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Original Article

Association between occurrence of urinary bladder cancer and treatment with statin medication

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ABSTRACT

Objective: The incidence of urinary bladder cancer (UBC) has increased in Sweden despite decreased smoking, indicating that other factors might be associated. The increased use of statin medication for elevated blood lipids might be one such influencing factor. The aim of the present study was to assess whether statins are afflicted with an increased incidence of UBC.

Material and methods: Data from the Swedish National Register of Urinary Bladder Cancer, National Population Register, and Swedish Prescribed Drug Register were extracted. There were 22,936 patients with new diagnosed UBC between 2005 and 2014. Statin prescription was defined as any medication prescribed with the Anatomical Therapeutic Classification code C10A. For each patient, 10 control individuals were matched by age, gender, and living area, comprising 229,326 individuals. The Cochran-Mantel-Haenszel test was used to evaluate the hazards ratios.

Results: Statins were more frequently used in patients with UBC (33.8%) than in controls (29.8%, p<0.0001). The use of statins was afflicted with a 23% increased odds ratio (OR) for UBC (OR 1.23 (1.19-1.27), p<0.001). Subgroup analyses showed that an increased OR was found in non-muscle invasive UBC only. There was a tendency that OR was stronger for men and for younger patients. Limitations include its retrospective register-based design and potential risk of bias of confounding factors, such as smoking and body mass index.

Conclusion: This nationwide register study suggests an association between the occurrence of UBC and patients using statins. The association was found in patients with non-muscle invasive disease only. Confounding factors, such as smoking, cannot be overruled.

Keywords: Diabetes; odds ratio; incidence; stage; smoking; statin medication; urinary bladder cancer.

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Introduction

During the last decades, there has been an increasing interest in public health and disease prevention by lifestyle alterations. In addition, different medications have been widely used to reduce risks of different diseases. One such preventive treatment is the use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). This group of drugs has become one of the most prescribed drugs worldwide after their introduction more than two decades ago. Statin therapy has been shown to be effective in lowering low-density lipoprotein cholesterol (LDL-C) levels, as well as triglyceride levels.[1] A Cochrane review in 2013, based on 18 randomized trials, found that statin therapy significantly reduced all-cause mortality, fatal and non-fatal cardiovascular events, and stroke.[2] In a meta-analysis study on 26 trials, an overall reduction in all-cause mortality of 10% for every 1.0 mmol/L reduction in LDL-C levels was revealed.[3] In addition, there were significant reductions in both myocardial infarction and stroke events.[3] Based on solid evidence supporting its use, the guidelines have recommended statin therapy to reduce atherosclerotic cardiovascular risk in adults.[4]

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There has been a continuous increase in the age-standardized incidence of urinary bladder cancer (UBC) during the last two decades in Sweden according to the National Board of Health and Welfare in Sweden.[5] The reason for this increase is unclear since the use of cigarette smoking, the most established risk factor for UBC, has substantially decreased in Sweden, as well as in Norway, during the last decades, especially among men.[6,7] In addition, occupational exposure, another established risk factor for UBC, has been reduced due to occupational regulations and increased awareness of different risk factors. Other factors appear to be involved in the increased incidence of UBC. Change in lifestyle and nutrition might be such factors. Metabolic syndrome is also associated with an increased risk of UBC[8], as well as with other malignancies.[9] One lifestyle medication is the increased prescription of statins in the population for elevated blood lipids. However, concerns have been raised on not only the overprescription of statins but also the risk for potential adverse effects including musculoskeletal symptoms, diabetes, and hepatic and renal dysfunction.[10] Some published data indicate a reduced risk for malignancies by the use of statins in humans and increased overall survival.[11] In contrast, Vinogradova et al.[12] found an elevated risk for UBC in patients on statin treatment.

The objective of the present study was to assess whether the use of statin medications is afflicted with an increased incidence of UBC, evaluating a total nationwide population of patients with primary diagnosed UBC.

Material and methods

Study design and data sources

This register-based study included data from three national Swedish registries, including Swedish National Register of Urinary Bladder Cancer (SNRUBC), National Population Register, and Swedish Prescribed Drug Register. Inclusion criterion was patients with new diagnosed UBC between 2005 and 2014 registered in the SNRUBC. Virtually all patients with new diagnosed UBC are registered in the SNRUBC with a 98% coverage rate compared with the Swedish National Cancer Register, in which registration of all new diagnosed neoplasms is mandatory by law. Statin prescription was defined as any medication prescribed before the diagnosis of UBC with the Anatomical Therapeutic Classification (ATC) code C10A. Diabetes medication was defined by the ATC codes A10A and A10B prescribed before the diagnosis of UBC. For each of the patients collected from the SNRUBC, 10 control individuals were matched from the National Population Register, with the same age, sex, and living in the same county. The patient population and the control persons were merged with data from the National Cancer Register and the Swedish Prescribed Drug Register (July 2005-onwards) using personal identification numbers. All data were made anonymous before use in the analysis. The study was approved by the institutional review board and the regional ethical board (Dnr 2013-62-31M and amendments: Dnr 2013-400-32M, Dnr 2014-367-32M, and Dnr 2014-384-32M).

Statistical analysis

All data were summarized descriptively. Categorical variables were expressed as frequency and relative frequency. Continuous variables were expressed as mean, median, and range. The chi-square test was used to compare groups. When odds ratio (OR) between cases and controls are evaluated, the Cochran-Mantel-Haenszel test was used. All tests were two-sided. A p value <0.05 was considered as statistically significant. In the subgroup analysis of non-diabetes, only patients with UBC and their controls, who did not use diabetes medications, were included in the analysis.

Results

Patients

Between 2005 and 2014, 22,936 patients were registered with new detected UBC. The study included 17,182 (74.9%) male and 5754 (25.1%) female patients. The mean age of the patients was 72.9 (median 74, ranging 18-104) years. Patient and disease characteristics for the UBC population are listed in Table 1. The control persons, collected from the National Population Register in Sweden, comprised 229,326 individuals (Table 2).

Statin and diabetes medication

Among the 22,936 patients with UBC, 7754 (33.8%) patients were treated with statins before the diagnosis of UBC, significantly more frequently than 68,247 of the 229,326 controls (29.8%, $p<0.0001$). In addition, diabetes medication was more frequently used among patients with UBC (2987, 13.0%) than among the control population (25,673, 11.2%, $p<0.0001$). The distribution of statin use in patients with UBC in relation to patient and tumor characteristics is shown in Table 3. The use of statin medication was significantly associated with the risk of occurrence of UBC (OR 1.23 (1.19-1.27), $p<0.001$, Table 3). This OR was observed only in the non-muscle invasive UBC (1.31 (1.26-1.35)), whereas there was no increased OR in patients with muscle invasive UBC. As shown in Table 3, a significant OR was also shown for all non-muscle invasive TNM stage groups.

Further, there were significant increased ORs of statin medication in all age groups analyzed, albeit the youngest patients had the highest OR (1.36 (1.26-1.47)), and the oldest patient group the lowest OR (1.16 (1.09-1.22), Table 3). Among genders, both males and females had significant ORs, but there was

Table 1. Patient and disease characteristics in 22,936 patients with new diagnosed urinary bladder cancer between 2005 and 2014

	n	%
Gender		
Male	17,182	74.9
Female	5754	25.1
Age at diagnosis		
Mean (median, Q1-Q3)	72.9 (74.0, 66-81) years	
T stage		
Ta	11,198	48.8
Tis	606	2.6
T1	512	22.3
T2-T4	5508	24.0
T0/TX*	503	2.2
N stage		
N0/NX*	22,195	96.8
N1-N3	741	3.2
M stage		
M0	22,189	96.7
M1	747	3.3
Tumor grade		
G1/LMP	6079	26.5
G2	6845	29.8
G3/G4	9008	39.2
GX*	1004	4.3
TNM and G grouping		
TaG1-2	10,009	43.6
TaG3	1096	4.8
TIS	604	2.6
T1	5011	21.8
T2-T4N0M0	4501	19.6
N+ and/or M+	1210	5.3

*Includes missing values.

stronger OR for men than for women (Table 3). After exclusion of all patients and control individuals with diabetes, the ORs remained similar, indicating that diabetes mellitus had less or no impact on the risk for UBC (Table 3). When analyzing the impact of diabetes in patients with non-muscle invasive UBC only, there were merely limited differences in ORs as compared with the ORs analyzed in all patients (data not shown). In a subgroup analysis of 12,144 patents primarily diagnosed between 2010 and 2014, there were 5041 (42%) patients treated with statins during this period. When dividing these patients into those treated with statins for >5 years and those treated <5 years, we found similar ORs in these groups with ORs of 1.26 and 1.23, respectively (data not shown).

Table 2. Number of patients with new diagnosed urinary bladder cancer in relation to year of diagnosis including 22,936 patients and 229,326 control individuals, matched with the same age, sex, and area of living

Year of diagnosis	Patients	Control individuals	Total
2005	2065	20,642	22,707
2006	2057	20,570	22,627
2007	2142	21,420	23,562
2008	2230	22,296	24,526
2009	2298	22,973	25,271
2010	2321	23,210	25,531
2011	2417	24,167	26,584
2012	2298	22,971	25,269
2013	2630	26,297	28,927
2014	2478	24,780	27,258
Total	22,936	229,326	252,262

Discussion

In the present study, using a nationwide population-based cohort, we found that patients on statin medication were significantly associated with an increased risk to be diagnosed with UBC. This association was independent of diabetes mellitus and indicates a relationship between statin medication and diagnosis of UBC, although no causality can be confirmed. Confounding factors cannot be overruled as smoking and body mass index (BMI). These factors were not registered in the SNRUBC.

The public health registries in Sweden provide a unique opportunity to perform truly population-based studies. Virtually all patients with new diagnosed UBC during the study period were included through the SNRUBC.[13] By linking these patients with UBC to two other national Swedish registries, we could design a large control population, matched to the patients on gender, age, and county of living from the entire population of patients in Sweden. The use of statin and diabetes medications was linked to patients with UBC, as well as to the control population, by using the Swedish Prescribed Drug Register.

We found a significant increased risk for the occurrence of UBC for individuals treated with statins. That finding remained when adjusted for diabetes, one known confounding risk factor promoting UBC.[14] One novel finding in our study is that significant ORs were observed in patients with non-muscle invasive UBC only, whereas no association was found in muscle invasive and

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Table 3. Use of statin medication in 22,936 patients (cases) with primary UBC diagnosed between 2005 and 2014 and in 229,326 matched control individuals

		All cases and control individuals			Cases and controls without diabetes mellitus		
Variables		**%**		**OR (95% CI)**	**%**		**OR (95% CI)**
	Case	33.8	7754 of 22,936	1.23 (1.19-1.27)	28.1	5299 of 18,866	1.20 (1.16-1.25)
	Controls	29.8	68,247 of 229,326	p<0.0001	25.4	48,034 of 193,202	p<0.0001
Age at diagnosis (year)							
<65	Case	20.4	973 of 4764	1.36 (1.26-1.47)	15.5	626 of 4048	1.35 (1.23-1.48)
	Control	16.1	7659 of 47,640	p<0.0001	12.2	5147 of 42,272	p<0.0001
65-74	Case	37.3	2736 of 7341	1.23 (1.17-1.29)	29.8	1739 of 5835	1.17 (1.10-1.25)
	Control	32.9	24,135 of 73,410	p<0.0001	26.8	16,197 of 60,485	p<0.0001
75-79	Case	42.7	1721 of 4030	1.26 (1.17-1.35)	36.5	1170 of 3207	1.21 (1.12-1.31)
	Control	37.6	15,154 of 40,300	p<0.0001	32.4	10,688 of 32,957	p<0.0001
≥80	Case	34.2	2324 of 6801	1.16 (1.09-1.22)	30.5	1764 of 5776	1.17 (1.10-1.24)
	Control	31.3	21,299 of 67,976	p<0.0001	27.8	16,002 of 57,488	p<0.0001
Muscle-invasive UBC							
No	Case	35.1	6087 of 17,344	1.31 (1.26-1.35)	29.1	4112 of 14,117	1.27 (1.22-1.32)
	Control	29.8	51,734 of 173,433	p<0.0001	24.9	36,326 of 146,129	p<0.0001
Yes	Case	29.9	1648 of 5508	1.02 (0.96-1.08)	25.1	1174 of 4683	1.02 (0.95-1.10)
	Control	29.6	16,297 of 55,053	p=0.60	24.9	11,562 of 46,379	p=0.54
Gender							
Male	Case	35.8	6147 of 17,182	1.25 (1.21-1.30)	29.8	4131 of 13,860	1.23 (1.18-1.28)
	Control	31.2	53,625 of 171,786	p<0.0001	26.1	37,195 of 142,731	p<0.0001
Female	Case	27.9	1607 of 5754	1.15 (1.08-1.23)	23.3	1168 of 5006	1.13 (1.05-1.22)
	Control	25.4	14,622 of 57,540	p<0.0001	21.5	10,839 of 50,471	p=0.001
TNM/grade							
Ta, G1-2	Case	34.6	3460 of 10,009	1.34 (1.28-1.40)	28.4	2305 of 8109	1.29 (1.22-1.37)
	Control	28.8	28,873 of 100,090	p<0.0001	23.8	20,183 of 84,635	p<0.0001
Ta, G3	Case	39.7	435 of 1096	1.45 (1.27-1.65)	34.9	317 of 908	1.51 (1.30-1.76)
	Control	31.9	3498 of 10,960	p<0.0001	26.8	2460 of 9180	p<0.0001
TIS	Case	38.9	235 of 604	1.52 (1.26-1.83)	33.4	164 of 491	1.54 (1.24-1.91)
	Control	30.5	1843 of 6040	p<0.0001	25.4	1281 of 5051	p=0.0001
T1, G1-3	Case	35.2	1763 of 5011	1.20 (1.13-1.28)	29.4	1200 of 4086	1.16 (1.08-1.25)
	Control	31.5	15,797 of 50,103	p<0.0001	26.6	11,169 of 42,015	p<0.0001
T2-T4	Case	30.5	1374 of 4501	1.04 (0.97-1.11)	25.8	980 of 3804	1.05 (0.97-1.14)
	Control	29.8	13,404 of 44,983	p=0.28	25.2	9564 of 37,942	p=0.25
N+ and/or M+	Case	27.2	329 of 1210	0.90 (0.79-1.04)	21.5	225 of 1046	0.86 (0.73-1.01)
	Control	29.0	3514 of 12,100	p=0.16	24.1	2437 of 10,107	p=0.076

The Cochran-Mantel-Haenszel test was used to evaluate odds ratios and confidence intervals in all cases and controls, subgroup of cases, and control individuals without diabetes, respectively. Subgroup analysis was done based on age at diagnosis, whether muscle invasive UBC, and gender and grouped on TNM stage and tumor grade.

advanced UBC. These findings might indicate that the use of statin medications is associated with the development of UBC, whereas advanced invasive UBCs might have other risk factors involved. Muscle invasive UBC thus can have different genomic alterations and etiology than non-invasive UBC. Another novel finding was that the highest ORs were found in the younger

ages. The lower OR in the elderly might be due to a possible accumulation of other risk factors. Our finding with an increased risk for UBC in statin users was supported by a previous nested case-control study finding an OR of 1.16.[12] In their study, Vinogradova et al.[12] found a significant increased risk for UBC but only after >48 months of statin medication. In a subgroup analysis in the present study, we could not duplicate their results since we found no significant difference in risk between patients treated with statins for more or less than 5 years. Our results were further supported by a retrospective study on long-term chemoprevention with statin and aspirin, aiming to reduce the risk of tumor recurrence in patients with non-muscle invasive UBC. Patients treated with statins only or with a combination of aspirin and statin showed increased recurrence rates. In contrast, long-term treatment with aspirin only reduced the risk of tumor recurrence.[15] These results indicate a tumor-promoting effect of statin medication in UBC, supporting our findings.

The reason for this increased risk of UBC in patients treated with statins is unclear. It can instead be due to confounding factors associated with the contemporary use of statins. Hypothetically, statins can affect the urothelial bladder cells by metabolic changes in the mitochondria both through the blood circulation and by a concentration of statins in the urinary bladder after excretion. The initial positive effects of statin medications in lowering LDL-C and triglyceride levels through the mitochondria might be different from the long-term adverse effects. Thus, long-standing metabolic changes in the cell mitochondria might be one plausible reason for the increased risk of UBC.[16-18]

In contrast to the results observed in the present study, as well as the results in the study by Vinogradova et al.[12], Zhang et al.[19] found no association between statin use and risk of UBC in a meta-analysis study. Their study was based on three randomized controlled trials, five cohorts, and five case-control studies with a substantial heterogeneity between the materials. For other malignancies, such as hematological, liver cancer, and malignancies in postmenopausal women, in contrast, statin treatment was associated with a reduced incidence.[20-22] In some other studies, such as the Cochrane review, the Cholesterol meta-analyses, and the West Scotland Coronary Prevention Study, no difference in the occurrence of malignancies was observed after long-term statin therapy.[2,3,23] In the study by Vinogradova et al.[12], it was concluded that prolonged use of statins may be associated with an increased risk of colorectal cancer, UBC, and lung cancer but found no overall cancer risk. In patients with non-muscle invasive UBC, Richard et al. found that cumulative statin use is associated with improved overall survival, but not with cancer-specific survival.[24] These findings were further verified in a meta-analysis study of urological malignancies displaying an advantage in the overall survival in patients with UBC and renal cell carcinoma on statin medication.[25]

The present study has several limitations. These include its register-based retrospective nature and the potential risk of bias of confounding factors, such as metabolic disorders, obesity, hip-to-waist ratio, and lifestyle. It cannot be ruled out that the found increased risk for UBC of statins is due to confounders. The absence of differences in ORs between patients with or without diabetes indicates that diabetes or the use of diabetes medication appears not to be an important confounder. In the present study, no data are available on smoking, a factor well associated with cardiovascular events and onset of UBC.[26] The general decline in smoking habits during the last decades in Sweden, especially in men (between 13% and 21% in 2004), has not been followed by a decreased UBC incidence. However, the impact of smoking on the risk for onset of UBC in the present study cannot be overruled. If smokers in general are more frequently prescribed with statins than non-smokers, the increased ORs in our study might instead depend on smoking. However, in the study by Vinogradova et al.[12], statin medication remained with an increased OR after adjusting for smoking, as well as diabetes, rheumatoid arthritis, hypertension, and BMI. Other confounders, such as obesity and metabolic syndrome, appear not to be important for the found increased risk of statins in the present study since we found no association between diabetes, a marker for metabolic syndromes, and increased risk for UBC. One of the advantages of the study is the large population of patients and their controls, comprising >250,000 individuals. Furthermore, since virtually all patients nationwide with new diagnosed UBC were included in the study, any risk for selection bias was reduced. Additionally, all prescriptions of statin and diabetes medication were available for all patients and control individuals through the Swedish Prescribed Drug Register.

In conclusion, this nationwide register study of the Swedish population suggests an association between statin medication and occurrence of diagnosis of UBC. The influence of confounding factors, especially smoking, cannot be overruled. This association of statins and UBC was limited to non-muscle invasive UBC only. Furthermore, there was a tendency for higher risk in younger than in older patients. The risk was independent of diabetes mellitus. Our results merit further studies to evaluate the possible drawbacks of medication to prevent lifestyle alterations.

Ethics Committee Approval: Ethics committee approval was received for this study from the Regional ethical board of Umeå, Sweden (Dnr 2013-62-31M, (2013-05-03) and amendments: Dnr 2013-400-32M, Dnr 2014-367-32M, and Dnr 2014-384-32M).

Informed Consent: Since all data were made anonymous before any use in the study, the ethical board approaved that the study was performed without any consent from neither patients, nor control individuals who participated in this study.

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