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Association between Statin Use and Bladder Cancer: Data Mining of a Spontaneous Reporting Database and a Claim Database

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Abstract

Purpose: To examine the association between statins and the risk of bladder cancer, data mining was performed using the US Food and Drug Administration Adverse Event Reporting System (FAERS) and a large organized claims database.

Materials and Methods: Relevant reports in the FAERS from the first quarter of 2004 through the end of 2012 were analyzed. Furthermore, event sequence symmetry analysis (ESSA) was applied to identify the risk of bladder cancer following treatment with statins over the period January 2005 to July 2013.

Results: In the FAERS database analyses, significant signals for bladder cancer were found for statins (Reporting odds ratio; 1.48, 95% CI; 1.36-1.61, information component; 0.55, 95% CI; 0.42-0.67). In the ESSA, significant associations between statin use and the diagnosis of bladder cancer were found, with adjusted sequence ratios (95% confidence interval) of 1.40 (1.08-1.82) at intervals of 24 months.

Conclusion: Multi-methodological approaches suggest that statins are associated with an increased risk for bladder cancer.

Keywords: Statin; FAERS; Claims database; Symmetry analysis; Disproportionality analysis; Multi-methodological approaches; Bladder cancer.

1. Introduction

Statins (HMG-CoA reductase inhibitors) are effective and widely utilized drugs for patients with hypercholesterolemia [1, 2]. Lowering cholesterol levels in the blood with statins reduces the risk of major cardiovascular events, such as ischemic heart disease and cerebral stroke. The efficacy and safety of statins have been studied in a number of large trials of long duration [1, 2]. Although the safety profile of statins is well-documented, and the majority of people treated with statins demonstrate favorable outcomes, no drug is without the potential for adverse effects. As such, rhabdomyolysis is the best-recognized and most feared complication associated with statins [3-5].

In recent years, the potential risk of statin-associated cancer has been a focus of heightened interest. A number of clinical trials and epidemiologic studies have examined the association between statin use and cancer risk [6-10]. Overall, these studies have reported inconsistent findings with some studies citing a reduced risk, some describing an increased risk, and others failing to identify any effect. Therefore, it remains uncertain whether or not statin therapy is associated with cancer risk. Several studies of bladder cancer have likewise demonstrated conflicting results [7, 9, 11-18]. Statin therapy has been recently recommended for individuals of a wide range of cardiovascular risk, including those with average and below-average lipid levels [19]. In particular,clinical guidelines recommend prescribing statins for patients with type 2diabetes mellitus irrespective of their baseline serum cholesterol levels [20-22]. Statins are promoted for widespread use for primary and secondary prevention of cardiovascular disease in adults of all ages. Inevitably, approximately 50% of adults are considered to be eligible for statin therapy [23]. Therefore, statin-associated cancer risk is of major concern in clinical practice.

Recently, data mining utilizing different methodologies and algorithms has been used to identify risk signals within medical databases, including spontaneous adverse drug reaction databases, claim databases, and prescription databases. We have reported that significant associations between statin use and some cancers were found in our previous study using these methodologies[24]. Although there are a number of studies for concerning about the association between statin use and bladder cancer, it still remains an open research question [12, 14, 18, 25]. The purpose of this study was to examine the association between statin use and the risk of bladder cancer by using different methodologies, algorithms, and databases.

2. Methods

2.1. Disproportionality Analysis

Data Source:

The association between statin use and bladder cancer risk was examined using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database,which contained reports of adverse events reported spontaneously by health care professionals, manufacturers and consumers worldwide. The FAERS is comprised of seven data sets: patient demographic and administrative information (file descriptor DEMO), drug and biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start of drug therapy and end dates (THER), and indications for use/diagnosis (INDI). A unique number for identifying a FAERS report allows all of the information from different files to be linked. The FAERS data can be downloaded freely from the FDA website (http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm).

In the study, the FAERS database is used for detection of safety signals [26, 27]. However, the FAERS data have some potential limitations [28, 29]. First, the causal relationship between drug use and the reported event (adverse event or medication error) was unclear. Second, every adverse event or medication error that occurs with a product was not exactly reported to the FDA; therefore, the FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the population. Thirdly, the database has missing data and drug names are frequently misspelled. Finally, there are a number of duplicate entries in the database. Despite these limitations, it is known that analyzing the FEARS database presents useful information on drug safety.

Relevant reports in the FAERS from the first quarter of 2004 through the end of 2012 were analyzed. A total of 4,052,885 reports were obtained. Reports with a common CASE number were identified as duplicated reports. We deleted duplicates and excluded from the analyses. Consequently, a total of 54,841,322 drug-reaction pairs were identified among 3,308,116 reports. The Medical Dictionary for Regulatory Activities (MedDRA® version 17.0) preferred terms (PTs) were used to classify the adverse events.

Identifying Statins and Adverse Events:

Arbitrary drug names including trade names, generic names, and abbreviations are permitted to register in the FAERS. All drug names were extracted from the DRUG file of the FAERS and recorded.

A drug name archive that included the name of all preparations, generic names, and synonyms of drugs marketed in the world was created using the Martindale website:https://www.medicinescomplete.com/mc/login.htm Simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, and pitavastatin were identified by linking this archive with the FAERS database. All records including statins in the DRUG files were selected, and the relevant reactions from the REACTION files were then identified.

Adverse events in the FAERS database are coded using the MedDRA® (the Medical Dictionary for Regulatory Activities terminology) PTs (Preferred terms), which are grouped by defined medical conditions or areas of interest. We identified PTs related to bladder cancer using the Standardized MedDRA® Queries (SMQ). Thirty-four PTs related to bladder cancer were identified in the SMQ category of malignant tumors (Table 1).

Table 1. Preferred terms related to bladder cancer identified in the tumors MedDRA® SMQ of malignant

SMQ	Preferred terms related to bladder cancer
Maglignant tumors	Bladder adenocarcinoma recurrent*
	Bladder adenocarcinoma stage 0*
	Bladder adenocarcinoma stage I*
	Bladder adenocarcinoma stage II*
	Bladder adenocarcinoma stage III
	Bladder adenocarcinoma stage IV*
	Bladder adenocarcinoma stage unspecified
	Bladder cancer
	Bladder cancer recurrent
	Bladder cancer stage 0 with cancer in situ
	Bladder cancer stage 0, without cancer in situ*
	Bladder cancer stage I, with cancer in situ
	Bladder cancer stage I, without cancer in situ
	Bladder cancer stage II
	Bladder cancer stage III
	Bladder cancer stage IV
	Bladder squamous cell carcinoma recurrent*
	Bladder squamous cell carcinoma stage 0*
	Bladder squamous cell carcinoma stage I*
	Bladder squamous cell carcinoma stage II
	Bladder squamous cell carcinoma stage III*
	Bladder squamous cell carcinoma stage IV*
	Bladder squamous cell carcinoma stage unspecified
	Bladder transitional cell carcinoma
	Metastases to bladder
	Urinary bladder sarcoma
	Metastatic carcinoma of the bladder
	Bladder transitional cell carcinoma stage 0
	Bladder transitional cell carcinoma recurrent
	Bladder transitional cell carcinoma stage I
	Bladder transitional cell carcinoma stage IV*
	Bladder transitional cell carcinoma stage II
	Bladder transitional cell carcinoma stage III
	Bladder transitional cell carcinoma metastatic

* No data in the FAERS database
MedDRA®, Medical Dictionary for regulatory activities with version 17.0
SMQ, Standardized MedDRA® Queries

Data Mining:

The reporting odds ratio (ROR) [30] and the information component (IC) [31] were utilized to detect spontaneous report signals. Signal scores were calculated using a case/non-case method [32, 33]. ROR and IC are widely used algorithms and have been employed by the Netherlands Pharmacovigilance Centre and the World Health Organization (WHO), respectively [30, 31]. Cases were defined as reports containing the event of interest (ie, bladder cancer); all other reports comprised the non-cases. Applying these algorithms and using a two-by-two table of frequency counts, signal scores were calculated to evaluate the association of statin use with an adverse event. These algorithms, so-called disproportionality analyses, differ from one another in that the ROR is frequentist (non-Bayesian), whereas the IC is Bayesian. For the ROR, a signal is detected if the lower limit of 95% two-sided confidence interval (95% CI) is >1 [30]. Signal detection using the IC is performed using the IC025 metric, a lower limit of the 95% CI of the IC. In this method, a signal is detected if the IC025 value exceeds 0 [31]. In the current study, two algorithms were used to detect signals, and the adverse events were listed as drug-associated when the two indices met the criteria indicated above.

2.2. Symmetry Analysis

Data Source:

A large organized claims database constructed by a database vendor (The Japan Medical Data Center Co., Ltd, Tokyo, Japan [JMDC]) was utilized for symmetry analysis, which is chronologically organized using standardized disease classifications and anonymous record linkage [34]. This database included about 1.2 million insured persons (approximately 1% of the population), comprised mainly of company employees and their family members. The JMDC claims database contained monthly claims from hospitals, clinics, and pharmacies submitted during the period from January 2005 to July 2013. The database provided information on the beneficiaries, including encrypted personal identifiers, age, sex, International Classification of Diseases, 10th revision (ICD-10) procedure and diagnostic codes, as well as the name, dose, and number of days supplied for prescribed and/or dispensed drugs. All drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification of the European Pharmaceutical Market Research Association (EphMRA). The claims data from different hospitals, clinics, and pharmacies were linked using an encrypted personal identifier. The patients who were prescribed statins at least once during the study period and the patients diagnosed with cancer were extracted from the JMDC claims database for the event sequence symmetry analysis (ESSA). This study was approved by the Ethics Committee of Kinki University School of Pharmacy.

Table 2: ICD-10 codes analyzed in the study

ICD-10 code	Malignant neoplasm of bladder
C67.0	Trigone of bladder
C67.1	Dome of bladder
C67.2	Lateral wall of bladder
C67.3	Anterior wall of bladder
C67.4	Posterior wall of bladder
C67.5	Bladder neck
C67.6	Ureteric orifice
C67.7	Urachus
C67.8	Overlapping lesion of bladder *
C67.9	Bladder, unspecified

ICD-10, International Classification of Diseases 10th revision
* No data in the JMDC database

Definition of Bladder Cancer and Statins:

Diagnoses in the JMDC claims database were classified by the ICD-10. Six available statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, pitavastatin, and simvastatin) were analyzed. There were no data for lovastatin in this claims database. The ICD-10 code C67 (Malignant neoplasm of bladder) was selected as bladder cancer (Table 2).

Study Design:

The ESSA was performed to test the hypothesis that statins increase the risk for bladder cancer. The ESSA method has been described in detail in several published studies [35, 36]. Briefly, asymmetry in the distribution of an incident event before and after the initiation of a specific treatment is evaluated in the ESSA. Asymmetry may indicate an association between the specific treatment of interest and the event. In this study, the association between statin use and diagnosis of bladder cancer was investigated. The crude Sequence Ratio (SR) was defined as the ratio of the number of patients newly diagnosed with bladder cancer after the initiation of statins versus the number of patients newly diagnosed with bladder cancer before the initiation of statins. A SR >1 signified an association between statin use and an increased risk of bladder cancer. The SR is sensitive to prescribing or event trends during the study period. Therefore, the SRs were adjusted for temporal trends in statins and events using the method proposed by Hallas [35]. In the absence of any causal relationship, the probability for the statins to be prescribed first can be estimated in a null-effect SR [35]. The null-effect SR produced by the proposed model may be interpreted as a reference value for the SR. Therefore, the null-effect SR is the expected SR in the absence of any causal association, after accounting for the incidence trends. An adjusted SR (ASR) can be obtained by dividing the crude SR by the null-effect SR, which is corrected for temporal trends. A slightly modified model was used to account for the limited time interval allowed between statin use and the diagnosis of bladder cancer [36]. The SR is robust towards significant confounders such as age, gender and genetic factors that are stable over time. Therefore, these confounders do not cause an asymmetrical distribution of statin use and diagnoses of bladder cancer.

Data Analysis:

All incident users of statins and all cases newly diagnosed with bladder cancer were identified during the period from January 2005 to July 2013 and were followed to July 2013. Therefore, different patients had different follow-up periods. Incidence was defined as the first prescription for statins and the first diagnosis of bladder cancer. To exclude prevalent users of statins, the analysis was restricted to users who presented their first prescription on July 2005 or later, that is, after a run-in period of 6 months. Likewise, the analysis was restricted to cases who presented their first diagnosis on July 2005 or later. To ensure that our analysis was restricted to incident users of statins and cases newly diagnosed with bladder cancer, the waiting time distribution analysis was carried out [37]. An identical run-in period was also applied to patients enrolled into the cohort after June 2005. Incident users of statins were identified by excluding patients who had received their first prescription for statins before July 2005, and cases newly diagnosed with bladder cancer were identified by excluding those patients who had a first diagnosis of bladder cancer before July 2005. All patients who initiated a new statin therapy and had a first diagnosis of bladder cancer within 3-, 6-, 12-, 24-, 36-, and 48-month period were identified. Patients who were prescribed their first prescriptions for statins and had a first diagnosis of bladder cancer within the same month were excluded from determination of the SR. The results of the analyses were expressed as the means ± standard deviation (SD) for quantitative data and as frequencies (percentage) for categorical data. A model for exact confidence intervals for binomial distributions was used to calculate the 95% confidence intervals (95% CI) for the ASRs [38].

2.3. Additional Analysis

A multivariate logistic regression analysis was performed to identify predictive factors of the ‘diagnosing bladder cancer after the initiation of statin therapy’ order compared with the reverse order. We focused on age, sex, and comorbidities (hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular diseases). It should be noted that the odds ratios (OR) calculated in the multivariate model are not risk factors for bladder cancer but rather effect modifiers of the event order ‘diagnosing bladder cancer after the initiation of statin therapy’. Patients who initiated a new statin therapy and had a first diagnosis of bladder cancer within 24-months were analyzed.

Statistics:

Data management and analyses were performed using Visual Mining Studio software (version 7.3; Mathematical Systems, Inc. Tokyo, Japan). Logistic regression analysis was performed using JMP 11.2.0 (SAS Institute Inc.)

3. Results

3.1. FAERS Database Analyses

A total of 8,270 PTs were identified in reports for simvastatin, 5,923 for rosuvastatin, 5,815 for pravastatin, 9,014 for atorvastatin, 1,258 for pitavastatin, 3,417 for fluvastatin, and 4,196 for lovastatin. The total number of drug-reaction pairs for statins was1,433,826, including 487,237 for simvastatin, 177,763 for rosuvastatin, 122,768 for pravastatin, 556,579 for atorvastatin, 5,424 for pitavastatin, 28,010 for fluvastatin, and 56,045 for lovastatin. The number of drug-reaction pairs was 14,597 for bladder cancer. Figure 1 presents the RORs and ICs corresponding 95% CI of bladder cancer for statins. The signal scores suggested that the statins were associated with bladder cancer (ROR; 1.48, 95% CI; 1.36-1.61, IC; 0.55, 95% CI; 0.42-0.67). In the analysis of individual statins, significant signals were found for simvastatin (ROR; 1.49, 95% CI; 1.30-1.72, IC; 0.57, 95% CI; 0.36-0.78), rosuvastatin (ROR; 1.61, 95% CI; 1.28-2.02, IC; 0.67, 95% CI; 0.34-1.00), pravastatin (ROR; 1.56, 95% CI; 1.19-2.06, IC; 0.63, 95% CI; 0.23-1.03) , atorvastatin (ROR; 1.25, 95% CI; 1.08-1.45, IC; 0.32, 95% CI; 0.11-0.53) , pitavastatin (ROR; 10.43, 95% CI; 6.28-17.31, IC; 2.71, 95% CI; 1.99-3.43) , fluvastatin (ROR; 1.88, 95% CI; 1.11-3.17, IC; 0.83, 95% CI; 0.08-1.57), and lovastatin (ROR; 1.61, 95% CI; 1.08-2.40, IC; 0.65, 95% CI; 0.07-1.23).

Data on gender were available in 52,917,276 (96.5%) of the 54,841,322 drug-reaction pairs, with 21,312,272 drug-reaction pairs for males and 31,605,004 drug-reaction pairs for females. Figure 2 presents the signal scores for statin-associated bladder cancer in male and female patients. A significant ROR and IC were found only in males (ROR; 1.44, 95% CI; 1.31-1.59, IC; 0.51, 95% CI; 0.36-0.65).

3.2. Event Sequence Symmetry Analysis

The ESSA characteristics of the study population are summarized in Table 3. During the study, the number of claims including statins totaled 1,624,438. Of the 95,941 statin users, 38,402 were incident users. The mean age of statin incident users was 51.8±10.4 years. Figure 3 shows the associations between statin use and the risk of bladder cancer. Of the 38,402 statin users, 389 patients were identified as incident cases with bladder cancer before or after the initiation of statins. Statin use and the diagnosis of bladder cancer was significantly associated with ASRs of 1.40 (1.08-1.82), 1.49 (1.18-1.89) and 1.48 (1.18-1.86) at intervals of 24, 36 and 48 months, respectively. Analyzing the individual statins, significant associations were found for rosuvastatin with ASRs of 1.76 (1.22-2.58), 1.56 (1.12-2.20), and 1.55 (1.13-2.15) at intervals of 24, 36, and 48 months, respectively, and for atorvastatin with an ASR 1.41 (1.01-1.97) at interval of 48 months (Table 4).

Figure 4 presents the SRs for bladder cancer in male and female patients. Significant associations were found in males with ASRs of 1.47 (1.03-2.09) and 1.51 (1.08-2.11) at intervals of 36 and 48months, respectively, and in females with ASRs of 1.51 (1.05-2.19), 1.48 (1.07-2.06), and 1.43 (1.05-1.96) at intervals of 24, 36 and 48months, respectively.

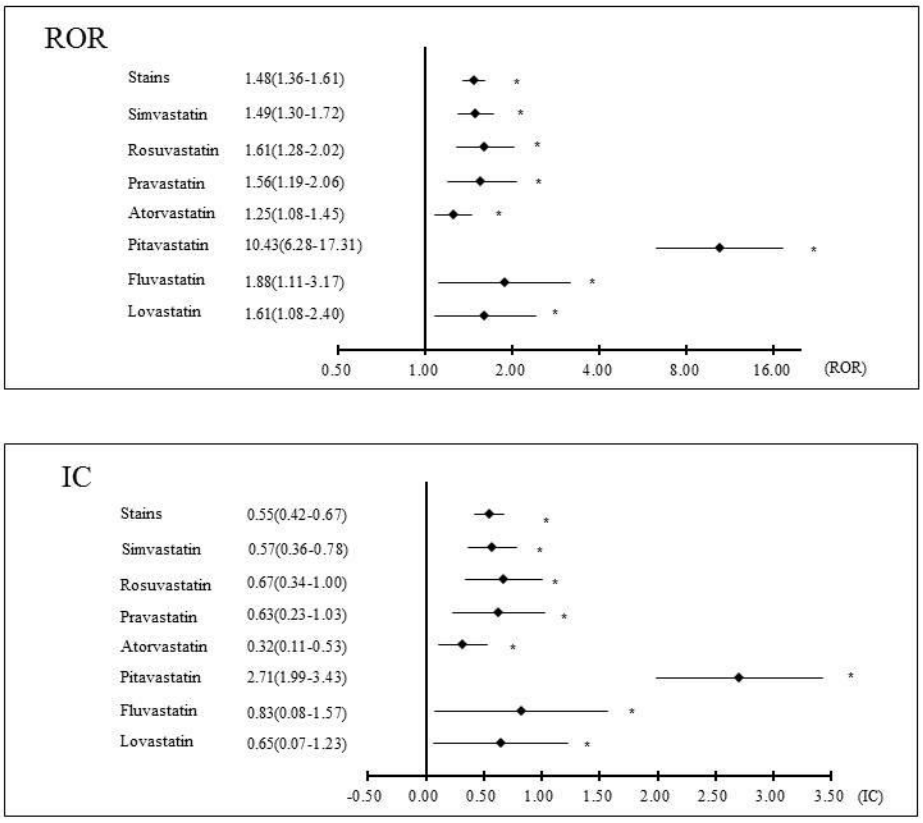


Figure 1. Signal scores for statin-associated bladder cancer

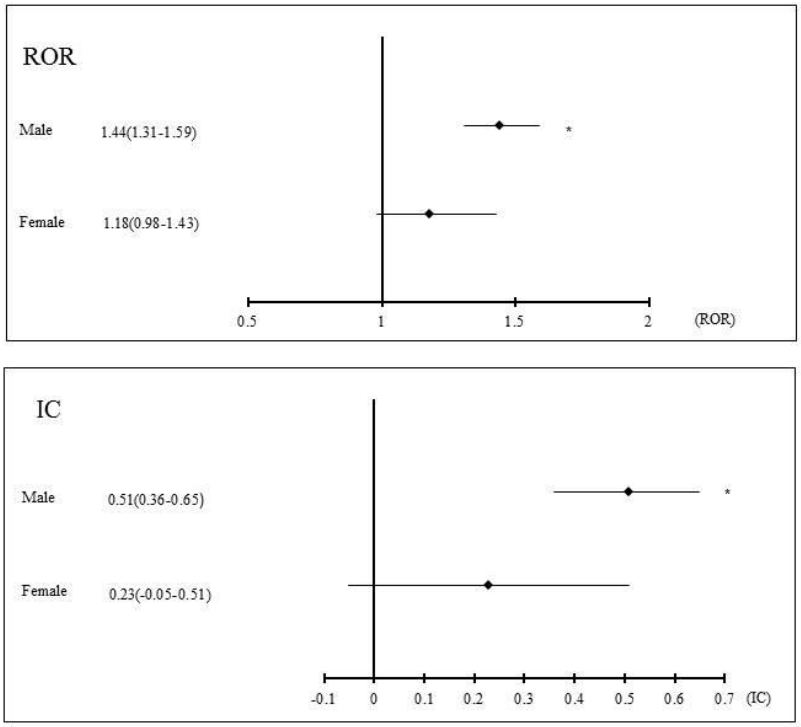
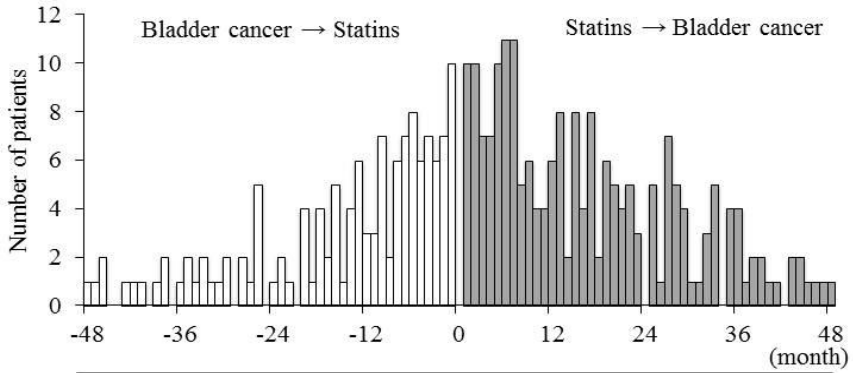


Figure 2. Signal scores for statin-associated bladder cancer in male and female patients

Table 3. Characteristics of the study population for statin users (January 2005 to July 2013)

	Total	Male	Female
Users, n	95,941		
Claims, n	1,624,438		
Incident users, n (%)	38,402	22,708(59.1)	15,694(40.9)
Age, years, n (%)			
<20	78 (0.20)	39 (0.17)	39 (0.25)
20-39	4,696 (12.2)	3,753 (16.5)	943 (6.01)
40-59	24,757 (64.0)	14,674 (64.6)	10,083 (64.3)
60-79	8,790 (22.9)	4,234 (18.7)	4,556 (29.0)
≧80	81 (0.21)	8 (0.04)	73 (0.47)
Mean ±SD	51.8±10.4	49.8±10.1	54.8±10.0

SD: Standard deviation



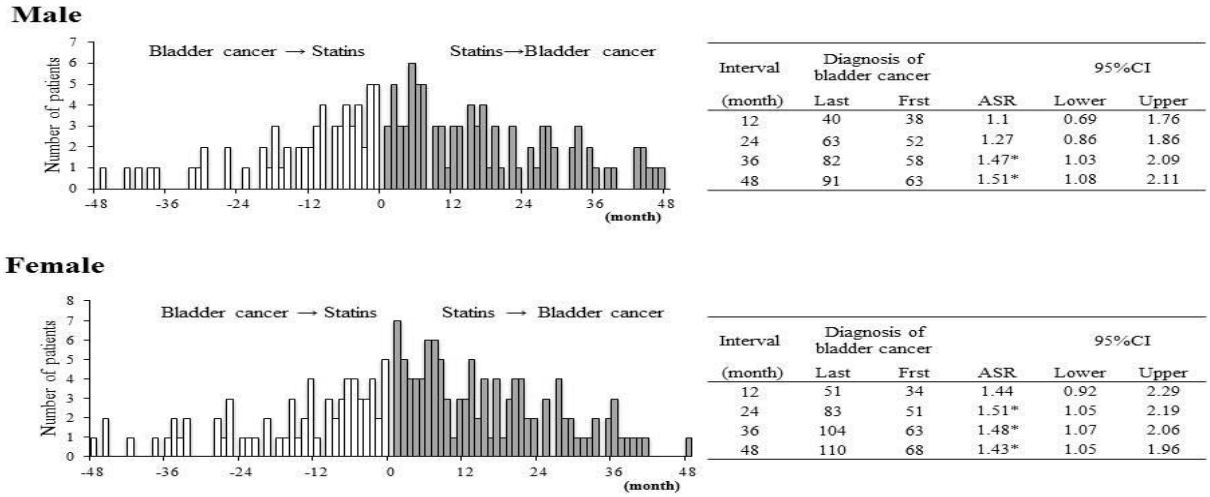
Interval	Diagnosis of bladder cancer		95%CI		
(month)	Last	Frst	ASR	Lower	Upper
12	91	72	1.26	0.92	1.75
24	146	103	1.40*	1.08	1.82
36	186	121	1.49*	1.18	1.89
48	201	131	1.48*	1.18	1.86

Figure 3. Event sequence symmetry analysis: association between statin use and bladder cancer

Table 4. Event sequence symmetry analysis：associations of individual statins with bladder cancer

	Incident users	No.of cases	Simultaneous start	Interval (months)	Diagnosis of bladder cancer		Crude SR	Null-Effect SR	Adjusted SR	95% CI	
					last	first				Lower	Upper
Simvastatin	2,118	10	0	12	2	3	0.67	0.52	0.60	0.05	5.27
				24	3	4	0.75	0.55	0.62	0.09	3.67
				36	6	4	1.50	0.56	1.16	0.28	5.61
				48	6	4	1.50	0.58	1.11	0.26	5.34
Rosuvastatin	17,515	189	8	12	52	33	1.58	1.00	1.57	1.00	2.51
				24	84	47	1.79	1.01	1.76*	1.22	2.58
				36	94	59	1.59	1.02	1.56*	1.12	2.20
				48	102	65	1.57	1.01	1.55*	1.13	2.15
Atorvastatin	14,359	169	6	12	44	36	1.22	0.96	1.27	0.80	2.03
				24	63	57	1.11	0.94	1.18	0.81	1.72
				36	78	63	1.24	0.94	1.32	0.93	1.87
				48	86	65	1.32	0.94	1.41*	1.01	1.97
Fluvastatin	1,678	18	1	12	2	5	0.40	1.12	0.36	0.03	2.18
				24	2	6	0.33	1.21	0.27	0.03	1.54
				36	4	6	0.67	1.31	0.51	0.11	2.14
				48	5	7	0.71	1.39	0.51	0.13	1.88
Pitavastatin	8,942	106	8	12	23	19	1.21	0.98	1.23	0.64	2.40
				24	35	30	1.17	0.98	1.19	0.71	2.02
				36	45	39	1.15	0.98	1.18	0.75	1.86
				48	49	43	1.14	0.98	1.16	0.76	1.79
Pravastatin	9,327	104	8	12	22	19	1.16	1.05	1.10	0.57	2.16
				24	36	31	1.16	1.11	1.04	0.63	1.74
				36	46	34	1.35	1.18	1.15	0.72	1.84
				48	49	36	1.36	1.22	1.11	0.71	1.76

Diagnosis of bladder cancer last indicates the number of patients with diagnosis after statin use
Diagnosis of bladder cancer first indicates the number of patients with diagnosis before statin use
CI, confidence interval; SR, sequence ratio
*Signal detected, and a signal means a drug-associated adverse event.



Male					
Interval	Diagnosis of bladder cancer			95%CI	
(month)	Last	Frst	ASR	Lower	Upper
12	40	38	1.1	0.69	1.76
24	63	52	1.27	0.86	1.86
36	82	58	1.47*	1.03	2.09
48	91	63	1.51*	1.08	2.11

Female					
Interval	Diagnosis of bladder cancer			95%CI	
(month)	Last	Frst	ASR	Lower	Upper
12	51	34	1.44	0.92	2.29
24	83	51	1.51*	1.05	2.19
36	104	63	1.48*	1.07	2.06
48	110	68	1.43*	1.05	1.96

Figure 4. Event sequence symmetry analysis: associations between statin use and bladder cancer in male and female patients

3.3. Additional Analysis

The results of the multivariate logistic regression analysis are presented in Table 5. Mean ages of patients diagnosed with bladder cancer after the initiation of statin therapy and patients diagnosed with bladder cancer before the initiation of statin therapy were 55.7 ± 8.9 and 57.4 ± 8.3, respectively. Hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular diseases, age, and sex were not significant predictors of the event order 'diagnosing bladder cancer after the initiation of statin therapy'.

Table 5. The predictive variables for diagnosing bladder cancer following statins initiation

Variable	Diagnosis of bladder cancer		Odds Ratio	95%CI	
	Last n = 146 (%)	First n = 103 (%)		Lower	Upper
Hypertensive diseases (ICD10, I10-I15)	59 (40.4)	37 (35.9)	1.31	0.74	2.35
Diabetes mellitus (ICD10, E10-E15)	52 (35.6)	37(35.9)	0.98	0.55	1.75
Ischemic heart diseases (ICD10, I20-I25)	22 (15.1)	12 (11.7)	1.52	0.69	3.48
Cerebrovascular diseases (ICD10, 60-69)	17 (11.6)	12 (11.7)	1.05	0.46	2.46
Male gender	63 (43.2)	52 (50.5)	0.70	0.41	1.18
Age (per year)	-	-	0.97	0.94	1.00

Diagnosis of bladder cancer last indicates the number of patients with diagnosis after statin use.
Diagnosis of bladder cancer first indicates the number of patients with diagnosis before statin use.
Mean ages of patients diagnosed with bladder cancer after statins initiation and patients diagnosed with bladder cancerbefore statins initiation were 55.7 ± 8.9 and 57.4 ± 8.3, respectively.
ICD-10, International Classification of Diseases 10th revision
CI, confidence interval

4. Discussion

In the present study, significant signals for bladder cancer were found for the whole class of statins in analyses of the FAERS database and the JMDC claims database. Consistent findings from these independent analyses using different methodologies, algorithms, and databases suggest that statin use may be associated with the risk of bladder cancer.

There are many conflicting reports among various types of studies investigating the association between statin use and risk of cancer. First, statins may exert potential anticancer effects by inducing apoptosis [39, 40], suppressing angiogenesis [41, 42], arresting cell cycle progression [43], and inhibiting tumor growth and metastasis [44, 45]. For bladder cancer, an experimental study indicated that statins may be a potential chemo preventive agent [46]. In contrast, other evidence suggests that statins may be carcinogenic [47]. Second, clinical studies likewise offer contradictory information concerning the association between statin use and the risk of bladder cancer. Whereas several clinical studies have failed to identify any effect [7, 9, 11-14, 17, 48-51], others have reported an increased risk of bladder cancer [15, 18, 52]. Third, a number of epidemiological studies have also reported conflicting data on the association between statin use and the risk of bladder cancer. Previous meta-analyses have concluded that statins did not reduce the incidence or mortality of cancer [9, 53-55]. Specifically, a meta-analysis by Zhang et al. detected no association between statin use and risk of bladder cancer [25]. A case-control study by Kuo et al. failed to find any significant association between statin use and bladder cancer [14]. Several studies reported a statistically non-significant inverse association between statin use and bladder cancer risk [13, 51]. In contrast, other studies have detected a slightly elevated risk of bladder cancer associated with regular statin use; however, statistical significance was not achieved [7, 11, 12, 16, 17]. Along these lines, other epidemiological studies have suggested that long-term use of statins was associated with an increased risk of bladder cancer [18, 52]. A large population-based case-control study by Vinogradova et al. revealed that long-term use of statins may be associated with an increased risk of bladder cancer [18]. In another population-based cohort study utilizing administrative health databases in northern California, statin use exceeding 5 years in duration was associated with a 60% increase in the risk for bladder cancer [52]. However, association between short-term use of statins and bladder cancer risk was not demonstrated in these prior studies. This is contrary to our study, which detected significant risk signals for bladder cancer associated with relatively short-term use of statins. In the ESSA, we identified a significant association at an interval of 24 months. Further, the FAERS analysis showed that about 50% of cases were reported within two years after initiating statin therapy. Thus, our findings implicate that relatively short-time use as well as long-term use of statins may increase the risk of bladder cancer.

Although a plausible pharmacological mechanism for statin-associated bladder cancer is unknown, there are several noteworthy potential explanations. An excessively low level of cholesterol may increase the risk for cancer mortality [56-59]. Lower circulating total cholesterol [57, 60, 61], high-density lipoprotein [62] and low-density lipoprotein cholesterols [63] have been associated with an overall increase in the risk of any cancer, as well as specific cancers of the lung, prostate, stomach or colon [58]. Kikuchi et al. suggested that lower serum total cholesterol levels may be associated with higher oxidative DNA damage and therefore may be linked to an increased risk of cancer [56]. Oxidative DNA stress is thought to play a major role in carcinogenesis [64]. In our claims database analysis, we found significant associations between the risk for bladder cancer and high potency statins, such as rosuvastatin and atorvastatin.

In addition, the FAERS analysis showed that use of pitavastatin greatly increased the risk of bladder cancer. As our study did not examine serum cholesterol levels, the association between cholesterol levels and bladder cancer risk is unknown. However, given that these high potency statin therapies could substantially reduce cholesterol levels, our findings may imply that excessively reducing the serum cholesterol level by high potency statins is associated with an increased risk of bladder cancer.

Statins increase the number of regulatory T cells (Tregs) [65]. Although this effect may be beneficial in stabilizing the atherosclerotic plaque by reducing the effector T-cell response within the atheroma [66], it might impair both the innate [67] and adaptive [68] host antitumor immune responses. The number of Tregs present in many solid tumors correlates inversely with patient survival [69]. The elderly are relatively immunosuppressed and are more likely to have occult cancers [70]. Therefore, it is highly plausible that the elderly may be particularly sensitive to a statin-induced increase in Tregs, which may further impair their immune response to cancer. Some statin trials have revealed an association between statin therapy and an increased risk for incident cancers in specific populations including the elderly [71-73]. Given these findings, it is reasonable to assume that statin-induced impairment of the immune response may play an important role in the development of cancer.

Analyzing spontaneous reports is a useful method for identifying signals, and the FAERS database is considered a large source for these data. However, there are a potential limitation that should be taken into account when interpreting results obtained from the FAERS database [74]. Slightly increased ROR and IC values do not imply an unmistakable risk of bladder cancer in clinical practice.

Although these data mining algorithms and criteria were assessed from the standpoint of early and timely signal detection when used for pharmacovigilance [75-77], these quantitative methods and criteria may assist in providing additional information on the known adverse event. Indeed, a number of studies in this area have been conducted and reported [78-81]. However, no individual algorithm for detecting signals is adequate, and the concurrent use of other algorithm is essential. Therefore, we employed both the ROR and IC algorithms in the FAERS database analysis and detected weak but reliable signals for bladder cancer. Additionally, utilizing a different methodology, the ESSA, our analysis of the JMDC claims database produced consistent findings and thereby supported the results of the FAERS database analysis.

Nevertheless, the ESSA may be also potentially limited by the following shortcomings. First, our study population was selected from beneficiaries enrolled in the employees' health insurance system. Because most beneficiaries are working adults or their family members, the proportion of elderly patients aged ≥65 years was low. Second, the date information for prescribing, dispensing and diagnosis was not available, because the insurance claims included a monthly summary of health care services provided by health care providers. Consequently, the two events were regarded as having been simultaneously initiated when the initiation month of each event was the same. Third, the diagnoses listed in the claims were not validated. We generally needed to consider the diagnosis contained in the claim, which is listed for health insurance claims. However, it is obvious that a serious disease such as cancer may not be listed in the claim only for the purpose of health insurance claims; that is, the patient is likely to actually have the disease. In the present study, individual cases were not reviewed, and other causes were not considered. Finally, potential confounders including smoking history, health history, race/ethnicity, and occupation, which are associated with bladder cancer, could not be controlled in the study. However, the major advantage of the symmetry analysis is that it is robust for confounders including gender, age, race/ethnicity, and occupation, which are stable over time. Therefore, these confounders did not cause an asymmetrical distribution of the statins and the diagnoses of bladder cancer.

In the ESSA, significant signals for bladder cancer were evident for both genders. In contrast, the analyses of the FAERS database found a significant signal for males but not for females. It is unclear whether gender differences contribute to the risk for statin-associated bladder cancer.

Some risk factors such as diabetes mellitus and hypertension are already found to be associated with cancer [82-84]. Therefore, it is required to determine modifiers of the event order 'diagnosing bladder cancer after the initiation of statin therapy'. The logistic regression analysis suggested that age, sex, and comorbidities (hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular diseases) did not influence the event order 'diagnosing bladder cancer after the initiation of statin therapy'. In our recent study, we have reported that statins were associated with colorectal and pancreatic cancer, but not with other cancers [24]. It is reasonable to assume that statins may be associated with some specific cancers including bladder cancer.

Significantly increased risk for bladder cancer was found in patients treated with statins in this study. In general, a large amount of data was required to detect a slightly increased risk. We used two large databases for this study. FAERS contains about 4 million reports, and JMDC claims database included about 1.2 million insured persons (approximately 1% of the population). Disproportionality analyses using spontaneous reporting database such as the FAERS is particularly robust for detecting serious, unexpected adverse drug events [26].

In addition, the ESSA using large claim database is an efficient method to identify safety signals with the moderate sensitivity and high specificity [85]. The ESSA using claims data may be a complementary pharmacovigilance to enhance the quantitative methods that use spontaneous reporting data in detecting safety signals of drugs [86]. Using different methodologies, algorithms, and databases, unexpected drug adverse events can be detected and could potentially strengthen the safety surveillance of post-marketing medicine.

5. Conclusions

In conclusion, multi-methodological approaches using different methodologies, algorithms, and database strongly suggest that statin use is associated with an increased risk for bladder cancer. Although conflicting reports concerning the association between statin use and risk of bladder cancer exist, our study demonstrated an association. With the widespread use of statin therapy, statin-associated adverse events represent a growing major concern in clinical practice. Although the biological mechanism remains unknown, the risk of bladder cancer associated with statin use is a noteworthy finding in clinical practice. Therefore, bladder cancer associated with statins should be closely monitored in clinical practice. Further studies are needed to confirm our findings and elucidate the mechanism for statin-induced bladder cancer.

Authorship

Conception and design of study: Mai Fujimoto and Mitsutaka Takada

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Conflicts of Interest

No sources of funding were used to assist in the preparation of this study. Mai Fujimoto, Tomoya Higuchi, Kouichi Hosomi, and Mitsutaka Takada have no conflicts of interest that are directly relevant to the content of this study.

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