STATINS USE AND RISK OF DISEASE RECURRENCE AND DEATH AFTER RADICAL PROSTATECTOMY

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KESKIVÄLI TEEMU: STATINS USE AND RISK OF DISEASE RECURRENCE AND DEATH AFTER RADICAL PROSTATECTOMY

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Statiinien käytön on todettu liittyvän alentuneeseen eturauhassyövän uusiutumiseen riskiin sekä pienempään kuolleisuuteen radioterapialla hoidetuilla miehillä. Tämä yhteys on kuitenkin ristiriitainen operatiivisesti hoidetuilla potilailla. Me pyrimme selvittämään onko statiinien käytöllä yhteyttä eturauhassyövän progressioon tai kuolleisuuteen radikaalin prostatektomian jälkeen.

Tutkimusaineisto koostui 1314 eturauhassyöpäpotilaasta joille oli suoritettu radikaali prostatektomia Tampereen yliopistollisessa sairaalassa vuosina 1995−2009. Statiinien käyttötiedot saatiin kansallisesta reseptitietokannasta. PSA relapsin riskiä ja kuolleisuutta statiinien käytön yhteydessä arvioitiin monivakioidulla Coxin regression avulla. Oletetut eturauhassyövän ennusteelliset kudosmerkkiaineet mitattiin 323 mieheltä.

Mediaaniseuranta-aika leikkauksen jälkeen oli 8.6 vuotta, jonka aikana tauti uusiutui 484 miehellä ja 244 kuoli (32 eturauhassyöpään). Yleisesti statiinien käyttö ei ollut yhteydessä taudin uusiutumiseen tai kuolemaan. Kuitenkin pitkäaikainen statiinien käyttö ennen leikkausta oli yhteydessä kohonneeseen uusiutumisriskiin, mutta myös matalampaan kuolleisuusriskiin. Myös leikkauksenjälkeinen käyttö oli yhteydessä alentuneeseen kuolleisuusriskiin.

Kohonnut taudin uusiutumisriski statiinien käyttäjillä ennen leikkausta voi heijastaa taustalla olevaa dyslipidemiaa. Alentunut kuolemanriski statiinien käyttäjillä viittaa statiinien suotuisiin vaikutuksiin myös operatiivisesti hoidetuilla potilailla.

Sisällysluettelo

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ABSTRACT

BACKGROUND: Statins have been linked with improved prostate cancer survival and lower risk of recurrence in men treated with radiation therapy. However, the association is unclear for surgically-treated men. We studied the risk of prostate cancer recurrence and death by statin usage after radical prostatectomy in a cohort of prostate cancer patients treated with radical prostatectomy.

METHODS: A cohort of 1,314 men who underwent curative-intent radical prostatectomy at the Tampere University Hospital, Tampere, Finland during 1995-2009 were linked to national prescription database to obtain detailed information on statin purchases. The risk of PSA recurrence and death (overall and prostate cancer-specific) by statin use before and after the surgery were evaluated using Cox regression with model adjustment for tumor characteristics and simultaneous use of antidiabetic and antihypertensive drugs. Tissue expression of putative prognostic markers were measured from a subgroup of 323 men.

RESULTS: During the median follow-up of 8.6 years after surgery 484 men recurred, while 244 men died (32 due to prostate cancer). In general statin use was not associated with risk of recurrence or death. However, long-term statin use before surgery was associated with elevated risk of recurrence (HR 1.48, 95% CI 1.01-2.16), but lowered risk of death (HR 0.28, 95% CI 0.09-0.88). Long-term statin use after surgery was also linked with lowered risk of death (HR 0.64, 95% CI

0.40-1.01). Tissue expression of Ki-67 modified the association between statin use and risk of progression and death; the risk estimates were lower in men with Ki-67 expression above the median in the tumor tissue.

CONCLUSIONS: Elevated risk of disease recurrence by statin use before surgery depends on tumor proliferation activity. This may reflect the effect of underlying long-term dyslipidemia, as similar association was not observed if statin use had started after surgery. Lower risk of death among statin users suggests that statins have beneficial effects on survival also in surgically-treated prostate cancer patients.

Keywords: Prostate cancer; Disease progression; 3-hydroxy-3-methylglutaryl-CoA-reductase inhibitors; Tissue markers

1 INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer and second most common cause of cancer death in developed countries. In 2012, prostate cancer was diagnosed in an estimated 1.1 million men, and it was estimated to have caused about 307,000 deaths. (1) At present, there are no established means to prevent prostate cancer formation or death due to disease because information on modifiable risk factors is controversial. However, prostate cancer is a slow-growing cancer, and this allows the opportunity to influence tumor progression from latent tumor to clinically significant cancer and thus reduce deaths from prostate cancer (2).

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are widely used cholesterol-lowering drugs which have been proven to prevent cardiovascular disease (3). In addition, statins are well-tolerated drugs with few side effects (4). Previous studies have shown that statins reduce prostate cancer cell growth *in vitro* (2). Increasing amount of evidence show that statins may also reduce mortality from prostate cancer and reduce the risk of advanced prostate cancer, particularly in long-term usage (2,5). Statins have been linked with lower risk of biochemical recurrence after curative-intent definitive treatment (6). However, this may depend on the choice of primary treatment; a recent concluded that statins reduce prostate cancer recurrence among men treated with external-beam radiation therapy but the results for men treated with radical prostatectomy are conflicting (6,8).

In this study we evaluated the association of statin use before and after surgery with prostate cancer recurrence and survival in a cohort of Finnish men who underwent radical prostatectomy. In addition, we assessed how prostate cancer characteristics and patient characteristic affect the association between statin use and prostate cancer outcomes.

2 MATERIALS AND METHODS

Study cohort

The study population consisted of 1,314 men who underwent radical prostatectomy as definitive prostate cancer treatment at the Tampere University Hospital (TAUH) during 1995-2009. Pirkanmaa region has a population of approximately 500,000 inhabitants and all prostatectomies in this area are performed at TAUH. Men who agree to participate in the study and give written informed consent are included in the TAUH prostate cancer database.

Database contains information on pathological TNM-stage, Gleason score, surgical margin positivity and perineural invasion for each man. Information also includes PSA at the time of diagnosis, date of PSA recurrence or radiological progression and time and cause of death.
Post-operatively the men were followed with PSA measurements and clinical examination every 6 months for the first year and annually thereafter. Prostate cancer recurrence was defined as two consecutive PSA values of 0.2 ng/ml or above or radiological progression after prostatectomy.

All deaths and causes of death until the end of 2013 were obtained from the Finnish Cancer Registry which comprehensively contains information on cancer diagnoses made in Finnish health care units and deaths among cancer patients. Patient was considered to have died of prostate cancer if the cause of death was recorded as ICD-10 code C61. The study has been approved by the ethics committee of the Pirkanmaa Hospital district.

Information on medication use

Individual information on cholesterol-lowering drug use during 1995-2009 was obtained from the Finnish national prescription database maintained by the Social Insurance Institution. Every Finnish

citizen is entitled to a reimbursement for the cost of medicines prescriped by a physician (with the expection of hospital inpatients) as part of the National Health Insurance (9). Social Insurance Institution has granted reimbursement status for the majority of drugs in clinical use in Finland, including all statins, and they are available only through physicians' prescription. The reimbursement is 50-100% of the price of the drug, depending on the severity of the disease and it is usually received as price discount at the pharmacy. Each reimbursed prescription drug purchase is recorded in the prescription database. The information for each purchase contains the date, dose, package size and number of packages bought.

The cholesterol-lowering drugs in clinical use in Finland during the study period were statins (atorvastatin since 1998, cerivastatin from 1999 to 2001, fluvastatin since 1996, lovastatin, pravastatin, rosuvastatin since 2003 and simvastatin), fibrates (bezafibrate, clofibrate until 1998, fenofibrate since 2002 and gemfibrozil), bile-acid binding resins (cholestipol and cholestyramin), acipimox from 1995 to 1999 and ezetimibe since 2004. Nicotinic acid was the only cholesterol-lowering drug not recorded by the prescription database. Also information on use of antidiabetic and antihypertensive drugs and 5-alpha reductase inhibitors were obtained from the national prescription database.

The annual amount of cholesterol-lowering medication use was standardized using defined daily doses (DDD) recommended by the World Health Organization (10). The annual usage of a given statin (in milligrams) was standardized by dividing the total yearly amount of purchases with the quantity corresponding to one DDD. Duration of statin use was calculated as number of years with reimbursed statin purchases. Yearly dosage was evaluated by calculating intensity of usage (DDDS/year) by dividing the yearly amount of DDDs with the number of years of usage.

Measurement of tissue expression

Tissue expression of putative prostate cancer risk markers was determined immunohistochemically from the prostatectomy sample for 323 randomly selected men (24.6% of the cohort). The measured markers included Ki-67, EZH2, ERG, TMPRSS:ERG fusion, TP53, AR expression in the nucleus, PTEN and SPINK1. The immunohistochemistry protocol has been previously described (11-14).

Statistical analysis

Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for prostate cancer recurrence and mortality. Follow-up started at the date of prostatectomy, and was carried on until disease recurrence, death or common closing date December 31, 2013, whichever came first (analysis on risk of recurrence), or until death or the common closing date (analysis on risk of death). Cox regression model was adjusted for age, pathological TNM-stage, tumor Gleason score, surgical margin positivity and preoperative PSA. Baseline differences between statin users and non-users were compared using the chi-square test.

The drug usage was categorized into pre-operative and post-operative use. Post-operative drug use was time-dependent variable, the usage status being updated yearly starting from the year of surgery. Men who were not statin users at baseline were categorized as non-users until the first purchase of the drug. After this, they were categorized as users for years with continued purchases. If statin usage was discontinued for a full year the men were categorized as previous users. Cumulative amount, duration and intensity of statin use increased progressively during the follow-up along with continued purchases. Men who discontinued statin use remained in the category of cumulative usage they had reached before the discontinuation.

Pre-operative users were categorized as current users (patient was a drug user in the year of prostatectomy) and previous users (prior use had been stopped before surgery). Nonusers were used as the reference group in all analyses.

Effect modification by patient, tumor and tissue characteristics were evaluated by stratifying the analysis by the characteristics and additionally by adding an interaction term with statin use into the Cox regression model.

Analyses were calculated using IBM SPSS statistics 21 statistical software. All reported P values are two-sided.

3 RESULTS

Population and tumor characteristics

Of the 1,314 men, 528 (40.2%) were ever-users of statins, 251 (19.1%) had used statins before the surgery (Table 1). Non-statin cholesterol-lowering drugs had been used by 38 men**.** After surgery 484 men recurred during the median follow-up of 7.3 years after surgery, while 244 men died (32 from due prostate cancer) during the median follow-up of 8.6 years before death (Table 1).
Tumor characteristics or preoperative PSA did not markedly differ between statin users and non-users, with the exception of pathologic stage; statin users had less often locally advanced tumors than non-users (pT3 and/or N1 tumors23.7% vs 28.5%; P= 0.052) (Table 1).

Statin use did not correlate with tissue expression of putative tumor markers (Table 1).
Statin users were more often also users of antidiabetic medication (22.0% vs 6.1%) and antihypertensive drugs (79.0% vs 50.8%) (Table 1).

Table 1. Population and tumor characteristics. Cohort of 1,314 men with prostate cancer who underwent radical prostatectomy at the Tampere University Hospital during 1995-2009

	Statin use		
Patient characteristics	Yes	No	P-value
N of men	528	786	
N of progressions (%)	203 (38.4%)	281 (35.8%)	
N of deaths (%)	94 (17.8%)	150 (19.1%)	
N of Pca deaths	9 (1.7%)	23 (2.9%)	
Median follow-up until progression (years)	7.8	6.9	
Median follow-up until death (years)	9.5	8.3	
Median age at surgery	63	63	
PSA at diagnosis			0.702
Median or below (4.8 ng/ml or lower)	261 (49.4%)	397 (50.5%)	

Above the median (above 4.8 ng/ml)	267 (50.6%)	389 (49.5%)	
Antidiabetic drug use; n of men (%)	116 (22.0%)	48 (6.1%)	<0.001
Antihypertensive drug use; n of men (%)	417 (79.0%)	399 (50.8%)	<0.001
Tumor characteristics			
Gleason_grade; n of men (%)			
<7	248 (47%)	332 (42.2%)	
7-10	272 (52.5%)	445 (56.6%)	0.179
Unknown	8 (1.5%)	9 (1.1%)	
Clinical stage; n of men (%)			
T1-2 N0/x M0/x	475 (99.2%)	677 (98.4%)	
T3 and/or N1 and/or M1	4 (0.8%)	11 (1.6%)	0.255
Unknown	49 (9.3%)	98 (12.5%))	
Pathologic stage; n of men (%)			
T1-T2N0Mx	403 (76.3%)	562 (71.5%)	
T3 and/or N1	125 (23.7%)	224 (28.5%)	0.052
Surgical margins positive; n of men (%)			
Yes	103 (19.5%)	170 (21.6%)	
No	142 (26.9%)	234 (29.8%)	0.206
Unknown	283 (53.6%)	282 (48.6%)	
Symptoms at diagnosis; n of men (%)			
Yes	84 (15.9%)	143 (18.2%)	
No	444 (84.1%)	643 (81.8%)	0.283
Perineural invasion; n of men (%)			
Yes	362 (68.6%)	530 (67.4%)	
No	166 (31.4%)	256 (32.6%)	0.667
Gleason upgrade from the biopsy; n of men (%)			
Yes	222 (42%)	304 (38.7%)	
No	306 (58%)	482 (61.3%)	0.222
Gleason downgrade from the biopsy; n of men (%)			
Yes	80 (15.2%)	100 (12.7%)	
No	448 (84.8%)	686 (87.3%)	0.209
Tissue markers *(available for 323 men)*			

TMPRSS2:ERG gene fusion; n of men (%)			
Yes	4 (33.3%)	35 (24.6%)	
No	8 (66.7%)	107 (75.4%)	0.51
Ki-67expression; n of men (%)			
Median or below (0-5%)	6 (40%)	116 (58%)	
Above the median (6-70%)	9 (60%)	84 (42%)	0.18
EZH2 expression; n of men (%)			
Median or below (0-27%)	7 (46.7%)	112 (53.8%)	
Above the median (28-88%)	8 (53.3%)	96 (46.2%)	0.59
ERG; n of men (%)			
No	38 (57.6%)	44 (47.8%)	
Yes	28 (42.4%)	48 (52.2%)	0.23

Statin use before surgery and risk of disease recurrence and death

Overall, pre-operative statin use was not associated with prostate cancer recurrence, disease-specific death or all-cause deaths (Table 2). However, risk of prostate cancer recurrence increased with increasing amount, duration and intensity of pre-operative statin use**.** Nevertheless, risk of prostate cancer death was not increased even in long-term usage, while all-cause mortality was decreased in men with three years or longer pre-operative statin use (Table 2).

Table 2. Risk of disease recurrence and death by statin use before prostatectomy. Cohort of 1,314 prostate cancer patients treated with radical prostatectomy at the Tampere University Hospital during 1995-2009

	Disease recurrence		Prostate cancer deaths		All deaths	
	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]
Statin use before prostatectemy[1]						

None	Ref	Ref	Ref	Ref	Ref	Ref
Ongoing use	0.97 (0.75-1.26)	1.12 (0.86-1.46)	0.67 (0.20-2.22)	1.14 (0.33-3.92)	0.77 (0.50-1.17)	0.80 (0.52-1.23)
Previous use	1.24 (0.66-1.23)	1.27 (0.67-2.40)	3.31 (0.78-14.01)	2.49 (0.58-10.79)	1.33 (0.55-3.24)	1.20 (0.49-2.94)
Amount of statin usage (DDDs)						
770 or less	0.85 (0.59-1.23)	0.98 (0.67-1.44)	1.23 (0.37-4.04)	1.45 (0.43-4.87)	0.92 (0.55-1.53)	0.90 (0.54-1.50)
over 770	1.24 (0.87-1.76)	1.29 (0.89-1.87)	0.58 (0.08-4.29)	1.39 (0.17-11.05)	0.56 (0.25-1.27)	0.63 (0.28-1.43)
P for trend	0.24	0.08	0.60	0.70	0.11	0.17
Years of statin usage						
2 or less	1.00 (0.70-1.42)	1.09 (0.76-1.57)	1.31 (0.40-4.32)	1.50 (0.45-5.06)	1.16 (0.72-1.85)	1.13 (0.70-1.83)
3 or longer	1.04 (0.71-1.52)	1.48 (1.01-2.16)	0.53 (0.07-3.93)	1.24 (0.16-9.77)	0.26 (0.08-0.80)	0.28 (0.09-0.88)
P for trend	0.73	0.41	0.91	0.37	0.08	0.12
Intensity statin usage (DDDs/year)						
280 DDDs/year or less	0.75 (0.51-	0.88(0.60-1.30)	2.58 (0.55-4.51)	2.40 (0.80-7.26)	0.84 (0.50-1.42)	0.83 (0.49-1.42)

	1.11)					
281 DDD/s/year or more	1.41(1.00-2.00)	1.44 (1.01-2.06)	-	-	0.69 (0.32-1.46)	0.75 (0.35-1.61)
P for trend	0.12	0.05	0.41	0.79	0.24	0.35

1 Ongoing use: statin usage at the year of prostatectomy; Previous use: statin usage after 1995 but discontinued before prostatectomy

2 Calculated with Cox regression model with model adjustment for age at surgery, tumor stage and Gleason grade, PSA-level at the time of diagnnosis, surgical margin positivity and use of antidiabetic and antihypertensive drugs

Statin use after prostatectomy and disease recurrence and death

Post-operative statin use was generally not significantly associated with prostate cancer recurrence, disease-specific deaths or all-cause mortality (Table 3).

As for statin use before surgery, also post-operative statin use was associated with increased risk of disease recurrence during the first two years of usage, but the risk returning to same level with non-users in continued usage (Table 3). In contrast, risk of death tended to decrease with continued post-operative statin use. This was clearest for the cumulative amount of usage; men who had used 1,997 statin DDDs or more after prostatectomy had decreased risk of death overall (HR 0.60, 95% CI 0.37-0.96) and a similar but statistically non-significant decrease also in the risk of prostate cancer deaths (HR 0.68, 95% CI 0.15-3.16) (Table 3).

Table 3. Risk of disease recurrence and death by statin use after prostatectomy. Cohort of 1,314 prostate cancer patients treated with radical prostatectomy at the Tampere University Hospital during 1995-2009

	Disease recurrence		Prostate cancer deaths		All deaths	
	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]	HR (95% CI)age-adjusted	HR (95% CI)multivar-adjusted[2]

Statin use after surgery						
None	Ref	Ref	Ref	Ref	Ref	Ref
Users	1.01 (0.79-1.29)	1.13 (0.88-1.46)	1.12 (0.48-2.61)	1.13 (0.45-2.84)	0.81 (0.56-1.18)	0.72 (0.49-1.05)
Previous users	1.28 (0.98-1.66)	1.39 (1.09-1.83)	0.40 (0.09-1.74)	0.44 (0.09-2.02)	1.23 (0.90-1.69)	1.22 (0.87-1.71)
Amount of statin usage (DDDs)						
883 DDDs or less	1.27 (0.98-1.64)	1.37 (1.05-1.78)	0.72 (0.22-2.40)	0.70 (0.21-2.41)	1.09 (0-74-1.60)	0.99 (0.66-1.47)
884-1,996 DDDs	1.07 (0.79-1.45)	1.16 (0.85-1.58)	1.08 (0.37-3.17)	1.06 (0.34-3.27)	1.39 (0.97-1.99)	1.30 (0.90-1.89)
1,997 DDDs or more	0.92 (0.65-1.31)	1.08 (0.75-1.55)	0.61 (0.14-2.72)	0.68 (0.15-3.16)	0.64 (0.41-1.02)	0.60 (0.37-0.96)
P for trend[3]	0.83	0.06	0.61	0.67	0.50	0.09
Years of statin usage						
2 years or less	1.21 (0.94-1.56)	1.33 (1.03-1.72)	0.70 (0.21-2.34)	0.75 (0.22-2.55)	1.07 (0.72-1.58)	1.05 (0.70-1.60)
3-5 years	1.14 (0.84-1.54)	1.19 (0.87-1.64)	0.79 (0.23-2.67)	0.76 (0.21-2.69)	1.34 (0.93-1.93)	1.20 (0.82-1.76)
6 years or longer	0.90 (0.62-1.31)	1.07 (0.73-1.58)	1.03 (0.28-3.76)	1.02 (0.27-3.85)	0.70 (0.45-1.09)	0.64 (0.40-1.01)
P for trend[3]	0.72	0.34	0.78	0.77	0.61	0.18
Intensity of statin usage (DDDs/year)						

260 DDDs/year or less	1.12 (0.85-1.47)	1.19 (0.89-1.58)	1.42 (0.57-3.53)	1.22 (0.47-3.18)	1.21 (0.85-1.72)	1.06 (0.74-1.53)
261-448 DDD/year	1.25 (0.94-1.66)	1.22 (0.98-1.94)	0.54 (0.13-2.30)	0.52 (0.12-2.31)	1.07 (0.73-1.57)	1.02 (0.69-1.51)
449 DDD/s/year or more	0.99 (0.72-1.36)	1.09 (0.78-1.52)	0.32 (0.04-2.37)	0.43 (0.06-3.33)	0.72 (0.44-1.17)	0.69 (0.42-1.14)
P for trend[3]	0.47	0.16	0.24	0.32	0.48	0.34

1 Users: statin usage continued until the end of follow-up; Previous use: statin usage after surgery but discontinued before the end of follow-up

2 Calculated with Cox regression model with model adjustment for age at surgery, tumor stage and Gleason grade, PSA-level at the time of diagnosis, surgical margin positivity and use of antidiabetic and antihypertensive drugs

3 Calculated by adding DDDs, years or DDDs/year of statin usage into the Cox regression model as continuous, time-dependent variable

Stratified analysis

In stratified analysis patient characteristics did not significantly modify the risk of disease recurrence or death by statin use before and after prostatectomy, with the exception of diabetes; statin users had lower overall risk of death only in men who had not used antidiabetic drugs (Table 4). The result was similar when antidiabetic drug users were limited to metformin users only. No difference by antidiabetic drug use was observed for risk of disease recurrence.

Gleason grade or pathological stage did not significantly modify the risk of disease recurrence or death among statin users (Table 4).

Of the tissue level risk markers Ki-67 modified the association between statin use before surgery and disease recurrence and death, the risk estimates being lower among statin users with higher expressions, i.e. unfavorable tissue markers (Table 4). The effect modification was not significant for statin use after surgery, although lower risk estimates for death among men with higher Ki-67 tumor expression were observed. Also EZH2 and ERG expression modified the association with

disease recurrence for both statin use before and after surgery.

Table 4. Risk of prostate cancer recurrence and death by statin use before and after prostatectomy. Analysis stratified by population and tumor characteristics. Cohort of 1,314 prostate cancer patients treated with radical prostatectomy at the Tampere University Hospital during 1995-2009

	Disease recurrence		Prostate cancer deaths		All deaths	
	Pre-operative use	Post-operative use	Pre-operative use	Post-operative use	Pre-operative use	Post-operative use
	HR (95% CI) multivar adj	HR (95% CI) multivar adj	HR (95% CI) multivar adj	HR (95% CI) multivar adj	HR (95% CI) multivar adj	HR (95% CI) multivar adj
Patient characteristics						
Age at surgery						
63 or younger	1.18 (0.82-1.70)	1.21 (0.85-1.73)	-	0.78 (0.14-4.40)	0.53 (0.24-1.16)	0.66 (0.34-1.30)
64 or older	1.07 (0.72-1.60)	1.02 (0.70-1.48)	2.55 (0.66-9.84)	1.26 (0.42-3.82)	0.99 (0.59-1.67)	0.73 (0.45-1.17)
P for interaction	1.00	0.85	0.26	0.50	0.45	0.79
PSA at diagnosis						
4.8 ng/ml or lower	1.08 (0.73-1.60)	1.23 (0.86-1.76)	0.85 (0.10-7.12)	0.90 (0.24-3.35)	0.97 (0.55-1.72)	0.74 (0.44-1.25)
Above 4.8 ng/ml	1.1 (0.76-1.59)	1.04 (0.72-1.49)	1.77 (0.37-8.65)	1.46 (0.40-5.39)	0.70 (0.35-1.36)	0.74 (0.42-1.32)
P for interaction	0.81	0.47	0.10	0.77	0.79	0.49
Pre-oper statin use						
Yes	-	1.30 (0.51-	-	-	-	0.53 (0.14-

		3.33)				2.03)
No	-	0.89 (0.62-1.28)	-	0.60 (0.17-2.14)	-	0.78 (0.50-1.22)
P for interaction		0.81		0.13		0.50
Antidiabetic drugs						
Yes	0.99 (0.52-1.87)	1.07 (0.59-1.95)	-	0.66 (0.03-13.05)	1.31 (0.61-2.82)	1.19 (0.55-2.59)
No	1.08 (0.81-1.45)	1.06 (0.80-1.41)	1.66 (0.47-5.87)	1.24 (0.48-3.21)	0.61 (0.35-1.06)	0.60 (0.38-0.96)
P for interaction	0.97	0.87	1.00	0.27	0.49	0.14
Antihypertensive drugs						
Yes	1.04 (0.76-1.43)	1.12 (0.84-1.49)	1.43 (0.41-5.02)	1.41 (0.55-3.58)	0.76 (0.47-1.23)	0.77 (0.51-1.16)
No	1.36 (0.82-2.25)	1.14 (0.64-2.01)	-	-	1.06 (0.37-3.03)	0.42 (0.10-1.76)
P for interaction	0.74	0.36	0.23	-	0.56	0.66
Tumor characteristics						
Gleason grade						
6 or lower	1.12 (0.72-1.74)	1.39 (0.94-2.06)	-	-	0.53 (0.27-1.05)	0.54 (0.31-0.95)
7-10	0.96 (0.69-1.34)	0.81 (0.57-1.14)	1.79 (0.50-6.41)	1.28 (0.49-3.35)	1.18 (0.67-2.11)	0.85 (0.48-1.52)
P for interaction	0.29	0.37	1.00	0.53	0.54	0.68
Pathologic stage						
T1-T2N0Mx	0.98 (0.70-1.35)	1.08 (0.78-1.49)	0.98 (0.12-8.30)	0.67 (0.08-6.00)	0.64 (0.38-1.09)	0.74 (0.46-1.20)

T3 and/or N1	1.25 (0.78-1.99)	0.93 (0.62-1.40)	1.48 (0.33-6.75)	1.10 (0.40-3.02)	1.27 (0.60-2.70)	0.63 (0.33-1.22)
P for interaction	0.35	0.75	0.37	0.95	0.32	0.73
Tissue markers						
Ki-67expression						
Median or below (0-5%)	5.73 (1.84-17.83)	1.56 (0.79-3.09)	-	1.02 (0.06-18.39)	3.88 (0.47-32.29)	1.10 (0.49-2.50)
Above the median (6% or more)	0.48 (0.11-2.12)	1.65 (0.66-4.09)	-	0.31 (0.02-5.79)	0.44 (0.10-2.03)	0.51 (0.18-1.45)
P for interaction	0.04	0.40	-	0.82	0.056	0.65
ERG expression						
No	0.21 (0.03-1.57)	0.77 (0.37-1.61)	-	0.50 (0.03-8.54)	-	0.66 (0.24-1.82)
Yes	3.06 (0.89-10.52)	1.39 (0.41-4.66)	-	0.09 (0.01-1.66)	0.61 (0.07-5.04)	0.35 (0.07-1.74)
P for interaction	0.06	0.046	-	0.44	0.91	0.45
EZH2 expression						
Median or below (0-27%)	5.54 (1.84-16.70)	1.86 (0.93-3.72)	-	0.44 (0.03-5.82)	3.49 (0.43-28.18)	1.47 (0.70-3.12)
Above median (28% or more)	0.50 (0.11-2.19)	1.11 (0.49-2.52)	-	-	0.64 (0.14-2.92)	0.21 (0.05-0.91)
P for interaction	0.024	0.056	-	0.99	0.74	0.48

4 DISCUSSION

In this study of 1,314 men who underwent radical prostatectomy statin use before or after the surgery was generally not associated with prostate cancer recurrence. However, the risk of recurrence was elevated in men with long-term and/or high-dose usage before surgery, and also during the first two years of statin use after surgery with risk returning to normal along with

continued use. Differing association with recurrence by pre- and post-operative usage suggests that it is not caused by statin use as such, but more probably by underlying factors correlated with statin use, such as dyslipidemia, previously reported to increase the risk of disease recurrence after prostatectomy (15). Long-term pre-operative users have had dyslipidemia for a long time, whereas men starting statins after prostatectomy have a new-onset dyslipidemia which is resolved with continued usage.

The association between pre-operative statin use and increased risk of recurrence was observed only in men with low Ki-67 proliferation index. In contrast, among men with high-Ki-67 expression and thus high risk of recurrence (16) statin users had lowered risk of recurrence and death. This suggests that statins may prevent disease progression in high-risk men, which is in line with previous reports on lowered prostate cancer mortality in statin users (17). Other tissue markers did not modify the association with the risk of death, but the risk of progression differed by EZH2 and ERG expressions, although the direction was not consistent. However the number of men with available tissue expression data was limited and these results are only indicative.

Protective effect of statins was supported by lowered risk of death observed with long-term statin use. The dose-dependent inverse risk trend was observed for statin use both before and after the surgery. Our analysis was limited by low number of prostate cancer deaths. Nevertheless, decreased risk estimates were observed also for disease-specific deaths, which also supports previous findings of lowered mortality in prostate cancer patients using statins (17), and demonstrates that increased risk of recurrence does not translate to higher risk of death in statin users.

Previous evidence on the association between statin use and prostate cancer recurrence have been inconsistent. In a study of 3,828 surgically managed patients from which 1,031 were statin users, Krane et al found that statin use was not associated with biochemical recurrence (18). However the mean follow-up time was only 26 months which is a relatively short period for prostate cancer recurrence to occur. Mondul et al did not find association between statin use and biochemical recurrence in a cohort study which had a median follow up of 7 years (19). They also examined the dose-response relationship and reported that statin use for one year or more (pre- or post-operatively) is not associated with biochemical recurrence compared with shorter usage. In a study of 1,261 patients Ritch et al showed that statin users were at higher risk for biochemical recurrence after prostatectomy compared to non-users (20). Hamilton et al detected that statin users have a 30% reduced risk for biochemical recurence and the association was dose-related (21). However

median follow-up in this study was 24 months for users and 38 months for non-users and there were baseline differences between the two groups.

Most previous studies had a relatively low proportion of statin users (around 20%) compared to ours (40%). Further, because most previous studies did not have information on statin doses and duration of use they were unable to assess dose-dependence. Furthermore, most of the previous studies had information only on pre-operative statin use, being unable to assess post-operative usage. This could lead to a significant bias towards the null because patients labelled as non-users at surgery may start statin use after surgery, causing exposure misclassification. Thus the strength of our study compared to most previous studies was the accurate information on dose and timing of statin use.

Two recent studies have examined the effect of post-operative statin use on prostate cancer outcomes. Allot et al found that statin use was significantly associated with 36% reduced risk of biochemical recurrence in a cohort of 1,146 radical prostatetomy patient who never received statins before surgery (8). This association was significant in non-black but not in black men. Although stratified analyses were carried out to rule out selection bias, the baseline characteristics in statin users were significantly better than non-users and that could explain the observed results. Due to the small number of events they were unable to estimate the association between statin use and prostate cancer mortality (8). In a study similar to ours Chao et al found that pre-operative or post-operative use of statins was not associated with biochemical recurrence or clinical disease progression, but reported a significant inverse trend by duration of post-operative statin use (22). However due to the inconsistencies they deduced that this dose-response relationship doesn't reflect true causal association, but they also had relatively short follow-up after prostatectomy (up to 5 years) (22). Our results support the latter study, with median follow-up almost twice as long.

Two meta-analyses assessing statin use and prostate cancer outcome after definitive treatment found no association between statin use and prostate cancer recurrence among prostatectomy patients, but there was evidence of significant heterogeneity among studies in both meta-analyses (6,23). Park et al suggested that the reduced risk of biochemical recurrence among statin users might be limited to men treated with radiation therapy and the possible reason for this could be statins acting as radiosensitizers (6). Another possible explanation for the risk decrease being clearer among statin users treated with radiation therapy is selection; this form of therapy is being used for management of locally advanced prostate cancer, whereas prostatectomy is often chosen only for treatment of

localized disease. Therefore radiation-treated men recur and progress more often, but for surgically treated men significantly longer follow-up times are needed to demonstrate differences in disease outcomes. Few such studies are published to date. Decreasing risk of death by long-term statin use in our study supports that statins could have beneficial effects on survival also in surgically treated men.

Our study had some limitations that should be considered. Firstly, although our median follow-up was longer than in most previous studies, it was still relatively short and number of prostate cancer deaths was low. Two thirds of recurrences occur within 3 years after surgery (24) and thus we were able to capture most early biochemical relapses. However, considerably longer follow-up will be required for sufficient number of prostate cancer deaths and metastases after surgery. Another limitation is that we had no information on serum lipid profiles, and thus could not evaluate effects of dyslipidemia on our results.

A unique strength of our study was that we were able to analyze tissue level risk markers by statin use in a subgroup of prostatectomy patients. Also, we were able to control for effects of simultaneous use of antidiabetic and antihypertensive drugs.

In conclusion, the use of statins does not decrease the risk of prostate cancer recurrence compared to non-users after prostatectomy in general, but long-term statin users have better survival. Statins may have a beneficial effect also on the risk of recurrence in the subgroup of men most likely to recur. Further studies with longer follow-up time are needed to clarify the long-term effects of statin use on prostate cancer-specific survival after prostatectomy.

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