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Association between colorectal cancer and zolpidem use in a case-control study

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Abstract

This study aimed to examine the association between colorectal cancer and zolpidem use in Taiwan.

A case-control study was conducted using the database of Taiwan National Health Insurance Program from 2000 to 2013. Participants aged 20 to 84 years with newly diagnosed colorectal cancer were selected as the cases. Sex-matched and age-matched participants without colorectal cancer were randomly selected as the matched controls. The odds ratio and 95% confidence interval for colorectal cancer associated with zolpidem use were calculated by the multivariable logistic regression model.

There were 4912 cases with colorectal cancer and 4912 matched controls without colorectal cancer. The mean age was 63 years and 58% were male participants. After adjustment for co-variables, the multivariable logistic regression model disclosed that there was no statistical association between colorectal cancer and zolpidem use (adjusted OR 1.05, 95% CI 0.95–1.15).

No statistical association can be detected between colorectal cancer and zolpidem use in Taiwan.

Abbreviation: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: case-control study, colorectal cancer, Taiwan national health insurance program, zolpidem

1. Introduction

Zolpidem is a non-benzodiazepine hypnotic medication frequently prescribed for the management of insomnia.[1] Currently, there is not any in vitro study focusing on the association between zolpidem use and cancer, but some epidemiologic studies disclosed a positive association between zolpidem use and tumor.[2–4]

A cohort study disclosed that participants with zolpidem use had a higher hazard ratio of benign brain tumors, compared with those participants not administering zolpidem.[3] Another cohort study disclosed that participants with zolpidem use had a higher hazard ratio of developing any cancer, compared with those participants not administering zolpidem.[4] However, the relationship between zolpidem use and colorectal cancer has not yet been illustrated.

Colorectal cancer was the third leading cause of cancer-related death in Taiwan in 2018.[5] Totally, 5823 cases died of colorectal cancer in Taiwan in 2018, approximately accounting for 11.94% of 48,784 cancer deaths.[5] Two pharmacoepidemiologic studies disclosed that zolpidem had even been the most frequently prescribed non-benzodiazepine hypnotic medication in Taiwan.[6,7] We rationally hypothesized that there could be a link between zolpidem use and colorectal cancer. If the link is present, more pharmacoepidemiologic data could be obtained on this issue. A nation-based case-control study was performed to examine the relationship between zolpidem use and colorectal cancer in Taiwan.

2. Materials and Methods

2.1. Study design and data source

A nation-based case-control study was performed using the database of Taiwan National Health Insurance Program. The program was launched in March 1, 1995, and it has covered about 99.7% of 23 million persons living in Taiwan.[8–11] The details of study design and data source are noticed in previous studies.[12–15]

2.2. Study participants

Participants aged 20 to 84 years with newly diagnosed colorectal cancer from 2000 to 2013 were selected as the cases (based on International Classification of Diseases 9th Revision-Clinical

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Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers were scrambled to ensure confidentiality. Patient informed consent was not required.

This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

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Modification, ICD-9 codes 153 and 154). The date of a case being diagnosed with colorectal cancer was defined as the index date. For every one case with colorectal cancer, one participant without colorectal cancer was randomly selected as the matched control. The cases and the matched controls were matched with sex, age (every 5-year interval), comorbidities, and the year of the index date. To diminish the biased results, participants who had any other cancer before the index date were excluded from the study.

2.3. Comorbidities

Comorbidities studied were adapted from previous studies,[16] including alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, colorectal adenoma, diabetes mellitus, hyperlipidemia, hypertension, and inflammatory bowel disease.

2.4. Definition of zolpidem exposure

The definition of zolpidem exposure was adapted from previous studies.[17,18] Ever use of zolpidem was defined as participants having at least a prescription for zolpidem before the index date. Never use of zolpidem was defined as participants having not a prescription for zolpidem before the index date.

2.5. Statistical analysis

The initial analysis compared the distributions of demographic status, zolpidem use, and comorbidities between the cases and the matched controls by the Chi-square test for categorical variables and the *t* test for continuous variables. Variables found to be statistically significant in a univariable logistic regression model were further included in a multivariate logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the association between colorectal cancer and zolpidem use. The probability value $<.05$ was considered statistically significant (SAS software version 9.2, SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of the study population

Totally, there were 4912 cases with colorectal cancer and 4912 matched controls without colorectal cancer (Table 1). The cases and the matched controls had similar a distribution of sex. The mean ages (standard deviation) were 63.9 (12.6) years in the cases and 63.4 (12.7) years in the matched controls, with statistical significance (*t* test, $P=.02$). There was no statistical difference in zolpidem use and comorbidities between the cases and the matched controls (Chi-square test, $P>.05$ for all), except inflammatory bowel disease ($P=.002$).

3.2. Association between colorectal cancer and zolpidem use

Variables found to be statistically associated with colorectal cancer in a univariable logistic regression model were further examined by a multivariable logistic regression model. After adjustment age and inflammatory bowel disease, the multivariable logistic regression model disclosed that there was no statistical association between colorectal cancer and zolpidem use (adjusted OR 1.05, 95% CI 0.95–1.15, Table 2).

4. Discussion

In this nation-based case-control stud, no statistical association was detected between colorectal cancer and zolpidem use (Table 2). This findings were compatible with a cohort study disclosing no statistical association between colorectal cancer and

Table 1

Characteristics between cases with colorectal cancer and matched controls.

Variable	Matched controls N = 4912		Cases with colorectal cancer N = 4912		*P* value*
	n	(%)	n	(%)	
Sex					.37
Female	2025	(41.2)	2069	(42.1)	
Male	2887	(58.8)	2843	(57.9)	
Age group (yr)					.79
20–39	226	(4.6)	215	(4.4)	
40–64	2232	(45.4)	2216	(45.1)	
65–84	2454	(50.0)	2481	(50.5)	
Age (yr), mean ± standard deviation†	63.4 ± 12.7		63.9 ± 12.6		.02
Ever use of zolpidem	1115	(22.7)	1163	(23.7)	.25
Comorbidities					
Alcohol-related disease	195	(3.97)	204	(4.15)	.65
Cardiovascular disease	1758	(35.8)	1771	(36.1)	.78
Chronic kidney disease	371	(7.55)	375	(7.63)	.88
Chronic liver disease	862	(17.6)	890	(18.1)	.46
Chronic obstructive pulmonary disease	1075	(21.9)	1089	(22.2)	.73
Colorectal adenoma	852	(17.4)	872	(17.8)	.60
Diabetes mellitus	704	(14.3)	752	(15.3)	.17
Hyperlipidemia	1265	(25.8)	1268	(25.8)	.94
Hypertension	2553	(52.0)	2561	(52.1)	.87
Inflammatory bowel disease	97	(1.97)	58	(1.18)	.002

Data are presented as the number of participants in each group with percentages given in parentheses.

* Chi-square test.

† *t* test comparing cases with colorectal cancer and matched controls.

Table 2

Odds ratio and 95% confidence interval of colorectal cancer associated with zolpidem use and comorbidities by logistical regression model.

Variable	Crude		Adjusted†		*P* value
	OR	(95% CI)	OR	(95% CI)	
Sex (male vs female)	0.96	(0.89, 1.04)			
Age (every one year)	1.00	(1.00, 1.01)	1.00	(1.00, 1.01)	.046
Ever use of zolpidem (never use as a reference)	1.06	(0.96, 1.16)	1.05	(0.95, 1.15)	.36
Comorbidities (yes vs no)					
Alcohol-related disease	1.05	(0.86, 1.28)			
Cardiovascular disease	1.01	(0.93, 1.10)			
Chronic kidney disease	1.01	(0.87, 1.18)			
Chronic liver disease	1.04	(0.94, 1.15)			
Chronic obstructive pulmonary disease	1.02	(0.92, 1.12)			
Colorectal adenoma	1.03	(0.93, 1.14)			
Diabetes mellitus	1.08	(0.97, 1.21)			
Hyperlipidemia	1.00	(0.92, 1.10)			
Hypertension	1.01	(0.93, 1.09)			
Inflammatory bowel disease	0.59	(0.43, 0.82)	.60	(0.43, 0.84)	.003

† Variables found to be statistically associated with colorectal cancer in a univariable logistic regression model were further examined by a multivariable logistic regression model. Adjusted for age and inflammatory bowel disease.

zolpidem use (adjusted hazard ratio 1.04, 95% CI 0.83–1.32),[4] and also partially compatible with a case-control study disclosing no statistical association between zolpidem use and breast cancer (adjusted OR 1.11, 95% CI 0.95–1.30),[19] and also partially compatible with another case-control study disclosing no statistical association between zolpidem use and hepatocellular carcinoma (adjusted OR 1.05, 95% CI 0.97–1.13).[20] To the contrary, a cohort study disclosed that participants with zolpidem use ≥520 mg/year had a higher hazard ratio of benign brain tumors (hazard ratio 1.85, 95% CI 1.21–2.82), compared with those participants not administering zolpidem.[3] A cohort study disclosed that participants with zolpidem use had a higher hazard ratio of developing any cancer (adjusted hazard ratio 1.68, 95% CI 1.55–1.82), compared with those participants not administering zolpidem.[4] Based on the above reviews, there are no conclusive data about zolpidem use on cancer risk. The hypothesis that zolpidem use might increase the risk of colorectal cancer is not sound.

We conclude that from this nation-based case-control study in Taiwan, no statistical association can be detected between colorectal cancer and zolpidem use.

Author contributions

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