Original Article

Association between Selective Serotonin Reuptake Inhibitors Use and Colorectal Cancer in a Case-Control Study

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ABSTRACT

Objectives: This study's aim was to investigate whether selective serotonin reuptake inhibitors use was associated with the risk of colorectal cancer. **Methods:** From the claims data of Taiwan National Health Insurance Program, a retrospective case-control study was conducted to examine 4739 aged 20-84 cases with newly diagnosed colorectal cancer in 2000-2013 and 4739 sex-matched and age-matched controls without colorectal cancer. The prescription history of selective serotonin reuptake inhibitors and other comorbidities were compared between the cases and the matched controls. **Results:** After adjusting for the potential confounders, the multivariable logistic regression model showed that the odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer were lower than the odds of selective serotonin reuptake inhibitors use among matched controls (adjusted OR 0.77; 95% CI 0.66-0.89). **Conclusion:** The odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer are lower than among matched controls. This finding indicates that selective serotonin reuptake inhibitors use might be a protective factor against colorectal cancer.

Key words: Case-control study, Colorectal cancer, Selective serotonin reuptake inhibitors, Taiwan National Health Insurance Program.

INTRODUCTION

Selective serotonin reuptake inhibitors are widely used to treat depression.[1,2] Animal studies have shown that selective serotonin reuptake inhibitors possess potential anti-proliferative effects on tumor cells and further inhibit the growth of colorectal tumor.[3,4] However, epidemiologic studies showed controversial results. Three retrospective case-control studies showed that selective serotonin reuptake inhibitors use was significantly associated with 30%-53% risk reduction of colorectal cancer,[5-7] but other studies did not detect a significant association between selective serotonin reuptake inhibitors use and colorectal cancer.[8,9] A meta-analysis by Lee and colleagues also did not detect a significant association.[10]

Colorectal cancer was the third leading cause of cancer death in Taiwan in 2016.[11] There were 5722 (12%) case deaths due to colorectal cancer among 47760 total cancer deaths.[11] To date, no definite report is available on the association between selective serotonin reuptake inhibitors use and colorectal cancer in Taiwan. Therefore, we conducted a case-control study to investigate whether selective serotonin reuptake inhibitors use was associated with the risk of colorectal cancer.

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MATERIALS AND METHODS

Study design and data source

We conducted a case-control study utilizing the claims data of Taiwan National Health Insurance Program. The program was launched in March 1, 1995 and it has covered about 99.6% of 23 million people living on an independent country of Taiwan.[12-14] The details of the program were well documented in previous studies.[15-17]

Study subjects

Based on International Classification of Diseases 9th Revision-Clinical Modification (ICD-9 codes), we selected 4739 aged 20-84 subjects with newly diagnosed colorectal cancer in 2000-2013 as the cases (ICD-9 codes 153 and 154). For each case with colorectal cancer, we randomly selected one subject without colorectal cancer as the matched control. The cases and the matched controls were frequency matched with sex, age (every 5-year interval) comorbidities and the year of the index date. The date of a case being diagnosed with colorectal cancer was defined as the index date. To reduce the biased results, subjects with any other cancer before the index date were excluded.

Comorbidities studied

Comorbidities before the index date were selected as follows: alcohol-related disease, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, colorectal adenoma, diabetes mellitus, hyperlipidemia, hypertension, as well as inflammatory bowel disease. All comorbidities were identified based on ICD-9 codes, which has been validated in previous studies.[18-20]

Definition of drug exposure

We collected the prescription histories of selective serotonin reuptake inhibitors and other anti-depression drugs. In Taiwan, the group of selective serotonin reuptake inhibitors during 2000-2013 included fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. The definition of drug exposure was depicted in previous studies.[21-23] Subjects who ever had a prescription for drugs studied were defined as ever use. Subjects who never had a prescription for drugs studied were defined as never use.

Statistical analysis

The Chi-square test and the *t*-test were used to examine the differences of demographic status, drugs use and comorbidities between the cases and the matched controls. Variables which were found to be significantly associated with colorectal cancer in a univariable logistic regression model were further included in a multivariable logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were used to estimate the odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer and matched controls. Last, we performed an analysis about the duration-dependent effect of selective serotonin reuptake inhibitors use on the risk of colorectal cancer. The probability value < 0.05 was considered statistically significant (SAS software version 9.2, SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Characteristics of the study population

Table 1 shows 4739 cases with colorectal cancer and 4739 matched controls without colorectal cancer. The cases and the matched controls had a similar distribution of sex. The mean ages (standard deviation) were 63.8(12.7) years in cases and 63.1 (12.8) years in matched controls, with statistical significance (*t*-test, $P = 0.01$). The matched controls had a higher proportion of ever use of selective serotonin reuptake inhibitors than the cases, with statistical significance (8.59% vs. 6.79%, Chi-square test, $P = 0.001$). There were no statistic differences of other anti-depression drugs and comorbidities between the cases and the matched controls (Chi-square test, $P > 0.05$ for all), except inflammatory bowel disease.

Association between colorectal cancer and selective serotonin reuptake inhibitors use

Variables which were found to be significantly associated with colorectal cancer in a univariable logistic regression model were further included in a multivariable logistic regression model. Only sex and inflammatory bowel disease were compatible with the analysis criteria. The multivariable logistic regression model showed that the odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer were lower than the odds of selective serotonin reuptake inhibitors use among matched controls (adjusted OR 0.77; 95% CI 0.66-0.89, Table 2).

Association between colorectal cancer and cumulative duration of selective serotonin reuptake inhibitors use

Table 3 shows that the odds of cumulative duration of selective serotonin reuptake inhibitors use < 12 months among cases with colorectal cancer were lower than among matched controls (adjusted OR 0.80; 95% CI 0.67-0.95). The odds of cumulative duration of selective serotonin reuptake inhibitors use ≥ 12 months among

Table 1: Characteristics between cases with colorectal cancer and matched controls

	Matched controls N=4739		Cases with colorectal cancer N=4739		
Variable	**n**	**(%)**	**n**	**(%)**	***P* value***
Sex					0.92
Female	2018	(42.6)	2023	(42.7)	
Male	2721	(57.4)	2716	(57.3)	
Age group (years)					0.12
20-39	217	(4.5)	213	(4.4)	
40-64	2245	(47.4)	2149	(45.4)	
65-84	2277	(48.1)	2377	(50.2)	
Age (years), mean ± standard deviation†	63.1± 12.8		63.8± 12.7		0.01
Ever use of selective serotonin reuptake inhibitors use	407	(8.59)	322	(6.79)	0.001
Ever use of other antidepressants	1237	(26.1)	1183	(25.0)	0.20
Comorbidities before index date					
Alcohol-related disease	187	(3.95)	163	(3.44)	0.19
Cardiovascular disease	1656	(34.9)	1677	(35.4)	0.65
Chronic kidney disease	285	(6.01)	321	(6.77)	0.13
Chronic liver disease	774	(16.3)	786	(16.6)	0.74
Chronic obstructive pulmonary disease	727	(15.3)	756	(16.0)	0.41
Colorectal adenoma	748	(15.8)	735	(15.5)	0.71
Diabetes mellitus	652	(13.8)	685	(14.5)	0.33
Hyperlipidemia	1392	(29.4)	1416	(29.9)	0.59
Hypertension	2403	(50.7)	2429	(51.3)	0.59
Inflammatory bowel disease	84	(1.77)	53	(1.12)	0.01

Data are presented as the number of subjects in each group with percentages given in parentheses.
*Chi-square test and †*t*-test comparing cases with colorectal cancer and matched controls

Table 2: Odds ratio and 95% confidence interval of selective serotonin reuptake inhibitors use associated with colorectal cancer by logistical regression model

	Crude		Adjusted†	
Variable	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Ever use of selective serotonin reuptake inhibitors (never use as a reference)	0.78	(0.67, 0.90)	0.77	(0.66, 0.89)

†Variables which were found to be significantly associated with colorectal cancer in a univariable logistic regression model were further included in a multivariable logistic regression model. Adjusting for sex and inflammatory bowel disease

Table 3: Odds ratio and 95% confidence interval of cumulative duration of selective serotonin reuptake inhibitors use associated with colorectal cancer by logistical regression model

Variable	Case number / control number	Crude OR	(95% CI)	Adjusted OR†	(95% CI)
Never use of selective serotonin reuptake inhibitors as a reference	4417/4332	1.00	(reference)	1.00	(reference)
Cumulative duration of selective serotonin reuptake inhibitors use					
< 12 months	261/318	0.81	(0.68, 0.95)	0.80	(0.67, 0.95)
≥ 12 months	61/89	0.67	(0.48, 0.93)	0.66	(0.47, 0.92)

†Variables which were found to be significantly associated with colorectal cancer in a univariable logistic regression model were further included in a multivariable logistic regression model. Adjusting for sex and inflammatory bowel disease

cases with colorectal cancer were lower than among matched controls (adjusted OR 0.66; 95% CI 0.47-0.92).

DISCUSSION

We observed that the odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer were lower than among matched controls (adjusted OR 0.77, Table 2). This finding was statistically significant and indicated that selective serotonin reuptake inhibitors use might be a protective factor against colorectal cancer, which was compatible with previous epidemiologic studies showing that selective serotonin reuptake inhibitors use was associated with 30%-53% risk reduction of colorectal cancer.[5,6] We observed that there was a duration-dependent effect of selective serotonin reuptake inhibitors use on the risk of colorectal cancer (Table 3). That is, the longer the selective serotonin reuptake inhibitors use, the lower the risk of colorectal cancer.

The underlying pathogenesis between selective serotonin reuptake inhibitors use and colorectal cancer cannot be clarified in this observational study. The current evidence indicates that selective serotonin reuptake inhibitors possess potential anti-proliferative effects on tumor cells and further inhibit the growth of colorectal tumor.[3,4,24]

Some limitations should be mentioned. First, due to the limitation of a case-control study, the causal relationship cannot be determined. A prospective clinical trial or other real-world data are required to examine whether selective serotonin reuptake inhibitors can be used for chemoprevention of colorectal cancer. Second, due to the natural limitation of claims data, body mass index was not recorded in the database. We could not include obesity for analysis.

CONCLUSION

We conclude that the odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer are lower than among matched controls. This finding supports the evidence from previous animal and epidemiologic studies that selective serotonin reuptake inhibitors use might be a protective factor against colorectal cancer. In addition, the protective effect for colorectal cancer is stronger for longer cumulative duration of selective serotonin reuptake inhibitors use.

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Specific author contributions

Shih-Wei Lai contributed to the conception of the article, initiated the draft of the Article and revised the article.

Cheng-Li Lin and Kuan-Fu Liao conducted data analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL STATEMENT

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).

SUMMARY

The odds of selective serotonin reuptake inhibitors use among cases with colorectal cancer are lower than among matched controls. This finding indicates that selective serotonin reuptake inhibitors use might be a protective factor against colorectal cancer.

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