cases	Adjusted HR ^a (95% CI)
BBTs			
Non-BZD	62,050	62	1.00 (Reference)
BZD			
SD	16,705	41	2.23 (1.50, 3.31)***
Anxiety	9011	36	3.76 (2.49, 5.67)***
SD and anxiety	13,273	54	3.64 (2.52, 5.25)***
Neither	23,197	81	3.30 (2.36, 4.62)***
MBTs			
Non-BZD	62,050	9	1.00 (Reference)
BZD			
SD	16,705	3	0.80 (0.21, 3.02)
Anxiety	9011	1	0.56 (0.07, 4.43)
SD and anxiety	13,273	4	1.41 (0.43, 4.65)
Neither	23,197	9	1.62 (0.62, 4.26)

SD, sleeping disorder.

^a Adjusted HR: multivariable analysis including age, sex, urbanization and brain CT or MRI examinations.

*** p < 0.001.

disorder. These relevant findings should be shared with medical providers worldwide because they might affect the daily prescription of sleeping pills or other forms of benzodiazepine use. A possible explanation of our results is that patients with psychiatric conditions or sleep disorders had more opportunities to undergo imaging examinations, resulting in more brain tumor diagnoses in these groups. However, a previous population-based study did not find Taiwanese patients with depression to have a higher risk of overall cancer development [16]. Table 3 shows that the patients taking benzodiazepine without an anxiety or sleep disorder still had a higher risk of developing benign brain tumors. Another explanation is that slow-growing benign brain tumors are usually accompanied by dizziness, seizures, sleep disorders, and psychiatric conditions, which are frequently treated with benzodiazepines and warrant the patients that benzodiazepine use may harbor undiagnosed benign brain tumors [17,18].

Benzodiazepines enhance γ -aminobutyric acid neurotransmission by interacting with the GABA receptor-coupled chloride channel. Apart from its role as an inhibitory neurotransmitter, γ -aminobutyric acid is also believed to regulate various stages of cell proliferation and differentiation in the brain and periphery, and may be involved in the growth of benign tumors in various ways [19,20]. However, the potential mechanisms of benzodiazepines and brain tumor growth or

Table 2

Comparisons of incidence density of benign brain tumor and malignant brain tumor between BZD group and non-BZD group by characteristics.

Variables	BZD			Non-BZD			IRR ^b (95% CI)	Adjusted HR ^c (95% CI)
	No			Yes				
	Cases	PY	Rate ^a	Cases	PY	Rate ^a		
BBTs								
20–39	12	142,668	8.41	47	149,215	31.5	3.74 (3.41, 4.11)***	3.51 (1.84, 6.69)***
40–49	21	118,317	17.8	55	119,310	46.1	2.60 (2.37, 2.84)***	2.23 (1.33, 3.76)***
50–59	13	91,340	14.2	56	91,538	61.2	4.30 (3.84, 4.81)***	3.74 (2.02, 6.92)***
≥ 60	16	93,489	17.1	54	97,722	55.3	3.23 (2.91, 3.58)***	3.11 (1.76, 5.49)***
Overall	62	445,815	13.9	212	457,785	46.3	3.33 (3.17, 3.50)***	3.15 (2.37, 4.20)***
MBTs								
20–39	1	142,723	0.70	4	149,369	2.68	3.82 (3.44, 4.25)***	3.69 (0.39, 34.7)
40–59	2	209,797	0.95	5	211,289	2.37	2.49 (2.30, 2.69)***	1.31 (0.23, 7.49)
≥ 60	6	93,564	6.41	8	97,924	8.17	1.28 (1.16, 1.40)***	0.96 (0.32, 2.86)
Overall	9	446,084	2.02	17	458,583	3.71	1.84 (1.75, 1.93)***	1.21 (0.52, 2.81)

PY, person-year.

^a Rate, incidence rate, per 100,000 person-years.

^b IRR, incidence rate ratio, compared to non-BZD group.

^c Adjusted HR: multivariable analysis including age, sex, urbanization, co-morbidities and brain CT or MRI examinations.

*** p < 0.001.

Table 4

Cox proportional hazards regression analysis measured hazard ratio of benign brain tumor and malignant brain tumor by BZD dosage.

Dosage	No. of events/ No. of patients	Crude HR (95% CI)	Adjusted HR ^a (95% CI)
BBTs			
BZD average exposure (mg/year)			
None	62/62,050	1 (Reference)	1 (Reference)
<35	22/20,800	0.95 (0.59, 1.55)	0.93 (0.57, 1.52)
36–150	48/21,135	2.23 (1.53, 3.25)***	2.12 (1.45, 3.10)***
≥151	142/20,251	7.44 (5.52, 10.0)***	7.03 (5.19, 9.51)***
MBTs			
BZD average exposure (mg/year)			
None	9/62,050	1 (Reference)	1 (Reference)
<35	5/20,821	1.49 (0.50, 4.43)	1.33 (0.44, 4.01)
≥36	12/41,365	2.03 (0.85, 4.81)	1.63 (0.67, 3.97)

^a Adjusted HR: multivariable analysis including age, sex, urbanization, co-morbidities and brain CT or MRI examinations.

*** $p < 0.001$.

suppression still remain unclear and controversial. For instance, Gourdeau et al. found that ECO-4601, a benzodiazepine receptor ligand, was shown to bind the peripheral but not the central benzodiazepine receptor and inhibited the growth of CNS tumor cell lines [21]. Richardson et al. found benzodiazepine-GABA(A) receptor binding is very low in dysembryoplastic neuroepithelial tumor, a benign brain tumor [22]. Recently, Bode et al. reported that knock-down of the peripheral type benzodiazepine receptor (now known as translocator protein, TSPO) as well as exposure to TSPO ligands enhances brain tumor proliferation in an animal model [23]. Those implied that the expression of benzodiazepine binding affinity might also play a role in the neoplastic growth of the brain. The peripheral benzodiazepine receptors were reported as being present in most brain tumors. However, the lack of expressing its characteristics in a malignant brain tumor from the neuroepithelial tissues, anaplastic astrocytoma, might explain the lower risk of developing malignant brain tumors than developing benign ones in our results [24–26].

One of the strengths of this study is its nationwide population-based design and representativeness. However, the study has some limitations. First, detailed information, such as smoking habits, alcohol consumption, body mass index, socioeconomic status, and family history of cancer, were not available in the NHIRD, all of which are major risk factors for brain tumors and could plausibly be associated with benzodiazepine. However, because the NHIRD encompasses nearly all of Taiwan's population, and because the reimbursement policy is universal, it is unlikely that these factors would affect the prescription of benzodiazepine. Second, the evidence derived from a cohort study is generally lower than that from randomized control trials, because a cohort study design is subject to many biases related to confounding adjustment. Despite our meticulous study design with an adequate control of confounding factors, a key limitation is that bias could still remain if there are unmeasured or unknown confounders. Third, the diagnoses in NHI claims primarily serve the purpose of administrative billing and do not undergo verification for scientific purposes. We were not able to contact the patients directly about their benzodiazepine use because of the anonymity of their identification numbers. Moreover, prescriptions for these drugs before 1996 could not be used in our analysis. This could have resulted in an underestimated cumulative dosage and may have weakened the observed association. However, the data on the prescription of BZD and cancer diagnosis were highly reliable.

In conclusion, in this population-based retrospective cohort study, we found a significant increase in benign brain tumor risk. Additional large unbiased, population-based studies and randomized control trials, regarding the relationship between brain tumor development and the

use of various benzodiazepines, are necessary to support our findings before any conclusion can be drawn.

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Author contributions

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Manuscript writing: All authors

Final approval of manuscript: All authors

Conflicts of interest

The authors declare that they have no conflict of interest or financial interest invested in this work, either collectively or individually.

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