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STATINS AND BLADDER CANCER PROGNOSIS IN A POPULATION-BASED COHORT

Tampereen yliopisto
Lääketieteen ja biotieteiden tiedekunta
Syventävien opintojen kirjallinen työ
Marraskuu 2019

Tampere University

TIIVISTELMÄ

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Statiinit on yhdistetty parempaan ennusteeseen useissa eri syöpätyypeissä. Epidemiologisissa tutkimuksissa virtsarakkosyövän ja statiinien välinen yhteys on kuitenkin ollut ristiriitainen. Tutkimuksen tarkoituksena oli tutkia statiinikäytön yhteyttä virtsarakkosyöpäkuolemiin invasiivisissa syöpätapauksissa sekä virtsarakon höyläyksiin non-invasiivisissa syöpätapauksissa.

Aineistona toimi kaikki 14 065 Suomalaiseen syöpärekisteriin kirjattua virtsarakkosyöpädiagnoosia aikaväliltä 1996-2012. Syöpärekisteriin on kirjattu 99% kaikista syöpädiagnooseista Suomessa. Kirjattuna oli diagnoosipäivä, syövän morfologia, kasvaimen levinneisyys, hoitolinja, mahdollinen maastamuuttopäivä Suomesta sekä kuolinsyy ja –päivä. Tapaukset linkitettiin THL:n Hoitoilmoitusjäjestelmään sekä Kansaneläkelaitoksen reseptitietokantaan sosiaaliturvatunnusten perusteella, josta saatiin tiedot komorbiditeeteistä, kirurgisista toimenpiteistä sekä ostetuista lääkkeistä.

Kasvaimen levinneisyyttä diagnoosihetkellä analysoitiin pre-diagnostisen statiinikäytön mukaan logistisella regressiomallilla rajattuna henkilöihin, joiden rakkosyöpälevinneisyys tiedettiin ja vakioitiin iän, sukupuolen sekä Charlson komorbiditeetti-indeksin mukaan. Post-diagnostista statiinikäytön ja tehtyjen rakkohöyläystän suhdetta analysoitiin logistisella regressiomallilla rajattuna paikallisiin rakkosyöpätapauksiin. Virtarakkosyöpäkuoleman ja kaikkien kuolemien riskisuhteen arvioimiseen käytettiin Cox regressiota ja Competing risks regressio –analyysia kardiovaskulaarisen kuolleisuuden suhteen suoritettiin arvioimaan ei-syöpäkuolemien yhteyttä statiinikäyttöön ja rakkosyöpäkuoleman riskiin.

Pre- ja post-diagnostinen statiinikäyttö assosioitui alentuneeseen syöpäkuolleisuuteen annosriippuvaisesti viitaten mahdolliseen progression inhibitioon invasiivisessa virtsarakkosyövässä. Pre-diagnostinen statiinikäyttö oli käänteisesti verrannollinen rakkohöyläysten lukumäärään diagnoosin jälkeen viitaten mahdolliseen vaikutukseen non-invasiivisissa virtsarakkosyövissä.

Avainsanat: Virtsarakkosyöpä; Statiinit; Ennuste

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SISÄLLYS

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Abstract

Objectives:

To assess bladder cancer extent, risk of bladder cancer death and number of repeated transurethral resections of the bladder tumor (TURBs) after bladder cancer diagnosis among statin users in a population-based cohort of bladder cancer patients.

Materials and methods:

All bladder cancer cases diagnosed in Finland during 1996-2012 (14,065 cases) were identified from the Finnish Cancer Registry and linked to the national Care Register for Health Care and Social Insurance Institution of Finland to obtain extensive information on participants' medication use (statin and non-statin cholesterol-lowering drugs, antidiabetic and antihypertensive drugs) and co-morbidities during the same time period. Causes and dates of death were obtained from the Finnish Cancer Registry.

Logistic regression was used to analyze risk of having advanced tumor extent at diagnosis by pre-diagnostic statin use and the number of TURBs after diagnosis by cholesterol-lowering drug use.

Cox proportional hazards regression with adjustment for gender, tumor extent, primary treatment and Charlson Comorbidity Index was used to analyze risk of bladder cancer-specific death by cholesterol-lowering drug use. Usage before and after cancer the diagnosis were analyzed separately. Post-diagnostic use was analyzed as time-dependent variable.

Lag time analyses were performed to estimate long-term effects of statin use.

Results:

Overall, statin use before bladder cancer diagnosis was not associated with advanced tumor extent at diagnosis.

Both pre-diagnostic and post-diagnostic statin use were associated with lowered risk for cancer-specific death (HR 0.66 95% CI 0.60-0.72 and HR 0.47 95% CI 0.43-0.52 respectively) and the risk lowering effect was retained for ten years after usage in lag time analyses. The risk decrease was dose-dependent.

Statin use before the diagnosis was inversely associated with the number of TURBs after diagnosis; OR 0.82, 95% CI 0.73-0.91 and OR 0.69, 95% CI 0.59-0.81 for risk of having 2 or more and 5 or more TURBs,

respectively. Conversely, low-dosage statin use after the diagnosis was associated with increased risk for having more than 2 and 5 TURBs (OR 1.17 95% CI 1.01-1.35 and OR 1.29 95% CI 1.06-1.56 respectively).

Decreased risk for bladder cancer death was observed also for post-diagnostic use of non-statin cholesterol-lowering drugs, but the risk association was not dose-dependent.

Conclusions:

Compared to non-users, statin users had lowered risk of bladder cancer death, suggesting that statins may inhibit progression of invasive bladder cancer. Statin use before diagnosis was also associated with lower number of TURBs, suggesting a possible effect also on non-invasive forms of bladder cancer. However, the effect may depend on timing of statin use and tumor characteristics.

Keywords: Bladder Cancer; Statins; Survival

1 INTRODUCTION

Urothelial cancer of the urinary bladder (UBC) is the 7th most common cancer in men and the 17th most common in women worldwide [1]. Clinically, UBC can be divided into two types with differing prognosis based on tumor grade and depth of invasion into the bladder muscle. Low-grade non-muscle-invasive bladder cancer (NMIBC) is limited to bladder mucosa and has low five-year mortality (~10%) compared to high-grade muscle-invasive bladder cancer (~50%). Nevertheless, recurrence of NMIBC is common. Recurring NMIBC can usually be managed endoscopically with repeated transurethral resections of the bladder tumor (TURB). For high-grade muscle invasive disease the gold standard for treatment is radical cystectomy (RC) with pelvic lymph node dissection (PLND) [2,3].

Besides tumor grade and stage the risk factors for the disease progression are not well known. Smoking is an established modifiable risk factor but also other lifestyle patterns such as obesity, excessive drinking and lack of aerobic physical activity have been associated with higher UBC incidence, recurrence and mortality. [4, 5]

The use of cholesterol-lowering statin drugs has been associated with improved prognosis for several different cancer types. In bladder cancer statins have been reported to have a pro-apoptotic effect on human bladder cancer cells in vitro [6]. However, in epidemiological studies the association between UBC progression and statin use is unclear. Some studies suggest that statin use has no benefits against bladder cancer [7-9], whereas others have reported both adverse [10] and beneficial [11] effects on the disease recurrence and mortality. Further, it is unknown whether statins' anticancer effects in bladder cancer depend on tumor invasiveness and grade.

In this study we explored the association between statin use and two bladder cancer end-points: risk of bladder cancer death to explore possible effect on invasive bladder cancer and number of repeated TURBs after bladder cancer diagnosis to estimate possible effect on non-invasive bladder cancer.

2 MATERIALS AND METHODS

2.1 Study cohort

The nationally comprehensive Finnish cancer registry (FCR) was used to obtain information on all diagnosed bladder cancer cases in Finland from 1996 to 2012. FCR collects data on mandatory notifications of all cancer diagnoses made by Finnish health care units and pathology labs, covering 99% of cancer diagnoses in Finland [12]. The study cohort consisted of 14,065 bladder cancer cases, of which 10,720 were men, 3,345 women.

The information on bladder cancer cases included the date of diagnosis, morphology (recorded as ICD-O3 codes; 81% were transitional cell carcinoma (8120), 11.6% papillary transitional cell carcinoma (8130), 7.4% other), tumor extent at diagnosis (local vs. metastatic), primary treatment (surgery vs. other), possible date of emigration from Finland and date and cause of death (cancer death vs. death due to other causes) and primary cause of death as ICD-10 code. Cancer deaths with bladder cancer (ICD-10 C67) recorded as the primary cause were regarded as bladder cancer deaths.

The study cohort was linked to the national Care Register for Health Care (HILMO) based on individual personal identification numbers. Information obtained from HILMO contained comorbidities (diabetes, hypertension, COPD) and surgical procedures performed for bladder cancer treatment (RC, TURB) recorded during in- and outpatient visits to Finnish health care units from 1996 to 2012. Information for each recorded visit included dates, recorded diagnoses (ICD-10 codes) and performed procedures (recorded according to Nordic Classification of Surgical Procedures).

Patients were classified as having hypertension if the records included ICD-10 codes I10-I11, diabetes mellitus if codes included E10-E11 and obesity if codes E65-E66 had been recorded. Additionally, diagnoses of COPD (J33-J44) were searched. Recorded procedure codes for cystectomy included KCC00, KCC10, KCC20, KCC30 and KCC96. TURBs were identified based on codes KCD02, KCD05, KCD10, KCD11, KCD20, KCD21, KCD30, KCD32, KCD40, KCD96, KCD97 and KCD98.

Effect modification by underlying comorbidities was evaluated using Charlson Comorbidity index. The index was formed using ICD-10 codes obtained from HILMO-registry. We lacked information on the severity of liver disease and couldn’t separate between mild, moderate and severe liver disease. All liver diseases were

accounted as mild liver disease and the minimum score of two points was given on the Charlson index. The Charlson index was divided by median to low and high comorbidity groups.

2.2 Information on medication use

Individual-level information on medication use from 1996 to 2012 was obtained from the prescription database of the Social Insurance Institution of Finland (SII). Purchases of statins and other cholesterol-lowering drugs, as well as antidiabetic and antihypertensive medication were obtained. The study cohort was linked to the database using individual personal identification numbers.

SII is a governmental agency providing reimbursements on physician-prescribed medication as part of the national health insurance that covers all Finnish citizens. The reimbursements are received as price discounts at the pharmacy. The size of reimbursement varies between 50-100% depending on indication and severity of the disease. All reimbursements are recorded into the prescription database along with dose, size and quantity of packages and date of purchases. Prescription free drug purchases and drugs used during hospital inpatient periods are not recorded in the database [13].

Yearly purchases of each statin and non-statin cholesterol-lowering drugs were added together to obtain the total annual amount. The dosing between each drug was standardized by dividing the annual total use of a given drug in milligrams by the drug-specific Defined Daily Dose (DDD), as listed by WHO [14]. Each year with any recorded drug purchases was considered a year of usage regardless of the amount. Cumulative DDD amount during the 1996-2012 was divided by cumulative number of years of use for an average annual dose (intensity of use).

Persons who had either registered diagnosis of hypertension in the HILMO database or antihypertensive drug purchases in the SII database were considered to have hypertension. Similar categorization was done for diabetic participants.

2.3 Statistical analysis

Tumor stage (localized vs. metastatic) at diagnosis was analyzed by pre-diagnostic statin use using a logistic regression model limited to individuals with known bladder cancer extent and adjusted for age, gender and Charlson comorbidity index (CCI).

Cox proportional hazards regression method was used to estimate hazard ratios (HR) and 95% CI intervals for bladder cancer-specific death and death due to any cause. The time scale was years and months (as decimals of year) since bladder cancer diagnosis. Follow-up continued until death, emigration of Finland or common closing date of 1 January 2013, whichever came first. Individuals whose extent of bladder cancer was not known were filtered out. The analysis was adjusted for age and gender, and further for tumor extent at diagnosis, primary treatment (surgery vs. other) and CCI in multivariable-adjusted analyses.

The association between statin use and number of TURBs after bladder cancer diagnosis was evaluated with a logistic regression model by limiting the analysis to bladder cancers diagnosed at localized stage and analyzing the risk of having more than two TURBs performed after the diagnosis.

Statin use before and after bladder cancer diagnosis were analyzed separately. Statin use before the diagnosis was analyzed as a fixed (time-independent) variable. Status of statin use, cumulative amount, duration and intensity of pre-diagnostic statin use were determined for the whole time between beginning of 1996 and bladder cancer diagnosis.

Post-diagnostic statin use was analyzed as a time-dependent variable in order to minimize immortal time bias. The user status, cumulative amount, duration and intensity of statin use were updated separately for each year of follow-up based on recorded statin purchases. Participants who stopped statin usage during the study period were kept in the users category in order to minimize bias due to selective discontinuation of statin use in cancer patients with very limited life expectancy. People whose follow-up time was 0 were excluded from post-diagnostic analyses.

Competing risks regression with mortality due to cardiovascular disease (ICD-10 codes I20-I25) was performed to estimate impact of non-cancer deaths on the association between statin use and risk of bladder cancer death.

Statistical analyses were performed using IBM SPSS Statistics 23.0 software. Competing risks regression analysis was performed with Stata.

3 RESULTS

3.1 Population characteristics

Of the study population 5,287 (37.6%) had used statins between 1996 and 2012; 3,481 participants used statins before bladder cancer diagnosis and 4,723 after the diagnosis (Table 1).

Compared to non-users, statin users had more often localized bladder cancer (65.8% vs 57.6%) and less metastatic disease (9.8% vs 14.9%) (Table 1). Within median follow-up of 4 years after diagnosis, 2,297 (43.4%) statin users and 3,002 (34.2%) non-users died respectively. Of these 772 (33.6%) statin users and 2,602 (86.7%) non-statin users died of bladder cancer. Median number of TURBs was 2 for both statin users and non-statin users.

All comorbidities (diabetes, hypertension, hypercholesterolemia) aside from COPD, were more prevalent in statin users compared to non-users (Table 1).

Table 1 Population characteristics. Cohort of 14,065 bladder cancer patients diagnosed in Finland between 1996-2012.

	Statin use	
	None	Any
n of participants	8778 (62.4%)	5287 (37.6%)
men; n (%) *	6,517 (74.2%)	4,203 (79.5%)
women; n (%) *	2,261 (25.8%)	1,084 (20.5%)
Bladder cancer stage at diagnosis		
Localized; n (%)	5,057 (57.6%)	3,480 (65.8%)
Advanced; n (%)	1,311 (14.9%)	518 (9.8%)
Unknown; n (%)	2,410 (27.5%)	1,289 (24.4%)
Deaths; n (%)	3,002 (34.2%)	2,297 (43.4%)
Bladder cancer deaths; n (%)	2,602 (29.6%)	772 (14.6%)
Primary treatment: *		
Surgery; n (%)	4,073 (46.4%)	2,878 (54.4%)
Other; n (%)	2,773 (31.6%)	1,317 (24.9%)
Median (IQR) follow-up after diagnosis	3.4 (1.0-7.4)	5.4 (2.6-9.8)
Median (IQR) number of TURBs	2 (1-3)	2 (1-3)
Median (IQR) age at diagnosis*	74 (65-82)	72 (65-78)
Comorbidities:		
Median (IQR) Charlson co-morbidity index	4 (3-4)	4 (3-4)
Diabetes mellitus; n (%) *	1,283 (14.6%)	1,825 (34.5%)
Hypertension; n (%) *	5,932 (67.6%)	4,833 (91.4%)
Hypercholesterolemia; n (%) *	88 (1.0%)	5,287 (100%)
COPD; n (%)	979 (11.2%)	614 (11.6%)

* $P < 0.05$ for difference compared to non-users

3.2 Bladder cancer extent by pre-diagnostic statin use

Overall, risk of having metastatic bladder cancer did not differ by pre-diagnostic statin and non-statin cholesterol-lowering drug use (Table 2). However, participants with low cumulative amount of use (total amount of use less than 1,294 DDDs) were associated with lowered risk for metastatic bladder cancer (OR 0.84 95% CI 0.71-0.98).

Use of non-statin cholesterol-lowering drugs was not associated with bladder cancer extent at diagnosis (Table 2).

Table 2 Bladder cancer stage at diagnosis by cholesterol-lowering drug use before the diagnosis. Cohort of 10,366 bladder cancer patients diagnosed in Finland between 1996-2012 with known status of bladder cancer extent.

	Statin users				Users of non-statin cholesterol-lowering drugs		
Medication use	n of participants	OR (95% CI)$_{age\text{-}adjusted}$	OR (95% CI)$_{multivar\text{-}adjusted*}$	Medication use	n of participants	OR (95% CI)$_{age\text{-}adjusted}$	OR (95% CI)$_{multivar\text{-}adjusted*}$
None	10,584	Ref	Ref	None	13,887	Ref	Ref
Any	3,481	0.91 (0.81-1.03)	0.91 (0.81-1.03)	Any	178	0.86 (0.54-1.36)	0.86 (0.54-1.36)
Cumulative amount of use							
1,293 DDD or below	1,741	0.84 (0.71-0.98)	0.84 (0.71-0.98)	218 DDD or below	88	1.19 (0.66-2.15)	1.19 (0.66-2.14)
Over 1,293 DDD	1,740	1.00 (0.85-1.16)	1.00 (0.85-1.16)	Over 218 DDD	89	0.59 (0.28-1.23)	0.59 (0.28-1.23)
Cumulative years of use							
5 years or below	2,033	0.87 (0.75-1.01)	0.87 (0.75-1.01)	2 years or below	105	0.82 (0.44-1.52)	0.82 (0.44-1.52)
Over 5 years	1,448	0.98 (0.83-1.16)	0.98 (0.83-1.16)	Over 2 years	73	0.91 (0.46-1.79)	0.91 (0.46-1.80)
Average number of doses/year							
267 DDD/year or below	1,741	0.86 (0.73-1.00)	0.86 (0.73-1.00)	109 DDD/year or below	88	0.78 (0.40-1.53)	0.78 (0.40-1.53)
Over 267 DDD/year	1,740	0.98 (0.84-1.15)	0.98 (0.84-1.15)	Over 109 DDD/year	89	0.95 (0.51-1.77)	0.95 (0.51-1.77)

* Calculated using logistic regression with model adjustment for age, gender and Charlson co-morbidity index.

3.3 Risk of bladder cancer death by statin use before and after diagnosis

Statin use both before and after bladder cancer diagnosis was associated with lowered risk for cancer-specific death (Table 3). No dose-dependence was observed for the risk association between pre-diagnostic

statin use and risk for bladder cancer death, whereas the risk decrease by post-diagnostic statin use was greater with higher usage.

A risk lowering association was observed by low-dose usage (less than 109 DDDs/year) of non-statin cholesterol-lowering drugs in age-adjusted analysis (HR 0.52 95% CI 0.30-0.94) (Table 3). Additionally, post-diagnostic use was associated with decreased risk for bladder cancer death in multivariable-adjusted analysis (HR 0.60 95% CI 0.38-0.94).

Table 3 Risk of bladder cancer death by cholesterol-lowering drug use. Cohort of 10,366 bladder cancer patients diagnosed in Finland between 1996-2012 with known status of bladder cancer extent.

	Usage before bladder cancer diagnosis						
	Statin users				Users of non-statin cholesterol-lowering drugs		
Medication use	n of participants	HR (95% CI)$_{age-adjusted}$	HR (95% CI)$_{multivar-adjusted*}$	Medication use	n of participants	HR (95% CI)$_{age-adjusted}$	HR (95% CI)$_{multivar-adjusted*}$
None	10,584	Ref	Ref	None	13,887	Ref	Ref
Any	3,481	0.67 (0.61-0.73)	0.66 (0.60-0.72)	Any	178	0.71 (0.50-1.01)	0.72 (0.51-1.03)
Average number of doses/year							
267 DDD/year or below	1,741	0.68 (0.60-0.76)	0.68 (0.61-0.76)	109 DDD/year or below	88	0.52 (0.30-0.94)	0.59 (0.34-1.04)
Over 267 DDD/year	1,740	0.66 (0.58-0.74)	0.63 (0.56-0.71)	Over 109 DDD/year	89	0.91 (0.58-1.43)	0.85 (0.54-1.33)
	Usage after bladder cancer diagnosis						
None	9,342	Ref	Ref	None	13,952	Ref	Ref
Any	4,723	0.41 (0.37-0.44)	0.47 (0.43-0.52)	Any	113	0.75 (0.48-1.18)	0.60 (0.38-0.94)
Average number of doses/year							
14-250 DDD/year	1,574	0.59 (0.52-0.67)	0.68 (0.60-0.76)	13-21 DDD/year	41	0.88 (0.44-1.76)	0.55 (0.28-1.11)
251-447 DDD/year	1,576	0.41 (0.35-0.47)	0.48 (0.42-0.55)	22-100 DDD/year	37	0.69 (0.31-1.54)	0.61 (0.27-1.36)
Over 447 DDD/year	1,573	0.22 (0.18-0.26)	0.26 (0.21-0.31)	Over 100 DDD/year	35	0.67 (0.28-1.62)	0.67 (0.28-1.61)

* Calculated using Cox regression with model adjustment for age, gender, bladder cancer extent at diagnosis, primary treatment and Charlson co-morbidity index

3.4 Number of TURBs by statin use

In bladder cancer patients diagnosed at localized stage, statin use before the diagnosis was inversely associated with the number of TURBs performed after diagnosis; OR 0.82, 95% CI 0.73-0.91 and OR 0.69, 95% CI 0.59-0.81 for risk of having 2 or more and 5 or more TURBs after the diagnosis, respectively (Table 4). The risk decreased in inverse correlation with intensity of statin use. Conversely, low-dosage statin use (14-254 DDD/year) after the diagnosis was associated with an increased risk of having more than 2 and 5 TURBs (OR 1.17 95% CI 1.01-1.35 and OR 1.29, 95% CI 1.06-1.56).

Non-statin cholesterol-lowering drug use before or after bladder cancer diagnosis was not associated with the number of TURBs (Table 4).

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Table 4 Risk of having more than two transurethral resections of bladder tumor by statin use. Cohort of 8,537 bladder cancer cases diagnosed with localized disease in Finland during 1996-2012.

	Usage before bladder cancer diagnosis						
	Statin users				Users of non-statin cholesterol-lowering drugs		
		Risk for 2 or more TURBs	Risk for 5 or more TURBs			Risk for 2 or more TURBs	Risk for 5 or more TURBs
Medication use	n of participants	OR (95% CI)$_{multivar-adjusted*}$	OR (95% CI)$_{multivar-adjusted*}$	Medication use	n of participants	OR (95% CI)$_{multivar-adjusted*}$	OR (95% CI)$_{multivar-adjusted*}$
None	6,396	Ref	Ref	None	8,417	Ref	Ref
Any	2,141	0.82 (0.73-0.91)	0.69 (0.59-0.81)	Any	120	0.86 (0.57-1.28)	1.14 (0.67-1.94)
Average number of doses/year							
261 DDD/year or below	1,117	0.90 (0.78-1.04)	0.81 (0.66-0.99)	109 DDD/year or below	59	0.61 (0.33-1.13)	0.54 (0.20-1.49)
Over 261 DDD/year	1,024	0.73 (0.63-0.85)	0.57 (0.45-0.72)	Over 109 DDD/year	60	1.18 (0.69-2.02)	1.86 (0.98-3.50)
	Usage after bladder cancer diagnosis						
None	5,344	Ref	Ref	None	8,461	Ref	Ref
Any	3,193		1.17 (1.02-1.33)	Any	76	1.14 (0.69-1.89)	1.55 (0.85-2.82)
Average number of doses/year							
14-254 DDD/year	1,051	1.17 (1.01-1.35)	1.29 (1.06-1.56)	13-21 DDD/year	26	0.93 (0.38-2.26)	0.62 (0.15-2.64)
255-453 DDD/year	1,051	1.08 (0.94-1.25)	1.14 (0.93-1.39)	22-100 DDD/year	27	1.21 (0.55-2.66)	2.15 (0.86-5.33)
Over 453 DDD/year	1,091	1.05 (0.91-1.21)	1.08 (0.88-1.32)	Over 100 DDD/year	23	1.35 (0.52-3.48)	2.08 (0.77-5.62)

* Calculated using logistic regression with model adjustment for age and Charlson co-morbidity index.

Analysis limited to cases with localized tumor extent at diagnosis.

3.5 Long-term association between statin use after bladder cancer diagnosis and cancer-specific death

Lag-time analyses were performed to assess the relationship between post-diagnostic statin use and bladder cancer-specific death. The risk lowering effect on bladder cancer death was retained for ten years after the initial use of statins (Table 5).

Table 5 Long-term association between statin use after bladder cancer diagnosis and risk of cancer-specific death.

		Lag-time				
	Full follow-up	1yr	3yrs	5yrs	8yrs	10yrs
Statin use post-diagnosis	HR (95% CI)$_{multivar-adjusted*}$	HR (95% CI)$_{multivar-adjusted*}$	HR (95% CI)$_{multivar-adjusted*}$	HR (95% CI)$_{multivar-adjusted*}$	HR (95% CI)$_{multivar-adjusted*}$	HR (95% CI)$_{multivar-adjusted*}$
None	Ref	Ref	Ref	Ref	Ref	
Any	0.47 (0.43-0.52)	0.73 (0.67-0.80)	0.70 (0.64-0.77)	0.67 (0.60-0.75)	0.64 (0.55-0.73)	0.66 (0.55-0.78)

* Calculated using Cox regression with model adjustment for age, bladder cancer extent at diagnosis, primary treatment and Charlson co-morbidity index

3.6 Subgroup analyses

In subgroup analyses only COPD modified the risk for bladder cancer death both before and after bladder cancer diagnosis (P-value for interaction ≤ 0.002); the risk decrease was observed only in participants without COPD (Figure 1 and 2). No significant risk modification by background characteristics were observed for the quantity of TURBs.

3.7 Competing risks regression

In competing risks regression model with deaths due to cardiovascular disease as the competing cause of death statin use both before and after bladder cancer diagnosis remained to be associated with lowered risk of bladder cancer death (HR 0.66 95% CI 0.60-0.73 and HR 0.52 95% CI 0.48-0.57 respectively).

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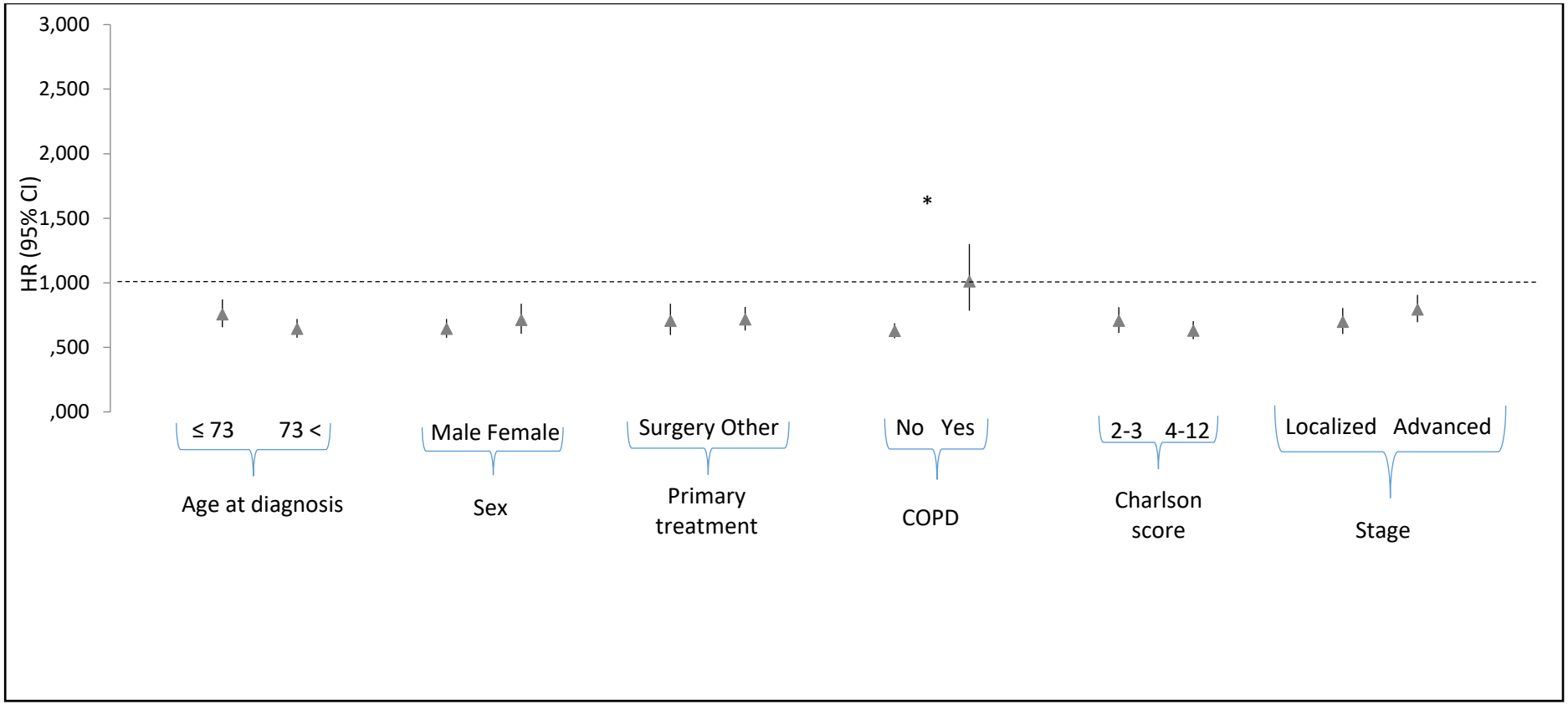
Figure 1 Risk of bladder cancer death by statin use before bladder cancer diagnosis. Cohort of 14,065 bladder cancer patients diagnosed in Finland between 1996-2012.



* P for interaction ≤ 0.002. Calculated using Cox regression where pre-diagnostic statin use is time-independent, model adjusted for age at diagnosis, tumor extent, primary treatment, COPD and Charlson co-morbidity index.

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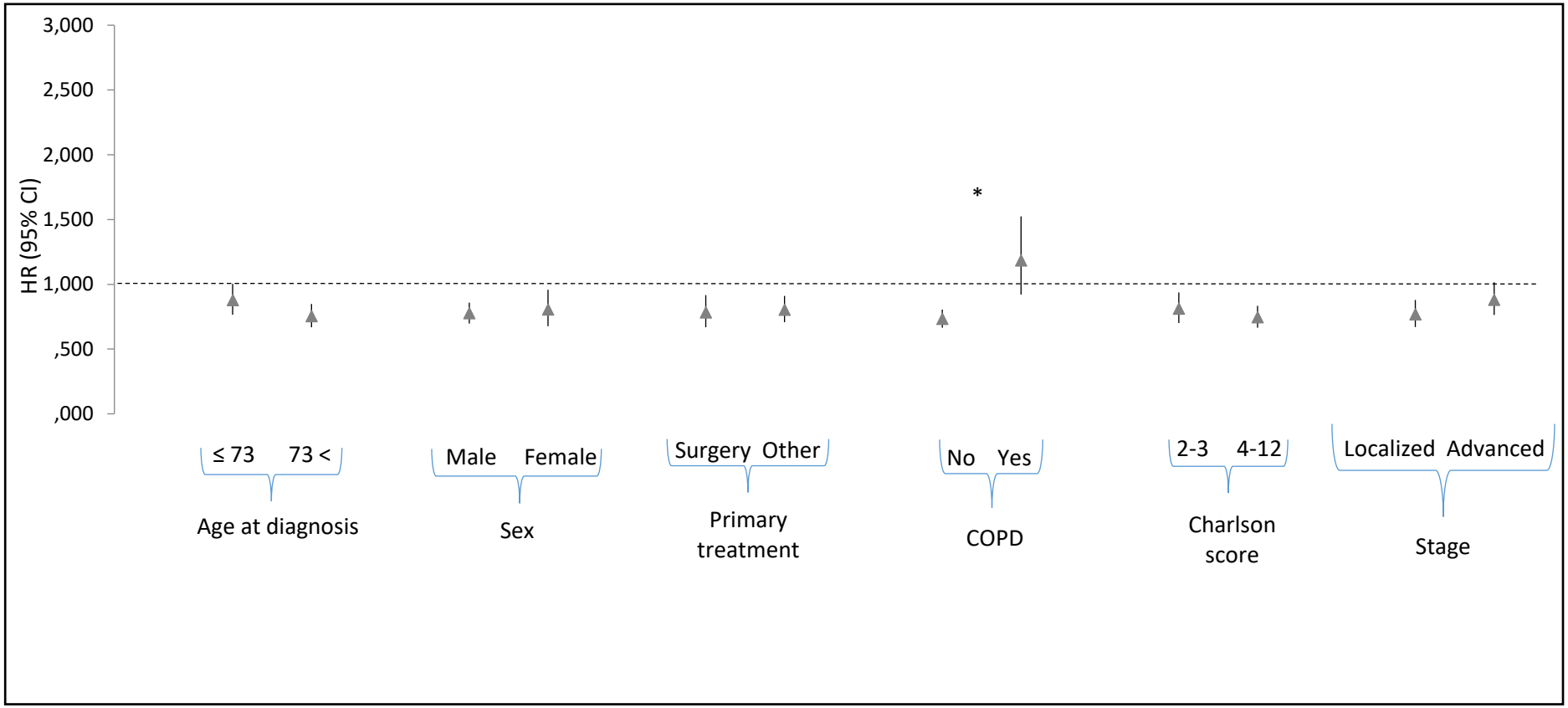
Figure 2 Risk of bladder cancer death by statin use after bladder cancer diagnosis. Cohort of 14,065 bladder cancer patients diagnosed in Finland between 1996-2012.



* P for difference between subgroups ≤ 0.000. Calculated using Cox regression where post-diagnostic statin use is time-dependent, model adjusted for age at diagnosis, tumor extent, primary treatment, COPD and Charlson co-morbidity index.

4 DISCUSSION

Statin users with low cumulative use had less often metastatic bladder cancer at diagnosis. The risk of bladder cancer specific death was also lower among statin users. The survival association was observed both for statin use before and after bladder cancer diagnosis. However, a dose-dependent risk decrease was observed only for post-diagnostic statin use, not for pre-diagnostic use.

Use of non-statin cholesterol-lowering drugs after bladder cancer diagnosis was also associated with lowered risk for bladder cancer death. Analysis of non-statin drugs allowed estimation of confounding by indication as the indications for use are the same as for statins. This suggests that despite extensive model adjustments our analysis of post-diagnostic use was somewhat affected by residual confounding. However, the risk association was dose-dependent only for statins, suggesting that statins may also have a causal effect.

Risk of having multiple TURBs after the first diagnosis was lowered in a dose-dependent manner among pre-diagnostic statin users compared to non-users. Conversely, low-dosage statin use after the diagnosis was associated with an increased risk of having more TURBs.

The differing risk associations between post-diagnostic statin use and risk of bladder cancer death and number of TURBs suggest that statins may have a differing effect on invasive and non-invasive bladder tumors.

In vitro statins inhibit cancer cell growth in several ways. Statins affect regulatory proteins and arrest cancer cell's cell-cycle in G1 or S phase as well as inhibit cell activity by affecting numerous molecular pathways of the cancer cell. It has also been shown that after statin treatment, almost all known mechanisms of apoptosis become activated. [14] In vitro studies statin use on bladder cancer cells have portrayed similar effects. [15, 16]. Thus it is logical to presume that statins may have stronger effect on progression of invasive high-grade cancers than in non-invasive, mainly low-grade tumors.

Strengths of this study are the large national study cohort, reliable data on dose and timing of medication use and the ability to separately study both the risk of bladder cancer death and the quantity of performed TURBs, allowing indirect estimation of the effect of statins on invasive and non-invasive bladder cancer. We were also able to estimate confounding by indication by analyzing non-statin cholesterol-lowering drugs.

Study limitations include absence of information on smoking status and other possible lifestyle choices from the registries. These could differ between users and non-users of statins, and smoking Is a known risk factor for bladder cancer progression. Additionally, we did not have information on indications of statin use. Statin use for primary prevention of cardiovascular disease has been linked with lower risk of various non-related health outcomes, such as traffic accidents use risk aversive behavior, introducing a healthy use bias [17]. Thus, residual confounding and bias is possible. Nevertheless, residual confounding or healthy user bias should not depend on dose of statin use. Thus, the observed dose-dependent risk associations support causal effects of statins.

In summary the use of statins, especially after bladder cancer diagnosis, is associated with a lower risk of bladder cancer death, whereas statin use before the diagnosis is linked with lower number of TURBs. This suggests that statins may inhibit bladder cancer progression, but the effect may be dependent on timing of statin use and tumor characteristics.

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5 ACKNOWLEDGEMENTS

Supported by non-restrictive cancer research grant from Pirkanmaa Hospital District, grant # 150640

6 CONFLICT OF INTEREST

Seppälä VJ – none

Kotsar A – none

Tammela TLJ – consultation fees from Astellas, GlaxoSmithKline, Pfizer, Orion Pharma and Amgen

Murtola TJ - consultation fees from Astellas, Janssen-Cilag and speakers' honorarium from Abbvie, Astellas, Janssen-Cilag and MSD.

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