




Research Paper

Association between Sedative-hypnotics and Subsequent Cancer in Patients with and without Insomnia: A 14-year Follow-up Study in Taiwan

Hui-Fen Fang¹, Tzu-Yin Lee^{2*}, King Cheung Hui^{2*}, Howard Chi Ho Yim³, Mei-Ju Chi⁴, Min-Huey Chung^{2,5}

1. Department of Nursing, Taipei Medical University Hospital, Taipei, Taiwan
2. School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan
3. Microbiome Research Centre, St George & Sutherland Clinical School, University of New South Wales, Sydney, Australia
4. School of Gerontology Health Management, College of Nursing, Taipei Medical University, Taipei, Taiwan
5. Department of Nursing, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

*These authors contributed equally to this work.

 Corresponding authors: Min-Huey Chung, RN, PhD, School of Nursing, College of Nursing, Taipei Medical University, No.250, Wu-Xing Street, Taipei, Taiwan, 110, R.O.C. E-mail address: minhuey300@tmu.edu.tw. Mei-Ju Chi, PhD, School of Gerontology Health Management, College of Nursing, Taipei Medical University, No.250, Wu-Xing Street, Taipei, Taiwan, 110, R.O.C. E-mail address: mjchi@tmu.edu.tw

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Received: 2018.10.15; Accepted: 2019.03.21; Published: 2019.05.21

Abstract

Background: The aim of this population-based 14-year historical and prospective study was to determine the relationships between the usage of sedative-hypnotics, including benzodiazepines and nonbenzodiazepines, and the risk of subsequent cancer in patients with or without insomnia among the Taiwanese population.

Methods: A total of 43,585 patients were recruited, 21,330 of whom had been diagnosed with insomnia and 8,717 who had been prescribed sedative-hypnotics during this study's following period of 2002 to 2015. Information from the claims data, namely basic demographic details, drug prescriptions, comorbidities, and patients' survival, was extracted from the National Health Insurance Research Database for χ^2 analysis. A Cox proportional hazards model was used to compute the 14-year cancer-free survival rates after adjustment for confounding factors.

Results: Patients with insomnia who used sedative-hypnotics had an adjusted hazard ratio of 1.49 compared with patients with insomnia who did not use any sedative-hypnotics, and patients without insomnia who used sedative-hypnotics had an adjusted hazard ratio of 1.68 compared with patients without insomnia who did not use any sedative-hypnotics. Regarding site-specific risk, patients with insomnia who used sedative-hypnotics had an increased risk of oral and breast cancers, and patients without insomnia who received sedative-hypnotics prescriptions had an increased risk of liver and breast cancers. The cancer-free survival rate of patients who had used sedative-hypnotics was significantly lower than that of patients who had never used sedative-hypnotics.

Conclusions: The use of sedative-hypnotics in patients either with or without insomnia was associated with subsequent cancer development in the Taiwanese population. Increased risks of oral, liver, and breast cancer were found in the patients with the use of sedative-hypnotics. The use of sedative-hypnotics should be discouraged for treating patients with or without insomnia in Taiwan.

Key words: Sedative-hypnotics, Insomnia, Cancer, Cancer-free survival rate, Immune function, Viral infection

Introduction

The prevalence of insomnia in Asian and Western countries ranges from 5% to 40% [1-7]. It has been found to correlate with a number of psychological diseases such as depression [5] and

physical illnesses such as diabetes [8], hypertension, and cardiovascular disease [9-12]. Thus, insomnia is a major public health concern with considerable personal and socioeconomic burdens [13]. Typical

treatments for patients with insomnia include psychological therapy and the use of medications [14]. The two most commonly prescribed medications to treat insomnia are benzodiazepines (BZDs) and non-benzodiazepines (non-BZDs), and other drugs such as gamma-aminobutyric acid agonists, melatonin receptor agonists, sedating antidepressants, antihistamines, and eugeroic drugs are also used but less frequently [15]. Sedative-hypnotics are also prescribed to patients with diseases such as generalized anxiety disorder, addiction, agitation, neurological disorders, muscle spasticity, involuntary movement disorder, alcohol withdrawal, and anxiety associated with cardiovascular or gastrointestinal conditions [16]. However, associations between the usage of sedative-hypnotics and potential side effects, such as cancer and death, have not yet been clearly established.

Concerns about the possible side effects of sedative-hypnotics in humans have existed since the Cancer Prevention Study I of the American Cancer Society first documented that the consumption of hypnotics was associated with excessive deaths in 1979 [17, 18]. Although a few population-based studies have investigated the correlation between the use of sedative-hypnotics and corresponding mortality [19-31], no consistent relationships have been established. Few local studies have attempted to determine the correlations between the use of sedative-hypnotics and potential carcinogenicity in the Taiwanese population, but the influence of both insomnia and the use of sedative-hypnotics has not been explored [32-35]. Moreover, most studies have analyzed either the use of BZDs [33, 34] or non-BZDs [32] alone, and thus the overall influence of how the use of sedative-hypnotics, including both BZDs and non-BZDs, correlates with carcinogenicity in the general Taiwanese population remains to be elucidated. To our knowledge, our study is the first to specifically investigate the correlations between subsequent cancer development, the use of sedative-hypnotics, and insomnia in the Taiwanese population.

Materials and Methods

Data Sources

The National Health Insurance (NHI) Project was initiated and maintained by the Health and Welfare Data Science Center of the Ministry of Health and Welfare. It captures all the reimbursable items of consolidated health insurance claims from every single payer. The NHI program has covered more than 96% of the Taiwanese population and it has

already established contact with 97% of the local clinics and hospitals since the end of 1996 [34]. The full population file from the NHI database was used to analyze the risk of subsequent cancer in a more accurate manner. Information from each of the medical claims records included 1) the patient's demographic details, 2) clinical details concerning diseases (according to the International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM), and 3) details of health care service such as drug prescription and cost. This study was reviewed and approved by the Joint Institutional Review Board of Taipei Medical University (N201611010).

Study samples

This study examined the risk of cancer in three sedative-hypnotics-exposed groups and one sedative-hypnotics-unexposed group. Patients who had been diagnosed with insomnia (ICD-9-CM Codes 307.40-307.42, 307.44, 307.49, or 780.52) and prescribed sedative-hypnotic medications were classified as the first exposure group (Inso-Hyp group). The date each patient was first diagnosed with insomnia was within January 1, 2002 and December 31, 2004. To avoid coding errors, only patients with at least two diagnosis records for insomnia within the same year were recruited. The index date was defined as the first outpatient visit for insomnia treatment. Prescription of sedative-hypnotic drugs was defined as at least 30 defined daily dose (DDD) per year [36] until the first diagnosis of cancer, death, or endpoint of the follow-up period. Patients with any two consecutive prescription intervals greater than three months were classified as having discontinued the prescription and were excluded [37]. In the second exposed group, all patients were diagnosed with insomnia but were not prescribed any sedative-hypnotics during the entire follow-up period (Inso-NonHyp). The third exposed group consisted of patients who had received a sedative-hypnotics prescription for any reason other than insomnia (NonInso-Hyp). The definition of insomnia for the Inso-NonHyp and NonInso-Hyp was same as for the Inso-Hyp group. Any patients in these three exposure groups were excluded if they had either been diagnosed with insomnia or prescribed a sedative-hypnotics drug between 2000 and 2001. The remaining beneficiaries without diagnosis of insomnia or sedative-hypnotic prescription between 2000 and 2013 were recruited into the unexposed group (NonInso-NonHyp), and the first record of medical service use was defined as their index visit. Common exclusion criteria for all four groups included any patients who had (1) a previous diagnosis of cancer between 2000 and 2001

or (2) a previous diagnosis of cancer before the index date, (3) who were aged under 18 years on the index date, or (4) who had a latency period less than two years. Patients for inclusion in the NonInso-NonHyp group were selected by matching to those in the NonInso-Hyp group according to age, sex, index year, and Charlson comorbidity score (CCI; four for each patient). Patients for the Inso-NonHyp group were selected to match with those in the Inso-Hyp group according to same way. Finally, 43,585 patients were included in this retrospective study.

Variables of Interest

The risk of subsequent cancer incidence in each cohort (codes according to the International Classification of Diseases for Oncology, third edition, in the Cancer Registry file) was evaluated. From the respective index dates to the day with first diagnosis of cancer, date of death, or the end of the follow-up period on December 31, 2015, the patients were individually followed for 2 to 14 years. We retrospectively investigated the risk of nine major cancer types in Taiwan, namely oral cancer (C00-C06, C09-C10, C12-C14), stomach cancer (C16), colon cancer (C18-C21), liver cancer (C22), lung cancer (C33-C34), skin cancer (C44), breast cancer (C50), corpus cancer (C54), and prostate cancer (C61) [38]. Only female subjects were included in the analysis of the associated risk of subsequent breast cancer.

Sedative-hypnotics were classified as either BZDs or non-BZDs. Alprazolam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, fludiazepam, flunitrazepam, flurazepam, lorazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, and triazolam were classified as BZDs, and zolpidem, zopiclone, and zaleplon were classified as non-BZDs [39]. Patients who received a prescription for both BZDs and non-BZDs during the study period were excluded from the drug type analysis. Three groups of different half-life duration of sedative-hypnotic drugs were further analyzed. We defined a drug as short acting, intermediate acting, or long acting if it had a half-life of less than 10 hours, 10 to 35 hours, or more than 35 hours, respectively [40]. Moreover, patients who had ever switched from using a long-acting drug to a short-acting drug were sorted into the long-acting group. Low-dose users were patients with a prescribed yearly mean DDD of 7 to 30 during the follow-up period, medium-dose users were those with a prescribed yearly mean DDD of 31 to 90, and high-dose users were patients with a prescribed yearly mean DDD of ≥ 91 [36].

Statistical Analysis

Demographic information for each patient was obtained from the Registry for Beneficiaries file. There were four groups for patient's age: younger than 30 years old, 30–44 years old, 45–64 years old, and 65 years or older. Patients were divided into three groups according to their average monthly income: < US\$640 (New Taiwan Dollars [NT\$]20,000), US\$640–\$1,280 (NT\$20,000–39,999), and \geq US\$1,281 (\geq NT\$40,000). Northern, Central, Southern, and Eastern administrative regions of Taiwan were used as criteria for classifying residential area. The urbanization level of patient's residence was defined as urban, suburban, or rural. CCI score was used to evaluate any preexisting comorbidities [41]. Patients were subsequently stratified into three groups according to the sum of points (range: 0 to 6): 0, 1, ≥ 2 points [42]. The chi-squared test was used to analyze differences in the demographic information of four patient groups. The incidence density rate of each at-risk population was defined as the number of incident cases divided by the sum of the person-years. The crude hazard ratios (CHRs) for developing cancer were estimated using univariate Cox proportional hazards model. The adjusted hazard ratio (AHR) represented the differing risks for the study groups after controlling for demographic information of patient. The between-group differences in the survival rates and curves of survival distributions for developing cancer were assessed by Kaplan-Meier method and log-rank test. SAS statistical package (SAS systems for Windows, Version 9.2; Cary, NC, USA) was used for all statistical analyses. The statistically significant *p* value was set at < 0.05.

Results

The cohort of this study consisted of a total of 43,585 patients from Taiwan's National Health Insurance Research Database (NHIRD); 4,266 patients were assigned to the Inso-Hyp group, 17,064 patients were sorted into the Inso-NonHyp group, 4,451 patients comprised the NonInso-Hyp group, and 17,804 patients constituted the Noninso-NonHyp group (Table 1). Significant differences were identified in the demographic characteristics of the patients in these four groups. In general, most of the subjects had a monthly income under \$640 (66.4%–78.8%) and lived in the Northern (48.6%–57.3%) and urban region (56.9%–57.7%). Compared with patients without insomnia, more patients in the Inso-Hyp and Inso-NonHyp groups were younger than 30 (4.4% and 4.6%, respectively) or were female (48.1%). In addition, patients who had not been prescribed any sedative-hypnotics exhibited significantly lower CCIs than those who had.

Table 2 displays the CHRs of subsequent cancer incidence in our study cohort. The patients with exposure to sedative-hypnotic prescriptions exhibited higher hazard ratios for cancer compared with those without sedative-hypnotic prescriptions: The CHR was 1.47 (CI: 1.21-1.79) for the Inso-Hyp group compared with the Inso-NonHyp group and 1.65 (CI: 1.36-2.01) for the NonInso-Hyp group compared with the NonInso-NonHyp group. In addition, patients aged 45 years or older were associated with higher densities of cancer incidence than those who were younger than 30 years old. The densities of cancer incidence were significantly higher in male patients (CHR: 1.55, 95% confidence interval (CI): 1.37-1.76), patients with a monthly income < \$640 (CHR: 1.34, 95% CI: 1.07-1.67), or who lived in the Southern region of Taiwan. Subjects with a CCI score equal to or greater than 1 were also more likely to subsequently develop cancer when compared with patients whose CCI score was zero.

As Table 3 presents, for patients receiving a diagnosis of insomnia, those prescribed long-acting sedative-hypnotic drugs exhibited a higher risk of developing cancer (AHR: 1.73, CI: 1.37-2.19) than those without sedative-hypnotic prescriptions. Patients having a prescribed mean DDD of at least 7 per year exhibited a higher risk of cancer than those without any sedative-hypnotic prescriptions. In particular, patients with a low dosage (AHR: 2.70, 95% CI: 1.12-6.54) had a 2.7-fold increased risk of a subsequent cancer incidence. Noninsomniac patients

with a prescription of BZD had a higher risk of cancer compared with those without sedative-hypnotic drugs (AHR: 1.51, CI: 1.17-1.95). With respect to the half-life of the prescribed sedative-hypnotics, it was found that the risk of subsequently developing cancer among the patients with either short-, intermediate-, or long-acting drugs was comparable (AHR: 1.75, 95% CI: 1.09-2.82; AHR: 1.65, 95% CI: 1.21-2.26; and AHR: 1.69, 95% CI: 1.31-2.17, respectively). Patients having a prescribed mean DDD of at least 7 per year exhibited a higher risk of cancer than those without any sedative-hypnotic prescription, especially for those receiving a low dosage (AHR: 5.47, CI: 4.10-7.30).

The incidence densities of each type of cancer for each of the four groups within the follow-up period are summarized in Table 4. In general, after adjustment for individual age, sex, income, residential region, urbanization, and CCI scores, patients who received sedative-hypnotic prescriptions exhibited higher hazard ratios for cancer compared with those without sedative-hypnotic prescriptions: AHR 1.49 (CI: 1.22-1.82) in Inso-Hyp group compared with the Inso-NonHyp group and 1.68 (CI: 1.38-2.05) in the NonInso-Hyp group compared with NonInso-NonHyp group (Table 4). In particular, the Inso-Hyp group exhibited a higher probability of developing oral and breast cancer than the Inso-NonHyp group did, and the NonInso-Hyp group exhibited a significantly higher risk of developing liver and breast cancers than the NonInso-NonHyp group did.

Table 1. Demographic characteristics of patients in the Inso-Hyp, Inso-NonHyp, NonInso-Hyp, and NonInso-NonHyp groups

Variable	Inso-Hyp (N = 4,266)		Inso-NonHyp (N = 17,064)		NonInso-Hyp (N = 4,451)		NonInso-NonHyp (N = 17,804)		p value
	N	%	N	%	N	%	N	%	
Age (y)									<0.001
Younger than 30	188	4.4	789	4.6	102	2.3	411	2.3	
30-44	1464	34.3	5813	34.1	1078	24.2	4306	24.2	
45-64	1987	46.6	7957	46.6	2258	50.7	9036	50.8	
65 or older	627	14.7	2505	14.7	1013	22.8	4051	22.8	
Sex									<0.001
Female	2051	48.1	8204	48.1	1816	40.8	7264	40.8	
Male	2215	51.9	8860	51.9	2635	59.2	10540	59.2	
Income (US\$)									<0.001
≥1281 (≥NT\$40000)	362	8.5	2029	11.9	408	9.2	1259	7.1	
640-1280 (NT\$20000-\$39999)	699	16.4	3706	21.7	707	15.9	2516	14.1	
<640 (<NT\$20000)	3205	75.1	11329	66.4	3336	75.0	14029	78.8	
Region									<0.001
Northern	2074	48.6	8865	52.0	2212	49.7	10193	57.3	
Central	946	22.2	3600	21.1	876	19.7	3003	16.9	
Southern	1171	27.5	4265	25.0	1277	28.7	4185	23.5	
Eastern	75	1.8	334	2.0	86	2.0	423	2.4	
Urbanization									<0.001
Urban	2426	56.9	9832	57.6	2558	57.5	10272	57.7	
Suburban	1450	34.0	5589	32.8	1460	32.8	5517	31.0	
Rural	390	9.1	1643	9.6	433	9.7	2015	11.3	
CCI									<0.001
0	1701	39.9	7760	45.5	1565	35.2	7932	44.6	
1	1124	26.4	4479	26.3	1123	25.2	3548	19.9	
≥2	1441	33.8	4825	28.3	1763	39.6	6324	35.5	

CCI, Charlson comorbidity index; Inso-Hyp, patients with insomnia and sedative-hypnotic prescriptions; Inso-NonHyp, patients with insomnia and without sedative-hypnotic prescriptions; NonInso-Hyp, patients with sedative-hypnotics and without insomnia; NonInso-NonHyp, patients with neither insomnia nor sedative-hypnotic prescriptions.

Table 2. Crude hazard ratios for cancer in patients in the Inso-Hyp, Inso-NonHyp, NonInso-Hyp, and NonInso-NonHyp groups

Variable	Cancer			
	Cases	PY	Incidence	CHR (95% CI)
Age (y)				
Younger than 30	7	10782.79	0.65	1.00
30-44	100	83935.98	1.19	1.88 (0.88-4.05)
45-64	494	137295.32	3.60	5.75 (2.73-12.12)**
65 or older	469	53457.42	8.77	14.00 (6.64-29.52)**
Sex				
Female	368	127644.11	2.88	1.00
Male	702	157827.40	4.45	1.55 (1.37-1.76)**
Income (US\$)				
≥1281 (≥NT\$40000)	84	27310.87	3.08	1.00
640-1280 (NT\$20000-\$39999)	144	50524.91	2.85	0.93 (0.71-1.22)
<640 (<NT\$20000)	842	207635.73	4.06	1.34 (1.07-1.67)*
Region				
Northern	530	152126.20	3.48	1.00
Central	224	55922.83	4.01	1.14 (0.98-1.33)
Southern	294	71482.77	4.11	1.18 (1.02-1.36)*
Eastern	22	5939.71	3.70	1.06 (0.69-1.63)
Urbanization				
Urban	583	164425.75	3.55	1.00
Suburban	362	92145.41	3.93	1.11 (0.97-1.26)
Rural	125	28900.35	4.33	1.23 (1.01-1.49)*
CCI				
0	285	117425.26	2.43	1.00
1	272	68558.74	3.97	1.59 (1.35-1.88)**
≥2	513	99487.52	5.16	2.04 (1.76-2.36)**
Group1				
Inso-NonHyp	392	119187.82	3.29	1.00
Inso-Hyp	133	28097.40	4.73	1.47 (1.21-1.79)**
Group2				
NonInso-NonHyp	410	113218.87	3.62	1.00
NonInso-Hyp	135	24967.32	5.41	1.65 (1.36-2.01)**

Incidence, incidence density (1000 per person-years). *: $p < .05$. **: $p < .001$. CHR, crude hazard ratio; CCI, Charlson comorbidity index; CI, confidence interval; PY, person years.

Table 3. Adjusted hazard ratios for cancer in the Inso-Hyp and NonInso-Hyp groups according to the type, half-life, and doses of sedative-hypnotics drugs

Variable	Cancer					AHR (95% CI)
	N	Cases	PY	Incidence	CHR (95% CI)	
Inso-Hyp vs. Inso-NonHyp						
Type ^a						
NonHyp	17064	392	119187.92	3.29	1.00	1.00
NonBZD	354	8	2305.16	3.47	1.08 (0.54-2.18)	1.11 (0.55-2.24)
BZD	840	22	5825.99	3.78	1.15 (0.75-1.77)	1.02 (0.67-1.57)
Half-life ^b						
NonHyp	17064	392	119187.92	3.29	1.00	1.00
Short-acting	483	12	3158.77	3.80	1.18 (0.67-2.10)	1.22 (0.68-2.16)
Intermediate-acting	1232	33	8074.47	4.09	1.27 (0.89-1.81)	1.16 (0.81-1.65)
Long-acting	2551	88	16864.17	5.22	1.62 (1.28-2.04)**	1.73 (1.37-2.19)**
Dose ^c						
NonHyp	17064	392	119187.92	3.29	1.00	1.00
Low	138	5	621.57	8.04	3.13(1.29-7.56)*	2.70(1.12-6.54)*
Medium	474	15	2130.92	7.04	2.75(1.64-4.61)**	2.07(1.23-3.49)*
High	5485	157	25001.66	6.28	2.43(2.01-2.94)**	2.46(2.02-3.00)**
NonInso-Hyp vs. NonInso-NonHyp						
Type ^d						
NonHyp	17804	410	113218.87	3.62	1.00	1.00
NonBZD	278	9	1462.55	6.15	1.97 (1.01-3.81)*	1.93 (1.00-3.75)
BZD	2492	70	13899.56	5.04	1.56 (1.21-2.01)**	1.51 (1.17-1.95)*
Half-life ^e						
NonHyp	17804	410	113218.87	3.62	1.00	1.00
Short-acting	592	18	3114.44	5.78	1.83 (1.14-2.94)*	1.75 (1.09-2.82)*
Intermediate-acting	1481	44	8075.53	5.45	1.70 (1.24-2.32)**	1.65 (1.21-2.26)*
Long-acting	2378	73	13780.34	5.30	1.59 (1.24-2.04)**	1.69 (1.31-2.17)**
Dose ^c						
NonHyp	17804	410	113218.87	3.62	1.00	1.00
Low	957	56	3555.39	15.75	6.79(5.11-9.02)**	5.47(4.10-7.30)**
Medium	1764	60	6157.22	9.74	4.57(3.46-6.03)**	3.77(2.85-5.00)**
High	5393	168	20844.67	8.06	3.32(2.75-4.00)**	3.42(2.82-4.14)**

^aOverall, 3,072 patients prescribed BZDs and nonBZDs were excluded. ^bIn total, 3,227 patients (75.64%) switched from short-acting to intermediate-acting (N=920) or long-acting (N=2307) sedative-hypnotic drugs, and 198 patients (4.64%) switched from intermediate-acting to long-acting sedative-hypnotic drugs. ^cLow, year mean defined

daily dose (DDD) of 7 to 30 during follow-up period; Medium, year mean DDD of 31 to 90 in during follow-up period; High, mean DDD of at least 91 during follow-up period. ^aOverall, 1,681 patients prescribed BZDs and nonBZDs were excluded. ^eIn total, 2,027 patients (45.54%) switched from short-acting to intermediate-acting (N=672) or long-acting (N=1355) sedative-hypnotic drugs, and 571 patients (12.83%) switched from intermediate-acting to long-acting sedative-hypnotic drugs. * $p < 0.05$. ** $p < 0.001$. AHR, adjusted hazard ratio (adjusted for patient age, sex, income, residential region, urbanization, and Charlson comorbidity index); BZD, benzodiazepine; CI, confidence interval.

Table 4. Incidence and AHR for cancer in patients in the Inso-Hyp, Inso-NonHyp, NonInso-Hyp, and NonInso-NonHyp groups

Cancer (n, %)	Inso-Hyp vs. Inso-NonHyp	NonInso-Hyp vs. NonInso-NonHyp	Inso-Hyp vs. NonInso-Hyp	Inso-NonHyp vs. NonInso-NonHyp
All	133 (3.12%) vs. 392 (2.30%)	135 (3.03%) vs. 410 (2.30%)	133 (3.12%) vs. 135 (3.03%)	392 (2.30%) vs. 410 (2.30%)
Incidence	4.73 vs. 3.29	5.41 vs. 3.62	4.73 vs. 5.41	3.29 vs. 3.62
AHR (95% CI)	1.49 (1.22-1.82)**	1.68 (1.38-2.05)**	1.04 (0.82-1.33)	1.08 (0.94-1.25)
Oral cancer	16 (0.38%) vs. 27 (0.16%)	12 (0.27%) vs. 30 (0.17%)	16 (0.38%) vs. 12 (0.27%)	27 (0.16%) vs. 30 (0.17%)
Incidence	0.56 vs. 0.22	0.47 vs. 0.26	0.56 vs. 0.47	0.22 vs. 0.26
AHR (95% CI)	2.44 (1.31-4.54)*	1.92 (0.97-3.81)	1.25 (0.58-2.68)	0.93 (0.55-1.59)
Stomach cancer	8 (0.19%) vs. 21 (0.12%)	4 (0.09%) vs. 19 (0.11%)	8 (0.19%) vs. 4 (0.09%)	21 (0.12%) vs. 19 (0.11%)
Incidence	0.28 vs. 0.17	0.16 vs. 0.17	0.28 vs. 0.16	0.17 vs. 0.17
AHR (95% CI)	1.60 (0.71-3.63)	1.32 (0.44-4.02)	2.32 (0.69-7.75)	1.52 (0.81-2.87)
Colon cancer	22 (0.52%) vs. 72 (0.42%)	19 (0.43%) vs. 75 (0.42%)	22 (0.52%) vs. 19 (0.43%)	72 (0.42%) vs. 75 (0.42%)
Incidence	0.77 vs. 0.60	0.75 vs. 0.66	0.77 vs. 0.75	0.60 vs. 0.66
AHR (95% CI)	1.35 (0.83-2.17)	1.25 (0.75-2.09)	1.33 (0.71-2.49)	1.13 (0.81-1.57)
Liver cancer	16 (0.38%) vs. 42 (0.25%)	22 (0.49%) vs. 40 (0.22%)	16 (0.38%) vs. 22 (0.49%)	42 (0.25%) vs. 40 (0.22%)
Incidence	0.56 vs. 0.35	0.87 vs. 0.35	0.56 vs. 0.87	0.35 vs. 0.35
AHR (95% CI)	1.54 (0.86-2.74)	2.53 (1.48-4.32)**	0.84 (0.44-1.62)	1.21 (0.78-1.88)
Lung cancer	10 (0.23%) vs. 53 (0.31%)	17 (0.38%) vs. 51 (0.29%)	10 (0.23%) vs. 17 (0.38%)	53 (0.31%) vs. 51 (0.29%)
Incidence	0.35 vs. 0.44	0.67 vs. 0.45	0.35 vs. 0.67	0.44 vs. 0.45
AHR (95% CI)	0.83 (0.42-1.63)	1.71 (0.98-3.00)	0.65 (0.29-1.43)	1.37 (0.93-2.03)
Skin cancer	4 (0.09%) vs. 9 (0.05%)	–	–	9 (0.05%) vs. 8 (0.04%)
Incidence	0.14 vs. 0.07	–	–	0.07 vs. 0.07
AHR (95% CI)	1.94 (0.59-6.41)	–	–	1.42 (0.54-3.75)
Breast cancer ^a	21 (1.02%) vs. 33 (0.40%)	11 (0.61%) vs. 26 (0.36%)	21 (1.02%) vs. 11 (0.61%)	33 (0.40%) vs. 26 (0.36%)
Incidence	1.53 vs. 0.57	1.06 vs. 0.56	1.56 vs. 1.06	0.57 vs. 0.56
AHR (95% CI)	2.85 (1.64-4.96)**	2.08 (1.01-4.28)*	1.67 (0.80-3.48)	0.97 (0.54-1.64)
Corpus cancer	–	–	–	9 (0.05%) vs. 6 (0.03%)
Incidence	–	–	–	0.07 vs. 0.05
AHR (95% CI)	–	–	–	1.04 (0.36-3.00)
Prostate cancer	4 (0.09%) vs. 26 (0.15%)	5 (0.11%) vs. 21 (0.12%)	4 (0.09%) vs. 5 (0.11%)	26 (0.15%) vs. 21 (0.12%)
Incidence	0.14 vs. 0.22	0.20 vs. 0.18	0.14 vs. 0.20	0.22 vs. 0.18
AHR (95% CI)	0.70 (0.24-2.01)	1.55 (0.57-4.23)	0.94 (0.24-3.71)	1.70 (0.94-3.05)

Incidence, incidence density (1000 per person-years); AHR: adjusted hazard ratio using Cox proportional hazards regression model after controlling for age, sex, income, region, area, and CCI; *: $p < .05$; **: $p < .001$; ICD-O-3 codes: Oral cancer: C00-C06, C09-C10, C12-C14; Stomach cancer: C16; Colon cancer: C18-C21; Liver cancer: C22; Lung cancer: C33-C34; Skin cancer: C44; Breast cancer: C50; Corpus cancer: C54; Prostate cancer: C61. _: not applicable because of the sample size; #: only data of female patients were analyzed.

Using the Kaplan–Meier method, the overall 14-year cancer-free survival curves for the four groups were calculated and are presented in Figure 1. Log-rank testing revealed that there were significantly lower cancer-free survival rates for Inso-Hyp and NonInso-Hyp groups than those for Inso-NonHyp and NonInso-NonHyp groups ($p < 0.001$).

Discussion

In this 14-year cohort study, we historically and prospectively analyzed the relationship between sedative-hypnotics usage and subsequent cancer risk on the basis of 21,330 patients with insomnia and 22,255 patients without insomnia collected from the NHIRD in Taiwan. The findings of the present study provided evidence that the use of sedative-hypnotics in patients either with insomnia or without was associated with an increased risk of subsequent cancer development in the Taiwanese population. Thus, the use of sedative-hypnotics to treat patients with or

without insomnia is discouraged. For patients who clinically require sedative-hypnotics, they should be advised and warned of the potential cancer risks before receiving a prescription.

The underlying mechanisms and reasons for the evident relationship between sedative-hypnotics and cancer incidence remain to be determined. A report has suggested that sedative-hypnotics usage leads to weakened immune function. For instance, some animal studies have discovered that BZDs such as diazepam and midazolam impaired the processes of spreading, phagocytosis, and oxidative bursting of macrophages [43, 44]. These impairments can be partially explained by the reduced release of the proinflammatory cytokines interleukin-6 and interleukin-13 in blood cells because of the activation of their BZD receptors [45]. Figure 2 shows how BZDs may contribute to increased risk of subsequent cancer through the above mechanism.

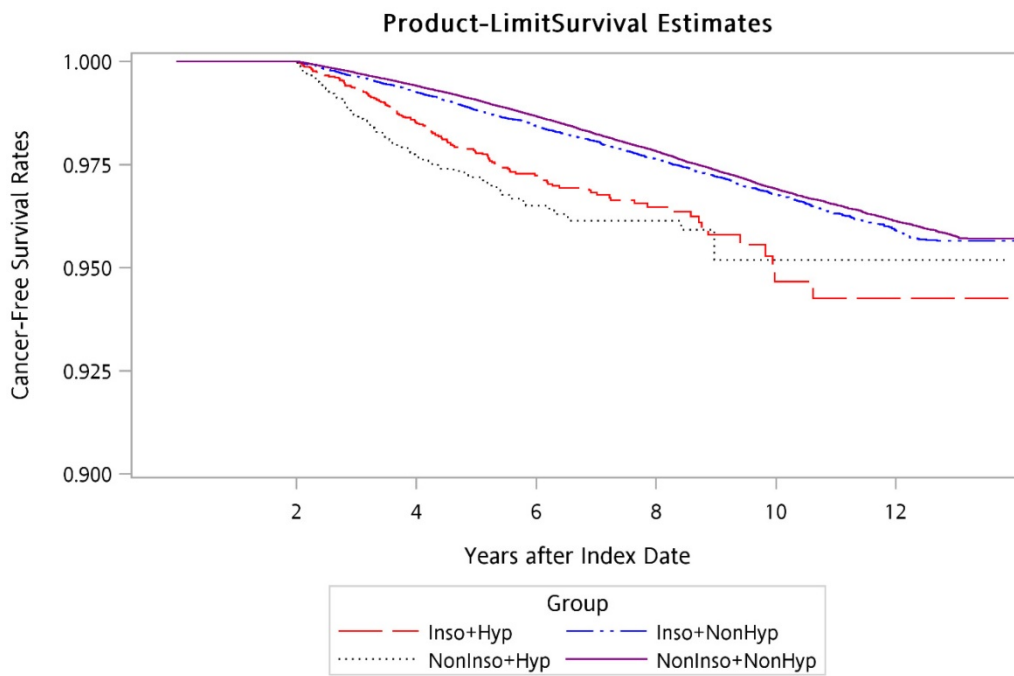


Figure 1. Cancer-free survival rates of patients in Inso-Hyp, Inso-NonHyp, NonInso-Hyp, and NonInso-NonHyp groups. Inso-Hyp, patients with insomnia and sedative-hypnotic prescriptions; Inso-NonHyp, patients with insomnia and without sedative-hypnotic prescriptions; NonInso-Hyp, patients with sedative-hypnotics and without insomnia; NonInso-NonHyp, patients with neither insomnia nor sedative-hypnotic prescriptions

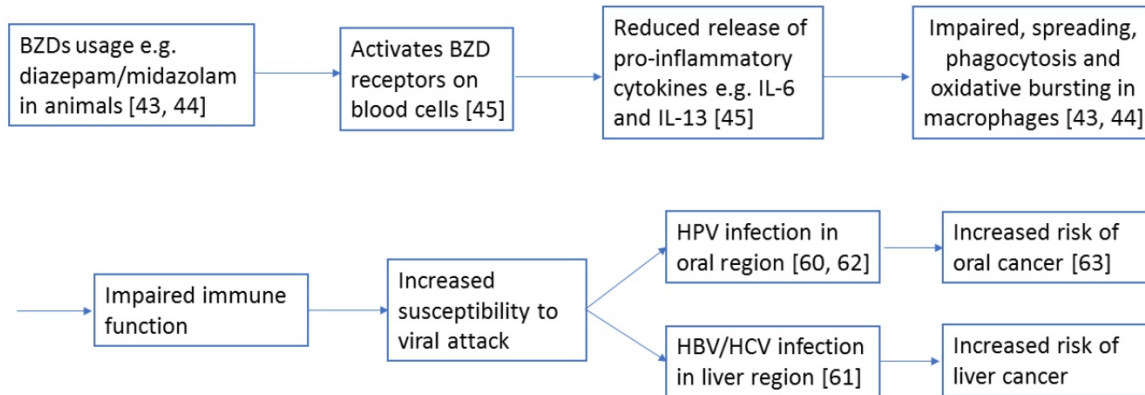


Figure 2. A diagram showing a potential mechanism how BZDs, such as diazepam or midazolam, contribute to the increased risk of subsequent cancers, such as oral and liver cancers, in this study. The numbers refer to the corresponding supporting references.

Sedative-hypnotics are also prescribed to patients with various types of psychiatric illnesses [46]. For instance, BZDs are commonly prescribed to patients with bipolar disorder [46] or schizophrenia [47] in Taiwan, and non-BZD drugs are prescribed to patients with depression [48]; this could account for the sedative-hypnotics prescribed to patients without insomnia in our study cohort (Table 3). Psychological parameters may alter immune function [49]. Moreover, individuals who regularly use sedative-hypnotics also tend to have more psychological problems. Indeed, one of our previous studies demonstrated that the use of sedative-hypnotics, including both BZDs and non-BZDs, increased the risk of developing various types of psychiatric disorders such as depressive disorder, bipolar disorder, and anxiety disorder [46].

Moreover, randomized controlled trials have demonstrated that the use of sedative-hypnotics increased the incidence of depression [50]. Non-BZDs such as zolpidem have been associated with a relatively high incidence of depression [50]. Taken together, these study findings suggest that the increased subsequent cancer risk can at least be partially accounted for by the weakened immune function that results from both intrinsic psychiatric weaknesses and extrinsic usage of sedative-hypnotics. Figure 3 shows the relationships between psychological illnesses, sedative-hypnotics and the impaired immune function. It has been recently suggested that sedative-hypnotics are clastogens that can transform normal cells into cancer through disruption or breakages of chromosomes [51, 52]. The author pointed out that non-BZDs such as zopiclone,

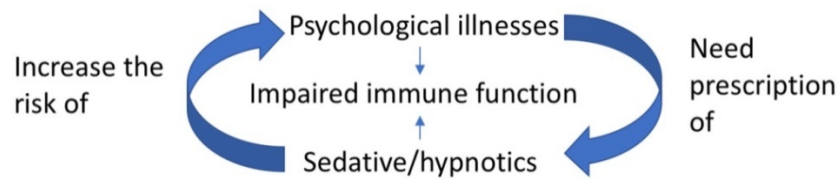


Figure 3. A diagram showing the relationships between psychological illnesses, sedative-hypnotics and impaired immune function.

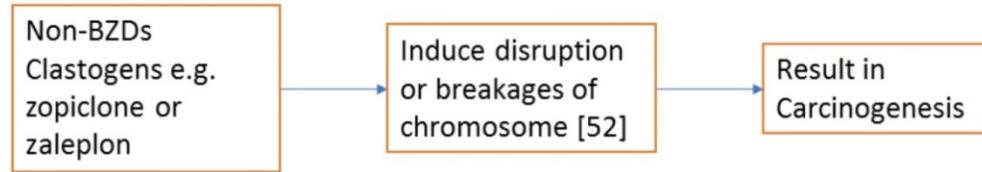


Figure 4. A diagram showing a potential mechanism how non-BZDs such as zopiclone or zaleplon contribute to increased risk of subsequent cancers. The number refers to the corresponding supporting reference.

zaleplon and ramelteon, based on the findings from the Center for Drug Evaluation and Research, are clastogenic in cell models [51]. Although both zopiclone and zaleplon usage were included in the non-BZDs group in our study, there was no significant increase in the risk of having subsequent cancers in subjects either with insomnia or without insomnia (Table 3). The conflict may be due to the fact that zolpidem was also included in the non-BZDs group in our analysis. Further in-vitro studies on the effect of non-BZDs in inducing cell transformation are warranted. Figure 4 depicted one of the possible mechanisms how non-BZDs induce carcinogenesis.

The use of long-acting sedative-hypnotics, but not short- or intermediate-acting ones, increased the risk of subsequent cancer development among patients with insomnia in our study. This suggests that the sedative-hypnotics having a half-life longer than 35 hours should be restricted and not prescribed to patients with insomnia. A possible reason for this is that longer duration of sleep that results from the use of short- or intermediate-acting sedative-hypnotics may help restore their normal immune function, which could compensate for the risk of subsequent cancer. By contrast, the use of long-acting sedative-hypnotics by patients with insomnia results in more than half the dose consumed the previous night remaining in the patient's system until just before the next dose is consumed. Thus, the negative effect of this carry-over effect may significantly interrupt the circadian rhythm of these patients. Disruption of the normal circadian rhythm has been reported to increase the risk of developing cancer [53]. Furthermore, Thompson et al has recently proposed that disruption of the circadian rhythm and suppression of nocturnal production of melatonin, which has been shown to promote DNA repair in animal models [54-56], could be potential mechanisms that contribute to an increased risk of colorectal

adenomas due to shorter sleep duration in a group of subjects who were having colonoscopy screening [57]. In contrast, no significant increase in the risk of colon cancer was observed in the Inso-NonHyp group when compared with the NonInso-NonHyp group. A possible reason to explain this is that the risk of colon/colorectal malignancy had been reduced because of the implementation of the Nationwide Colorectal Cancer Screening Program since 2004 in Taiwan [58]. Colon/colorectal malignancy can be prevented if early detection of precancerous stage and subsequent intervention can be achieved [59]. Thus, we suggest that more frequent cancer screening (e.g. for colon cancer) could be provided to individuals who are having sedative-hypnotics.

The use of sedative-hypnotics resulted in a 2.4-fold increase in the risk of oral cancer in patients with insomnia in our study, and a 2.5-fold risk of future liver cancer was evident in patients without insomnia who used sedative-hypnotics. As we discussed earlier, patients who use sedative-hypnotics are more likely to have weakened immune function; thus, they are more susceptible to various types of viral attack. The viral infection hypothesis has been suggested to explain the high risk of oral and liver cancers that is associated with sedative-hypnotics usage [60-62]. For example, human papillomavirus (HPV) has been determined to contribute to the development of oral cancer [63], and hepatitis B virus (HBV) and hepatitis C virus (HCV) infections account for the majority of primary liver cancer cases in Taiwan [64].

Experimental studies have suggested that diazepam, one of the BZDs family members, may promote breast cancer growth [65, 66]. However, this hypothesis was rejected by Kleinerman et al., who concluded that the breast cancer growth was not associated with the use of diazepam [67]. In addition, two other groups of researchers also failed to discern

a significant association between the use of sedative-hypnotics and breast cancer risk [68, 69]. Pottegard et al. concluded that the odds ratio for breast cancer among patients in their Danish cohort comprised of approximately 1.3 million individuals who used BZDs or BZD-related drugs was close to unity (AHR: 1.01, 95% CI 0.90-1.14) [70]. In Halapy's study, BZDs usage did not correlate with an increased breast cancer rate in their Canadian cohort [68]. However, we discovered that female patients in our study who used sedative-hypnotics had at least a 2.2-fold increased risk of developing subsequent breast cancer (Table 4). This finding is partially supported by Kao et al., who determined that the use of Zolpidem, the most commonly used non-BZDs drug, was associated with a 1.84-fold increase in breast cancer risk in Taiwanese women [32]. Further investigation into this area should be undertaken in the future. Different mechanisms of breast carcinogenesis may vary among patients of different ethnicities, which could account for the discrepant research findings.

Pottegard et al have recently concluded that the long term usage of either BZDs and BZD-related drugs did not significantly increase the overall risk of subsequent cancer [71]. However, significant increases (at least 1.35 folds) in the risks of site-specific cancers such as cancers of esophagus, stomach, liver, pancreas, lung, bronchus and pleura and melanoma of skin could still be demonstrated. In particular, a 1.8 folds increase in the risk of having liver cancer for patients taking sedative-hypnotics was observed. Although the author suggested that heavy alcohol usage could be a confounding factor which contributed to the increased risk [71], BZDs such as diazepam and oxazepam were CYP4A inducers in mice that could account for their ability to promote tumorigenesis in liver [72]. Furthermore, liver is the organ responsible for drug metabolism. Thus, the potential side effect of prolonged use of sedative-hypnotics on liver may be similar to that of the prolonged use of acetaminophen, which was associated with slightly increased risk of liver cancer [73], possibly due to liver glutathione depletion, increased oxidative stress, mitochondrial dysfunction [74]. Taking these together, it is possible that the ability of sedative-hypnotics to initiate/promote tumor growth may be different on different organs and it may exert a more direct and stronger carcinogenic effect on liver. Mechanistic study of hepatocarcinogenic effect exerted by sedative-hypnotics is warranted.

Compared with a recent Taiwanese study, Lan et al have shown that the use of Zolpidem was also associated with increased cancer risk [35]. Since this

study targeted at investigating the relationships between the use of BZDs and non-BZDs and various mortality, no further information was provided on the potential risk of subsequent cancer after prolonged usage of BZDs and non-BZDs in the general Taiwanese population. Thus, our study provided the most recent findings to indicate that the overall cancer risk was increased with prolonged usage of sedative-hypnotics in Taiwanese population (Table 4). Although prescription of sedative-hypnotics is still the main treatment regimen for patients with insomnia [14], cognitive behavior therapy (CBT) appears to be an alternative treatment option [75]. In consideration of the time and costs associated with the conventional face-to-face treatment session, a randomized controlled trial has suggested that video-based CBT (V-CBT) can also produces significant and sustainable treatment effects in a group of breast cancer patients with insomnia symptoms [76]. Therefore, the feasibility of the use of V-CBT to substitute sedative-hypnotics medication should be investigated.

This study has a few strengths. To the best of our knowledge, it is the first study to investigate the correlations between sedative-hypnotics usage (including both BZDs and non-BZDs) and subsequent cancer risk in patients with or without insomnia in the Taiwanese population. Moreover, the cohort in this study was derived from the NHIRD, which has a national coverage rate of approximately 96%, and thus this study is representative of the total population in Taiwan. The data included in this study encompass a period of 14 years (2002-2015), which is relatively longer than other local researches that have been conducted; thus, any potential bias could be minimized. In addition, patients enrolled in this study were carefully matched in terms of age, sex, index year, and CCI score. Last, only patients who received a cumulative DDD prescription of more than 30 per year were included for most of the statistical analyses with the exception of dosage analysis. This was done to eliminate the effect of sedative-hypnotics usage that was unlikely to have a significant effect on the development of subsequent cancers. Several limitations have also been identified. First, data from the NHIRD do not include factors that are potentially related to sedative-hypnotics usage and cancer risk such as drinking habit, smoking habit, exercise habit, and family history of cancer [77]. These are major risk factors for multiple cancers and thus these may have constituted residual confounding effects in this study. Second, the use of sedative-hypnotics in the claims data was inferred from prescription data. Thus, it might not accurately represent the actual usage among patients. The cancer risk associated with the

potential use of sedative-hypnotics could have been underestimated. However, the correlated cancer risk could also have been overestimated if some patients had obtained sedative-hypnotics from sources other than NHI, but this situation was unlikely because all sedative-hypnotics require a prescription in Taiwan. Third, a causal relationship could not be established because observational data was used in this study. Last, main findings from this current study have not been validated in another independent cohort due to limited number of subjects currently available.

Conclusions

This study presented evidence that the use of sedative-hypnotics in patients either with or without insomnia was associated with subsequent cancer development in the Taiwanese population. The use of long-acting and high dose of sedative-hypnotics increased the risk of subsequent cancer development. The use of sedative-hypnotics resulted in increased risks of oral, liver, and breast cancer in patients. The increased risk of cancer should be explained to patients who require sedative-hypnotics before a prescription is given. The use of sedative-hypnotics is discouraged in the long term, and other treatments, such as cognitive behavior therapy, should be considered to substitute the prescription of sedative-hypnotics in Taiwan. Cancer screening can also be provided to individuals who are receiving sedative-hypnotics in a more frequent manner.

Abbreviations

BZDs: benzodiazepines; non-BZDs: nonbenzodiazepines; NHI: National Health Insurance; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; Inso-Hyp: patients with insomnia and sedative-hypnotic prescriptions; Inso-NonHyp: patients with insomnia and without sedative-hypnotic prescriptions; NonInso-Hyp: patients with sedative-hypnotics and without insomnia; NonInso-NonHyp: patients with neither insomnia nor sedative-hypnotic prescriptions; DDD: defined daily dose; CCI: Charlson comorbidity score; CHR: crude hazard ratio; AHR: adjusted hazard ratio; NHIRD: National Health Insurance Research Database; CI: confidence interval.

Acknowledgements

The study was granted by Taipei Medical University Hospital (105TMU-TMUH-24).

Ethics Committee Approval and Patient Consent

The present study was approved by Joint Institutional Review Board of Taipei Medical

University (N201611010).

Competing Interests

The authors have declared that no competing interest exists.

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