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Is Long-term Use of Benzodiazepine a Risk for Cancer?

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Abstract: The carcinogenicity of benzodiazepines (BZDs) is still unclear. We aimed to assess whether long-term benzodiazepines use is risk for cancer.

We conducted a longitudinal population-based case-control study by using 12 years from Taiwan National Health Insurance database and investigated the association between BZDs use and cancer risk of people aged over 20 years. During the study period, 42,500 cases diagnosed with cancer were identified and analyzed for BZDs use. For each case, six eligible controls matched for age, sex, and the index date (ie, free of any cancer in the date of case diagnosis) by using propensity score. For appropriate risk estimation, we observed the outcomes according to their length of exposure (LOE) and defined daily dose (DDD). To mimic bias, we adjusted with potential confounding factors such as medications and comorbid diseases which could influence for cancer risk during the study period. The data was analyzed by using Cox proportional hazard regression and conditional logistic regression.

The finding unveils benzodiazepines use into safe and unsafe groups for their carcinogenicity. The use of diazepam (HR, 0.96; 95%CI, 0.92–1.00), chlorodizepoxide (HR, 0.98; 95%CI, 0.92–1.04), medazepam (HR, 1.01; 95%CI, 0.84–1.21), nitrazepam (HR, 1.06; 95%CI, 0.98–1.14), oxazepam (HR, 1.05; 95%CI, 0.94–1.17) found safer among BZDs. However, clonazepam (HR, 1.15; 95%CI, 1.09–1.22) were associated with a higher risk for cancers. Moreover, specific cancer risk among BZDs use was observed significantly increased 98% for brain, 25% for colorectal, and 10% for lung, as compared with non-BZDs use.

Diazepam, chlordiazepoxide, medazepam, nitrazepam, and oxazepam are safe among BZDs use for cancer risk. Our findings could help physicians to select safer BZDs and provide an evidence on the carcinogenic effect of benzodiazepines use by considering the LOE and DDD for further research.

(*Medicine* 94(6):e483)

Abbreviations: ATC = Anatomical Therapeutic Chemical, BZDs = benzodiazepines, CCI = Charlson comorbidity index, CI = confidence interval, DDD = defined daily dose, HIV = human immunodeficiency virus, HR = hazard ratio, LOE = length of exposure, NHI = Bureau National Health Insurance, ICD-9-CM = International Classification of Disease, Clinical Modification, Ninth Revision.

INTRODUCTION

Benzodiazepines (BZDs) is a group of central nervous system depressants which induce feelings of calm, drowsiness and sleep. It is one of the most frequently prescribed medicine in general population for nearly 50 years, with the wide range of use from 10% to 42% among elderly all around the world.[1,2] In US, approximately 6%–10% adults used benzodiazepines in 2010, and in Europe even higher percentage found in some parts of it.[3] In Taiwan, the prevalence of benzodiazepines use was found to be approximately 43% among elderly.[4]

The association between the use of benzodiazepines and risk for cancer is still unclear, however, it has been investigated in several animal studies as well for its carcinogenicity.[5–7] Some studies on animals reported the benzodiazepines relationship with risk for cancers as clonazepam with thyroid cancer,[8] diazepam would cause the risk for breast cancer[7] and oxazepam for liver cancer.[9] Kripke[10] remarked that there is no persuasive evidence for benefits from long term hypnotic's use. Several studies found that benzodiazepines or non-benzodiazepines hypnotic drugs use is associated with cancer risk but failed to show a definite relationship among them.[11–14]

The BZDs have several compounds which varies in potencies and their pharmacokinetic properties among its classes and as an individual benzodiazepine. Therefore, the post-marketing surveillance of drug safety known as pharmacovigilance that is important to evaluate the risk for cancer with exposure to benzodiazepines, which has been in many controversy. Recently, Pottegård et al[15] found that there is no association for overall cancer risk, Kripke et al[16] found the threefold greater risk, and Kao et al[2] studied the relationship between benzodiazepines use and cancer risk in Taiwanese population.

The aim of our study is to identify safe and unsafe benzodiazepines for cancer risk among Taiwanese population. Additionally, we estimated the benzodiazepines (ie, individual and overall class) with its defined daily dose (DDD) and length of exposure (LOE) for toxicity and carcinogenic effects.

Received: December 2, 2014; revised: December 16, 2014; accepted: December 26, 2014.

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This research is sponsored in part by Ministry of Science and Technology (MOST) under grant MOST 103-2221-E-038-014-, MOST 103-2221-E-038-016-, MOST 103-2622-E-038 -004 -CC2 , Ministry of Health and Welfare (MOHW), Taiwan, under grant MOHW103-TD-B-111-01, MOHW103-CC-EMR-05, Taipei Medical University under grant 99TMU-WFH-10, 101TMU-SHH-21, TMU102-AE1-B31, Taipei Medical University and Taipei Medical University Hospital (101-TMU-TMUH-03) and Ministry of Education, Taiwan, under grant TMUTOP103006-6

All authors declared no conflict of interests.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000483

METHODS

Data Source

In this study, we used reimbursement data from the Bureau National Health Insurance (NHI) system in Taiwan and has registered all medical claims since 1996.[2] More than 99% of the citizens of Taiwan are enrolled in the NHI, which offers mandatory and comprehensive medical care coverage to all Taiwanese residents.[2,17] For research and administrative use, the National Research Institute established a randomly selected claim database which represents the whole population, and provides all information of medical services received by each individual year from 1996 to 2011.[18] We obtained the randomly selected two million sample population of NHI beneficiaries claim data from 1998 to 2009 year in Taiwan.

Study Population

We identified all individuals in this study that were diagnosed cancers for the first time (*International Classification of Disease, Clinical Modification, Ninth Revision* [ICD-9-CM] codes 104-208) in between January 1, 2001 and December 31, 2008 who were eligible cases and used the date of the cancer diagnosis as the index date (S1 in Appendix http://links.lww.com/MD/A181). The individuals without any cancer diagnosis during 12 years of the study served as controls. For each case, we selected 6 controls randomly among all individuals in the sample population, a propensity-score was matched for sex, age at cancer diagnosis, and year of diagnosis. Controls were assigned an index date identical to the date of diagnosis for the corresponding case.

Benzodiazepines Exposure

Information regarding patients' medications was retrieved from the pharmacy prescription database. BZDs were classified as Anatomical Therapeutic Chemical (ATC) code N05BA (Anxiolytics), N05CD (Hypnotics and sedatives), N03AE (Anti-epileptics), and N05CF (Benzodiazepine related drugs) (Table S1 in Appendix http://links.lww.com/MD/A181). In each filled prescription for study participant, we recorded only oral drugs with drug name, dispensing data, and the total amount of the recommended defined daily dose (DDD)[19] (ie, the assumed average maintenance dose per day).

The daily dose for BZD users was estimated as dose_1 divided by $|t_1 - t_2|$, where dose_1 is the prescription of a BZD before the date of cancer diagnosis, then measured the average defined daily doses (ie, the average milligrams dispensed, divided by each defined daily dose for specific BZD) (Table S1 in Appendix http://links.lww.com/MD/A181). The value of $|t_1 - t_2|$ is the time duration of each BZD prescription prescribed before the index date (Figure S1 in Appendix http://links.lww.com/MD/A181). BZD doses were analyzed for defined daily dose per day in the following categories: 0.00 (reference), less than 0.10, 0.10 to 0.39, 0.40 to 0.69, 0.70 to 0.99 and more than or equal 1.00.

The BZD exposure was analyzed only before the cancer diagnosis/index date. We also considered whether individuals have had ever exposed to BZDs or not. In addition, we performed further analysis to compare individuals with cancer if they ever took a BZDs before their cancer diagnosis and compared with those who had never taken it (Figure S2 in Appendix http://links.lww.com/MD/A181).

Patients who had BZD prescriptions prescribed at least 2 months during the study period, were classified as BZD users (Figures S1 and S3 in Appendix http://links.lww.com/MD/A181). Exposure to drug was classified in windows size (ie, 61–90 days, 91–180 days, 181–1 years, 1–2 years, and over 2 years) before the index date. An additional category was created for ''no users'' where patients had been never or <2 months prescribed any benzodiazepines.[20]

Covariate Assessment

Propensity score was calculated using a logistic regression as proposed by Rosenbaum and Rubin[21,22] to estimate the probabilities for patient classifications into the cancer (case) and non-cancer (control) groups as shown in Table 1. The potential confounders were included in the study. The use of drugs known or suspected to modify the risk of some cancers, including aspirin (ATC: B01AC06, N02BA01, N02BA51), non-steroidal anti-inflammatory drugs (NSAIDs) (M01A, excluding M01AX), statins (C10AA) and angiotensin-II antagonists (C09C and C09D) were included in the study which might have potentials to influence for their carcinogenic effects.[15] Exposure to these confounder drugs was defined as if it was dispensed at least twice per year within a period of 3 years to the date of diagnosis.

Since the chance for cancer can be confounded by competing risk, therefore we also identified comorbidities that may be associated with mortality based on diagnostic codes from outpatient datasets prior to the outcome of interest. All diseases were included in the Charlson Comorbidity Index and analyzed except for human immunodeficiency virus (HIV).[23]

Moreover, the other confounding factors could influence to the risk of some cancers such as location (ie, Regions) and socio-economic status (ie, SES—based on the total amounts of payment to Taiwan's National Health Insurance) which were included in this study.

Data Analysis

We excluded from analyses patients with cancers who were <20 years of age, because such patients are unlikely prescribed benzodiazepines in Taiwan.

Two statistical approaches were used to analyze the data in the study. Firstly, all subjects of both case and control groups were measured the BZDs use 3 years before the date of diagnosis/index date (Figure S1 in Appendix http://links.lww.com/MD/A181). The conditional logistic regression were adjusted for potential confounders and used to investigate the association between exposure to the different drugs and risk for cancer. Our interest was to identify safer BZDs individual or each class on the occurrence of overall cancer. The results are expressed in an adjusted odds ratios (AORs) with 95% CI (confidence intervals).

Secondly, all 297,500 subjects were followed from the initial BZDs dispense date or the first visit date of the cohort database until a cancer diagnosis/index date or until the time subject was censored for loss to follow-up, or termination of insurance or to the end of 2009 (Figure S4 in Appendix http://links.lww.com/MD/A181). Subjects who were prescribed a BZD for at least 2 months before the date of diagnosis, defined as BZDs cohort use. Cox regression models with the time (in days) as the time scale were used to calculate hazard ratio with 95% CI. Multivariable Cox models were adjusted for these confounders listed in Table 1.

We used the SPSS 20 software to perform data analysis and the results calculations were expressed as the estimated numbers together with 95% CI. Based on statistical power at 0.9,

TABLE 1. Baseline Characteristics of Cancer Cases and Their Controls

	Cases (n = 42,500)	Controls (n = 255,000)	*P*-Value
Age			0.841
Mean (SD)	57.63 (15.48)	57.64 (15.51)	
Gender			0.271
Male (%)	214,54 (50.5)	127,989 (50.2)	
Female (%)	21,046 (49.5)	127,011 (49.8)	
Comorbid conditions, N (%)			
Myocardial infarction	444 (1.0)	2409 (0.9)	0.500
Congestive heart failure	2992 (7.0)	15,886 (6.2)	<0.0001
Peripheral vascular disease	1649 (3.9)	8252 (3.2)	<0.0001
Cerebrovascular disease	4288 (10.1)	24,730 (9.7)	0.012
Dementia	589 (1.4)	4215 (1.7)	<0.0001
COPD	11,234 (26.4)	58,604 (23.0)	<0.0001
Rheumatic disease	1571 (3.7)	7738 (3.0)	<0.0001
Peptic ulcer disease	12,512 (29.4)	59,597 (23.4)	<0.0001
Mild liver disease	10,660 (25.1)	42,816 (16.8)	<0.0001
Diabetes	7061 (16.6)	36,747 (14.4)	<0.0001
Hemiplegia or paraplegia	668 (1.6)	4108 (1.6)	0.551
Renal disease	2800 (6.6)	12,703 (5.0)	<0.0001
Moderate or severe liver disease	194 (0.5)	323 (0.1)	<0.0001
Charlson comorbidities index (CCI)			<0.0001
Mean (SD)	3.70 (2.54)	3.42 (2.43)	
Propensity score			0.993
Mean (SD)	0.013 (0.015)	0.013 (0.015)	
Other drugs, N (%)			
Aspirin	6452 (15.2)	36,283 (14.2)	<0.0001
Non-aspirin NSAIDs	34,322 (80.8)	202,214 (79.3)	<0.0001
Statins	3354 (7.9)	19,253 (7.6)	0.014
AT-II antagonists	8280 (19.5)	47,157 (18.5)	<0.0001
Regions, N (%)			<0.0001
Taipei	15,839 (37.3)	88,138 (34.6)	
Northern	5350 (12.6)	33,373 (13.1)	
Central	7374 (17.4)	45,246 (17.7)	
Southern	6587 (15.5)	39,169 (15.4)	
Pingtung	6127 (14.4)	40,088 (15.7)	
Eastern	866 (2.0)	6649 (2.6)	
Socioeconomic status-SES, N (%)			0.141
Low-income	27,841 (65.5)	167,056 (65.5)	
Mid-income	9397 (22.1)	57,508 (22.6)	
High-income	4966 (11.7)	28,529 (11.2)	

type I error rate at 0.05, and the individual numbers in both groups, the detectable risk difference was estimated to be 0.01.

Ethical Approval

This type of study was not required the Institutional Review Board review in accordance with the policy of National Health Research Institutes which provides the large computerized de-identified data. http://nhird.nhri.org.tw/en/

RESULTS

Study Sample

Among 297,500 patients 20 years of age or older, 42,500 patients had cancer diagnosis, whereas 255,000 patients did not during the study period. The baseline characteristics of patients are shown in Table 1. The mean (SD) of Charlson comorbidity index (CCI) was 3.70 (2.54) for case and 3.42 (2.43) for control group respectively. The prevalence of comorbidities and other drugs used in case were significant higher than in control group except myocardial infarction, cerebrovascular, and hemiplegia or paraplegia disease.

Benzodiazepines Use and Cancer Risk

The multivariable-adjusted hazard ratio for overall cancers among BZDs users, as compared with patients who had never used BZDs, was 1.14 (95% CI, 1.10–1.17) (Figure 1). We also found that the use of chlorodizepoxide (HR, 0.98; 95% CI, 0.92–1.04), diazepam (HR, 0.96; 95% CI, 0.92–1.00), lormetazepam (HR, 1.08; 95% CI 0.99–1.17), medazepam (HR, 1.01; 95% CI 0.84–1.21), nitrazepam (HR, 1.06; 95% CI, 0.98–1.14), oxazepam (HR, 1.05; 95% CI, 0.94–1.17) were not significantly risk for cancers, as compared with no BZDs use. These results were observed similar with the 3-year of benzodiazepines use before the cancer diagnosis (Table 2).

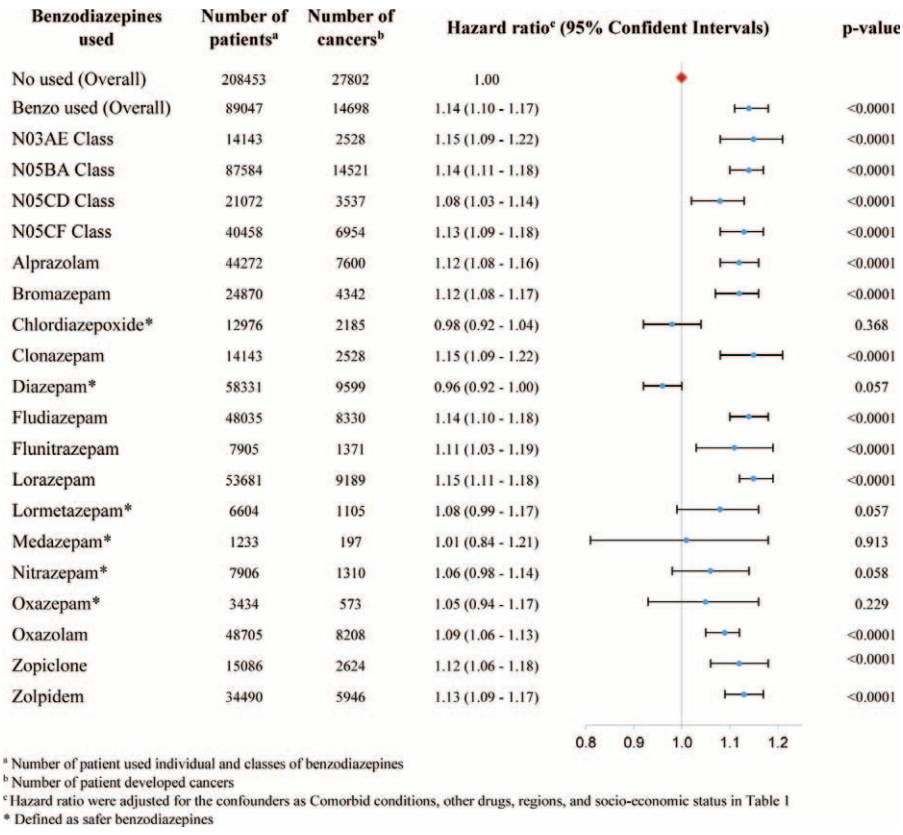

FIGURE 1. Benzodiazepines (classes and individuals) and their association with overall cancer risk.

Moreover, both multivariable-adjusted hazard ratios and adjusted odd ratios result were found consistent that oxazolam, zolpidem, and clonazepam (HR [95% CI], 1.15 [1.09–1.22]; AOR [95% CI], 1.22 [1.13–1.31]) were associated with a higher risk for cancers, as compared with no BZDs use. We also observed the risk of cancer for overall, individual and classes of benzodiazepines in both male and female (Figures S5 and S6 in Appendix http://links.lww.com/MD/A181).

TABLE 2. Safe and Unsafe Benzodiazepines for Cancer Risk

	Cases (n = 42,500) Exposed/Unexposed	Controls (n = 255,000) Exposed/Unexposed	Unadjusted Odd Ratio (95% CI)	*P*-Value	Adjusted Odd Ratio[a] (95% CI)	*P*-Value
Safe benzodiazepines						
Chlordiazepoxide	165/42,335	761/254,239	1.32 (1.11–1.56)	0.001	1.16 (0.97–1.37)	0.097
Diazepam	1273/41,227	6883/248,117	1.11 (1.04–1.18)	0.001	1.00 (0.94–1.06)	0.991
Medazepam	13/42,487	40/254,960	2.00 (1.07–3.75)	0.031	1.76 (0.94–3.32)	0.080
Nitrazepam	109/42,391	620/254,380	1.06 (0.87–1.30)	0.559	0.98 (0.80–1.21)	0.867
Oxazepam	65/42,435	353/254,647	1.12 (0.86–1.46)	0.414	0.99 (0.76–1.29)	0.944
Unsafe benzodiazepines						
Alprazolam	2566/39,934	11,860/243,140	1.32 (1.26–1.38)	<0.0001	1.18 (1.13–1.24)	<0.0001
Bromazepam	876/41,624	4054/250,946	1.30 (1.20–1.40)	<0.0001	1.16 (1.08–1.25)	<0.0001
Clonazepam	966/41,534	4408/250,592	1.32 (1.23–1.42)	<0.0001	1.22 (1.13–1.31)	<0.0001
Fludiazepam	2023/40,477	9088/245,912	1.35 (1.28–1.41)	<0.0001	1.19 (1.13–1.25)	<0.0001
Flunitrazepam	395/42,105	1849/253,151	1.29 (1.15–1.44)	<0.0001	1.16 (1.04–1.30)	0.009
Lorazepam	2426/40,074	11,189/243,811	1.32 (1.26–1.38)	<0.0001	1.18 (1.13–1.24)	<0.0001
Lormetazepam	209/42,291	972/254,028	1.30 (1.12–1.51)	0.001	1.19 (1.02–1.38)	0.027
Oxazolam	1269/41,231	6180/248,820	1.23 (1.16–1.31)	<0.0001	1.09 (1.02–1.16)	0.008
Zopiclone	558/41,942	2640/252,360	1.27 (1.16–1.39)	<0.0001	1.14 (1.04–1.25)	0.006
Zolpidem	2053/40,447	10,074/244,926	1.23 (1.18–1.30)	<0.0001	1.13 (1.07–1.18)	<0.0001

[a] Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, regions, and socio-economic status in Table 1.

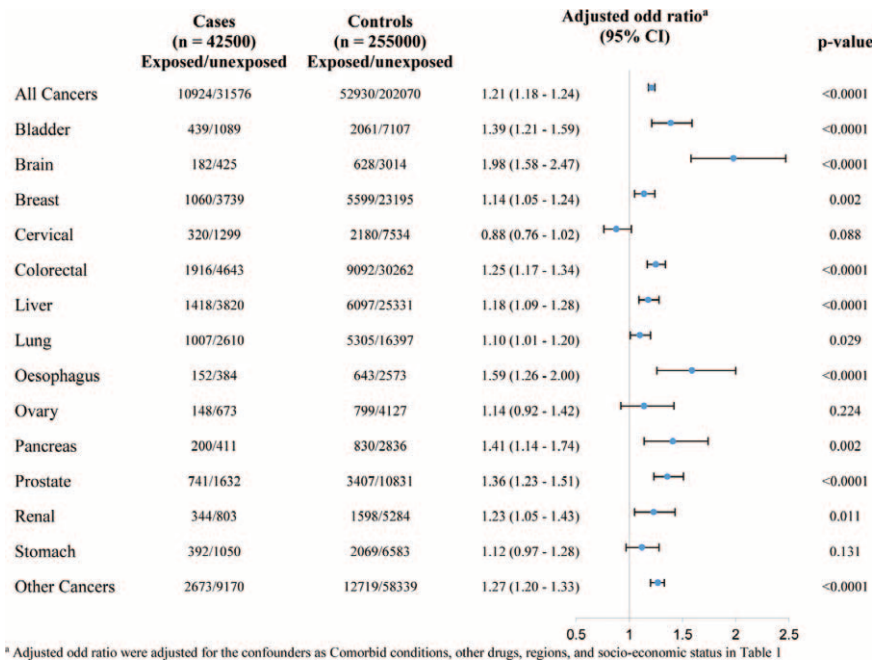

FIGURE 2. Overall benzodiazepines and their association with specific cancer risk.

Figure 2 presents the further analysis with types of specific cancer associated with benzodiazepines exposure. We observed the high risk for brain (AOR, 1.98; 95% CI, 1.58–2.47), colorectal (AOR, 1.25; 95% CI, 1.17–1.34), lung (AOR, 1.10; 95% CI, 1.01–1.20), oesophagus (AOR, 1.59; 95% CI, 1.26–2.00), and prostate (AOR, 1.36; 95% CI, 1.23–1.51) among BZDs users. However, there were not significant association found for ovary (AOR, 1.14; 95% CI, 0.92–1.42), stomach (AOR, 1.12; 95% CI, 0.97–1.28), and cervical cancer (AOR, 0.88; 95% CI, 0.76–1.02).

Benzodiazepines Exposure, Dose, and Cancer Risk

We calculated length of exposure for individual as well as class of benzodiazepine drug shown in Tables S2 and S3—Appendix http://links.lww.com/MD/A181. The increased risk of BZDs use for all cancers were observed 1.21 times more likely than controls (AOR, 1.12; 95% CI, 1.18–1.24). Based upon each BZD class, hypnotics, and sedatives were the only observed comparatively safer class (AOR, 1.16; 95% CI, 1.08–1.25) among antiepileptic's, anxiolytics, and other related BZD classes.

In addition, the multivariable-adjusted odds ratios for diazepam (ie, safer BZD) accordingly to the defined daily dose (DDD), as compared with no BZDs use were 0.89 (95% CI, 0.62–1.28) for a dose less than 0.10 DDD, 1.01 (95% CI, 0.92–1.11) for 0.10–0.39 DDD, 0.98 (95% CI, 0.74–1.29) for 0.70–0.99 DDD, and 0.95 (95% CI, 0.63–1.42) for higher than 1.00 DDD (Table 3). For each safer, unsafe and overall BZD classes, we have also calculated DDD as shown in Tables S4 and S5—Appendix http://links.lww.com/MD/A181.

DISCUSSION

We evaluated the exposure to oral benzodiazepines (ie, combined all BZDs, its classes and individual BZD) and the risk for cancer in our case-control Taiwanese population based study. We observed that hypnotic's class has less risk (HR, 1.08; AOR, 1.16) as compare to anti-epileptics, anxiolytics and other related drugs classes. It is important to note that we observed overall class and individual BZD accordingly to the length of exposure (ie, days and years) and their DDD, however, the slight fluctuation in relation to dose–response and proportion to duration of BZD use were recorded. In addition, we performed two statistical methods to strengthen our findings and both analysis supported these five safer drugs. Currently, in healthcare the outcomes accessed with randomized control trials compared with observational studies provided little evidence of difference, regardless to specific observational study design, heterogeneity or use of propensity score adjustment.[24–26]

Safe Benzodiazepines

From all BZDs, the chlordiazepoxide, diazepam, medazepam, oxazepam, and nitrazepam were observed to be safer drugs that means these drugs did not have any association with cancer. Our results are consistent with Rosenberg et al[12] that chlordiazepoxide and diazepam have no risk for cancer however, contradict with Horrobin and Trosko[27] that diazepam is possibly cancer promoters, and Iida et al[9] that oxazepam use is risk for liver cancer. Since, diazepam is most frequently prescribed BZD in Taiwan to treat anxiety, panic attacks and insomnia. It appears to be safer from our findings as compare to other BZDs which could be because of BZDs varies in their therapeutic spectrum and activity [28].

Unsafe Benzodiazepines

For unsafe BZDs, we observed clonazepam, lorazepam, alparazolam, bromazepam, zolpidem, and zopiclone have high risk for cancer as examined with DDD and exposure duration. We found that clonazepam users have had 15% higher risk to

TABLE 3. The Classification of Define Daily Dose for Safe Benzodiazepines

Safe Benzodiazepines[a]	Case (n = 42,500)	Control (n = 255,000)	Adjusted Odds Ratio[b] (95% CI)	*P*-Value
Chlordiazepoxide				
0.0 (never users)	42,335	254,239	1.00	*P* trend, 0.124
<0.10	1	10	0.54 (0.07–4.22)	
0.10–0.39	51	239	1.16 (0.86–1.58)	
0.40–0.69	61	235	1.38 (1.04–1.83)*	
0.70–0.99	16	119	0.71 (0.42–1.20)	
≥1.00	36	158	1.19 (0.82–1.71)	
Diazepam				
0.0 (never users)	41,227	248,120	1.00	*P* trend, 0.989
<0.10	34	216	0.89 (0.62–1.28)	
0.10–0.39	570	3022	1.01 (0.92–1.11)	
0.40–0.69	580	3132	1.00 (0.91–1.10)	
0.70–0.99	61	340	0.98 (0.74–1.29)	
≥1.00	28	170	0.95 (0.63–1.42)	
Medazepam				
0.0 (never users)	42,487	254,960	1.00	*P* trend, 0.202
<0.10	0	0	–	
0.10–0.39	1	5	1.03 (0.12–8.88)	
0.40–0.69	1	9	0.56 (0.07–4.41)	
0.70–0.99	6	16	2.24 (0.86–5.81)	
≥1.00	5	10	2.58 (0.87–7.65)	
Nitrazepam				
0.0 (never users)	42,391	254,380	1.00	*P* trend, 0.936
<0.10	0	0	–	
0.10–0.39	6	42	0.77 (0.32–1.81)	
0.40–0.69	12	65	1.00 (0.54–1.86)	
0.70–0.99	16	74	1.19 (0.69–2.04)	
≥1.00	75	439	0.97 (0.76–1.24)	
Oxazepam				
0.0 (never users)	42,435	254,647	1.00	*P* trend, 0.485
<0.10	2	2	4.82 (0.65–35.45)	
0.10–0.39	33	163	1.08 (0.74–1.58)	
0.40–0.69	18	120	0.82 (0.50–1.35)	
0.70–0.99	11	50	1.15 (0.60–2.23)	
≥1.00	1	18	0.34 (0.04–2.54)	

* $P < 0.05$.$P < 0.01$.$P < 0.001$.
[a] DDD, defined daily dose in milligram (mg).
[b] Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, regions, and socio-economic status in Table 1.

develop cancer among all other BZD drugs. Our findings consistent with Rosenberg et al[12] at some extent for few drugs which are safer but contradict with Kripke[11] and Kripke et al[16] investigations to have threefold greater cancer risk in hypnotic users. However, the benzodiazepines are relatively safer drugs as it rarely cause serious adverse effects.[29] We assume that this could be due to aggregated risk for long term use of BZDs in relation to polypharmacy or metabolic related drugs which could have effect.[30] Therefore, we need more attention to compute the aggregated risk of multiple drugs uses.

Benzodiazepines Use and Risk for Specific Cancer

We also observed that benzodiazepines exposure increased the overall cancer risk up to 21%, specifically for brain 98%, colorectal 25%, lung 10%, esophagus 59%, prostate 36%, bladder 39%, liver 18%, pancreas 41% and other cancers 27%. However, cervical, ovary, and stomach cancers were not observed statistically significant. These findings are important and have a positive impact for benzodiazepines users as it is commonly prescribed drugs. Our findings are consistent with Rosenberg et al,[12] Kripke and Langer,[31] and Cronin-Fenton et al[32] that the BZDs use have only selected cancer risks but contradict with Pottegård et al[15] that there is no association found in Danish BZDs users.

In Taiwan, the bladder cancer incidence is particularly high and reported as the sixth common cancer in the world[33] that we observed significantly risk for cancer among BZDs users. Moreover, our findings for breast cancer are consistent with Karmali et al[7] and Horrobin and Trosko[27] animal studies that breast cancer significantly associated with BZDs exposure but contradict with Halapy et al[13] that there is no association for breast cancer. We also found similar results with Kao et al[2] and Coogan et al[34] who reported that BZDs use have a significant risk for prostate cancer in men but there were no risk for ovarian and cervical cancer in women. Although, some researchers might think that anxiety leads to cancers instead of BZDs or

other drugs. However, Kao et al[2] studied in individuals without anxiety using benzodiazepines still have had higher risk for developing cancers in Taiwan. Therefore, we assume that risk of cancers could be associated with individual BZD, which might have some relationship only with particular cancers etiology need to be identified. Since it was also reported that BZDs might be useful as adjuncts to some specific cancer chemotherapies.

We recommend that the therapeutic effectiveness of BZDs should be monitored closely for long-term users. Furthermore, the metabolism of these drugs should be investigated in relation to their carcinogenicity in accordance to multiple drugs use and multiple diseases. We believe that some BZDs are safer among others and should need to investigate them on large population.

Limitations

The study strength is that it is a population-based design to evaluate the risk for cancers. However, this study also have some limitations regarding data information like alcoholism, smoking status and lifestyle which is not available in the BNHI database and could influence on the findings. Another limitation could be related to cohort study design regarding population sample and confounding adjustments, even after adjustments there could be unknown confounders which might create bias to results. The inclusion of non-users which might not be pure controls as we studied the cancer risk between users and nonusers. Another limitation could be the simplified e-claim by general physicians in Taiwan. It is always lower quality then the randomized control trial studies as BNHI data serves for administrative billing not for scientific validation purpose. Moreover, the number of drug uses are just for reference which might not provide accurate reflection whether the individuals taken drugs as recommended by practitioners. In Taiwan, the NHI reimburse for maximum 90 days prescription as well as the self-pay category was not included in this study. Since, in this study we observed BZDs exposure but not their mechanism and metabolism related to cancer which could be also limitation. Therefore, further animal or cellular model are needed to help in identifying a possible biological mechanism linking BZDs with risk of cancers.

CONCLUSION

In conclusion, we found diazepam, chlordiazepoxide, medazepam, nitrazepam, oxazepam, and lormetazepam are safer among all benzodiazepines for overall cancer risk. Our findings might provide clearer evidence about the benzodiazepines carcinogenic effects with respect to its classes, individual BZDs, defined daily dose and length of exposure.

The clinical trials for drugs are always expensive and could not be practical because of cost and ethical concerns however, it is important to clarify the carcinogenicity of benzodiazepines which is still unclear. Further investigations are needed to provide more information regarding the benzodiazepines carcinogenicity effects. At the same time, our results provided a strong evidence and warned physicians should select carefully best choice of benzodiazepine and patients from the possibly higher risk for cancers.

ACKNOWLEDGMENTS

This research was sponsored in part by National Science Council (NSC) under grant NSC 99-2511-S-038-005-MY3, Ministry of Health and Welfare (MOHW), Taiwan, under grant MOHW103-TD-B-111-01, Taipei Medical University under grant 99TMU-WFH-10, 101TMU-SHH-21, TMU102-AE1-B31, Taipei Medical University and Taipei Medical University Hospital (101-TMU-TMUH-03) and Ministry of Education, Taiwan, under grant TMUTOP103006-6.

REFERENCES

1. Madhusoodanan S, Bogunovic OJ. Safety of benzodiazepines in the geriatric population. *Expert Opin Drug Saf.* 2004;3:485–493.
2. Kao C-H, Sun L-M, Su K-P, et al. Benzodiazepine use possibly increases cancer risk: a population-based retrospective cohort study in Taiwan. *J Clin Psychiatry.* 2012;73:e555.
3. Fischer B, Bibby M, Bouchard M. The Global Diversion of Pharmaceutical Drugs Non-medical use and diversion of psychotropic prescription drugs in North America: a review of sourcing routes and control measures. *Addiction.* 2010;105:2062–2070.
4. Cheng JS, Huang WF, Lin KM, Shih YT. Characteristics associated with benzodiazepine usage in elderly outpatients in Taiwan. *Int J Geriatr Psychiatry.* 2008;23:618–624.
5. Stopper H, Körber C, Spencer DL, et al. An investigation of micronucleus and mutation induction by oxazepam in mammalian cells. *Mutagenesis.* 1993;8:449–455.
6. Préat V, de Gerlache J, Lans M, Roberfriod M. Promoting effect of oxazepam in rat hepatocarcinogenesis. *Carcinogenesis.* 1987;8:97–100.
7. Karmali R, Volkman A, Muse P, Louis T. The influence of diazepam administration in rats bearing the R3230AC mammary carcinoma. *Prostaglandins Med.* 1979;3:193–198.
8. Miyawaki I, Moriyasu M, Funabashi H, et al. Mechanism of clobazam-induced thyroidal oncogenesis in male rats. *Toxicol Lett.* 2003;145:291–301.
9. Iida M, Anna CH, Hartis J, et al. Changes in global gene and protein expression during early mouse liver carcinogenesis induced by non-genotoxic model carcinogens oxazepam and Wyeth-14,643. *Carcinogenesis.* 2003;24:757–770.
10. Kripke DF. Risks of Chronic Hypnotic Use. Sleep and Sleep Disorders.Springer US; 2006:141–145.
11. Kripke DF. Evidence That New Hypnotics Cause Cancer. University of California, San Diego: eScholarship; 2008.
12. Rosenberg L, Palmer JR, Zauber AG, et al. Relation of benzodiazepine use to the risk of selected cancers: breast, large bowel, malignant melanoma, lung, endometrium, ovary, non-Hodgkin's lymphoma, testis, Hodgkin's disease, thyroid, and liver. *Am J Epidemiol.* 1995;141:1153–1160.
13. Halapy E, Kreiger N, Cotterchio M, Sloan M. Benzodiazepines and risk for breast cancer. *Ann Epidemiol.* 2006;16:632–636.
14. Harlow BL, Cramer DW. Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: evidence from two combined case-control studies (Massachusetts, United States). *Cancer Causes Control.* 1995;6:130–134.
15. Pottegård A, Friis S, Andersen M, Hallas J. Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case–control study. *Br J Clin Pharmacol.* 2012;15:1356–1364.
16. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *Br Med J Open.* 2012;2:doi:10.1136/bmjopen-2012-000850.
17. Huang C-L, Nguyen PA, Kuo P-L, et al. Influenza vaccination and reduction in risk of ischemic heart disease among chronic obstructive pulmonary elderly. *Comput Methods Programs Biomed.* 2013;111:507–511.
18. Lu J-FR, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. *Health Affairs.* 2003;22:77–88.

19. Defined Daily Dose (DDD).2014:http://www.whocc.no/ddd/definition_and_general_considera/. Accessed 22, 2014.
20. Iqbal U, Syed-Abdul S, Nguyen PA, et al. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax.* 2013;68:591–592doi:10.1136/thoraxjnl-2013-203211.
21. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41–55.
22. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc.* 1984;79:516–524.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383.
24. Anglemyer A, Horvath HT, Bero L. Healthcare Outcomes Assessed With Observational Study Designs Compared With Those Assessed in Randomized Trials.2014:http://www.thehealthwell.info/node/763371. Accessed September 24, 2014.
25. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342:1887–1892.
26. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med.* 2012;367:1792–1802.
27. Horrobin DF, Trosko JE. The possible effect of diazepam on cancer development and growth. *Med Hypotheses.* 1981;7:115–125.
28. Lader M. Benzodiazepines revisited—will we ever learn? *Addiction.* 2011;106:2086–2109.
29. Triozzi PL, Goldstein D, Laszlo J. Contributions of benzodiazepines to cancer therapy. *Cancer Invest.* 1988;6:103–111.
30. Xu W, Tamim H, Shapiro S, et al. Use of antidepressants and risk of colorectal cancer: a nested case-control study. *Lancet Oncol.* 2006;7:301–308.
31. Kripke DF, Langer RD. Evidence for harm, comment on 'Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study'. *Br J Clin Pharmacol.* 2013;78:186–187.
32. Cronin-Fenton DP, Riis AH, Lash TL, et al. Antidepressant use and colorectal cancer risk: a Danish population-based case-control study. *Br J Cancer.* 2011;104:188–192.
33. Chen P-C, Tsai M-H, Yip SK, et al. Distinct DNA methylation epigenotypes in bladder cancer from different Chinese sub-populations and its implication in cancer detection using voided urine. *BMC Med Genomics.* 2011;4:45doi:10.1186/1755-8794-4-45.
34. Coogan PF, Rosenberg L, Palmer JR, et al. Risk of ovarian cancer according to use of antidepressants, phenothiazines, and benzodiazepines (United States). *Cancer Causes Control.* 2000;11:839–845.