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Statin use and the risk of recurrence after radical prostatectomy in a cohort of men with inherited and/or early-onset forms of prostate cancer

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Keywords

Prostate cancer recurrence; statin medications; biochemical recurrence; prostate cancer epidemiology; inherited prostate cancer; early-onset prostate cancer

Introduction

The effectiveness of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) inhibitors, or statin medications, in the treatment of hypercholesterolemia is well documented. As of 2004, 24 million Americans were using statin medications as part of a lipid lowering strategy.(1) In addition to reducing cholesterol, statins have a number of other beneficial effects that have led many to speculate whether this class of medications may be used for cancer chemoprevention. Although the role of chronic inflammation in prostate cancer is not completely understood, inflammation may create atrophic lesions serving as precursors to adenocarcinomas. (2) A study of lovastatin and simvastatin, two commonly prescribed statins, demonstrated the induction of apoptosis and cell growth arrest by these statins in prostate cancer cell lines. The underlying mechanism may be mediated through inactivation of Ras homolog gene family, member A (RhoA), which is overexpressed in many cancers and is associated with cell cycle and transcriptional control.(3)

The association between statin use and prostate cancer risk has been studied extensively with conflicting results. A meta-analysis of thirteen observational studies and six randomized controlled trials demonstrated that long-term statin use did not significantly affect the overall prostate cancer risk (Risk Ratio (RR)=0.93, 95% Confidence Interval (CI): 0.77–1.13). In contrast, five studies specifically examining statin use and the risk of advanced prostate cancer found a protective association between statin use and advanced disease (RR=0.77; 95% CI:0.64–0.93).(4) Radical retropubic prostatectomy (RRP) is the most common primary treatment for prostate cancer. Although RRP is curative for most patients with localized prostate cancer, approximately 20–30% will experience disease

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recurrence by 10 years post-surgery.(5) Statin medications have been hypothesized to alter the risk of recurrence after treatment for prostate cancer; however, studies findings have been conflicting. A meta-analysis of eight cohort studies assessing the risk of biochemical recurrence after definitive local therapy found that statins were not consistently associated with a reduced risk of recurrence and that the pooled estimate of hazard ratios did not differ from the null. (6)

Prostate cancer has a significant familial component and within families, prostate cancer risk is related to the number of affected men as well as the age of onset of affected relatives. Men with familial prostate cancer may be more motivated to use chemopreventative measures to reduce their risk of disease incidence and/or disease recurrence. To date, no studies of statin medication use have been conducted specifically focusing on men with inherited forms of prostate cancer. Therefore, we assess the association between statin use and risk of biochemical recurrence (BCR) after RRP men among men with inherited and early-onset forms of prostate cancer participating in a family-based study of genetic risk factors for prostate cancer.

Materials and Methods

Study subjects came from the University of Michigan Prostate Cancer Genetic Project (PCGP). Enrollment into the PCGP is restricted to (*a*) families with two or more living members with prostate cancer in a first- or second-degree relationship or (*b*) men diagnosed with prostate cancer at ≤55 years of age -regardless of a family history of the disease. Prostate cancer diagnoses are confirmed by medical record whenever possible. In addition, detailed clinical information relating to the diagnosis and treatment of prostate cancer, including Gleason score from biopsy and RRP, tumor stage, pre-operative PSA level, diagnosis date and pre-diagnostic and post-operative PSA, and age at diagnosis were obtained from medical records. Study procedures were approved by the University of Michigan-Institutional Review Board.

A biennial health update survey (HUS) was mailed to 1,362 eligible prostate cancer positive PCGP participants in June 2009 to obtain updates on information relevant to prostate cancer, overall health and statin medication use. Subjects who met the following inclusion criteria were included in this study: (i) diagnosed with prostate cancer, (ii) received RRP as their primary treatment, (iii) reported statin medication use status. A total of 539 subjects were available for analysis. The outcome of interest is biochemical recurrence defined as a single PSA test value of ≥0.4 ng/mL following an undetectable PSA (<0.1ng/mL) after RRP. Participants were asked to self-report all statin medication use data (name, start dates of use and end dates of use) over the last 10 years (1999–2009). In addition, statins were grouped into two classes 1) lipophilic or fat soluble statins including lovastatin (Altocor, Altoprev, Mevacor, Simcor), atrorvastatin (Lipitor, Caduet), simvastatin (Vytorin, Zocor), cerivastatin (Baycol, Lipobay) and 2) hydrophilic statins including pravastatin (Parachol), rosuvastatin (Crestor), and fluvastatin (Lescol). Potential confounders considered included daily NSAID use at time of survey (y/n), BMI, kg/m^2, at time of diagnosis (<25, 25–29.9, ≥30), decade of surgery (1990s, 2000s), Gleason grade at RRP (≤6, 7=3+4, 7=4+3 – 10), natural-log transformed pre-diagnostic PSA (continuous), age at time of surgery (continuous) and

pathologic stage (T2a, T2b and T3). All covariates were obtained from medical record review except for NSAID use and height and weight. In a subset of patients, Gleason grade at RRP was unavailable and substituted with Gleason grade at biopsy (n= 22). Descriptive statistics were calculated for all participants and by statin use status (ever users vs. never users). Descriptive analysis was performed using contingency tables and chi-square tests for categorical variables and using Student's T tests to compare means of continuous variables. Both crude (unadjusted) and covariate-adjusted Cox proportional hazard models were constructed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of BCR among ever-statin users compared with the referent group, never-statin users. Statin users were categorized as 1) current-users vs. non-current users and 2) ever-users vs. never-users. Statin medication use was categorized as a time-dependent variable initially defined in 1999 and updated annually until 2009 using the Lexis function implemented in the R Statistical Package 2.14.1 (http://www.r-project.org/) to split exposure time into annual increments.(7)In addition, separate stratified analyses were performed for lipophilic and hydrophilic statin users. The follow-up period was calculated from the time of surgery to the time of survey or recurrence. Statistical analyses were performed using SAS 9.2 (Statistical Analysis Systems Inc., Cary, NC, USA).

Results

Demographic, clinical and pathologic characteristics of study participants, by statin medication use, are displayed on Table 1. The overall mean (SD) age at surgery was 56.5 (7.6) years. Among the 539 participants, 97% were Caucasian and 2.4% were African-American. Subjects received their RRP treatment between 1995 and 2009. Based on self-report, 258 subjects were classified as ever-statin users and 281 subjects were never-statin users. Statin users were older at time of surgery as compared to non-statin users (58.0 years and 55.2 years, respectively; p value <0.001), had longer follow up times (101.5 months and 88.8 months, p value =0.009), and were more likely to have BMI values at time of diagnosis above 30 kg/m2, p value=0.003). Among subjects, 39.3% (n=212) and 48.4% (n=261) had one and two, respectively, prostate cancer affected family members. Statin users and non-statin users did not differ with respect to clinical characteristics including Gleason grade, clinical stage at diagnosis and pre-diagnostic PSA value. The mean duration of overall statin use among ever-users was 86.5 months. A recurrence was reported by 115 (21.3%) subjects during the follow up period. The percentage of ever-statin users reporting BCR was 23% as compared to 19.6% of and non-statin users reporting BCR (p value =0.30). [Table 1]

Of the 115 subjects who experienced recurrence, 60 (52.2%) were statin users and 55 (47.8%) were non-statin users. In Cox proportional hazard models, the HR of BCR among ever-statin users, modeled as a time-dependent covariate, was 0.96 (95% CI= 0.66–1.39 p =0.82) in crude analyses. This association between ever-statin use and BCR was similar after adjustment for age at surgery (years), BMI, Gleason, pre-diagnostic PSA, clinical stage and decade of surgery (HR=1.06, 95% CI=0.68–1.64, p value=0.81). In adjusted analysis, Gleason 7=3+4 pattern (compared to referent Gleason ≤ 6), Gleason 7=4+3 and 8–10 pattern (as compared to Gleason ≤ 6) and pre-diagnostic PSA (log transformed), as well as having RRP after 2000 (as compared to prior to 2000) were each associated with BCR. [Table 2] Further, no association between the duration of statin use and recurrence was observed

comparing subjects using statins for 5 years or more (n=149) to subjects whose total statin use duration was less than 5 years (n=100) (HR=0.932, 95% CI=0.53–1.63, *p* value =0.932)

No association between statin use and BCR was observed in analyses comparing lipophilic (n=196) statin users to non-statin users HR =1.20 (95% CI= 0.80–1.81), *p* value =0.43. Further, no association between statin use and BCR was observed in analyses comparing hydrophilic (n=81) statin users to non-statin users (HR=0.735 (95% CI= 0.35–1.54), *p* value =0.42). Nor was any association observed when comparing lipophilic (n=196) statin users to non-statin users. [Table 3] To assess whether the association between statins and BCR may be specific to advanced prostate cancers, men with high Gleason grade cancers were compared to men with low Gleason grade cancer. Among men with Gleason grade of 7=4+3 and 8–10 pattern cancers (n=87) (as compared to Gleason grade 6 or less cancers), statin use was not associated with BCR. Among men with Gleason grade 7=3+4 pattern cancers (n=255), statin use likewise was not associated with BCR (HR=1.15, 95% CI=0.72–1.83, *P* value=0.57). [Table 4]

Comment

In this retrospective cohort study of 539 men with inherited forms of prostate cancer treated with RRP, statin use was not associated with BCR. Furthermore, there was no association observed between statin useand BCR when stratifying by Gleason grade. A 21% rate of recurrence was observed in this study and is comparable to the rate of recurrence expected with 10 years of RRP.

Previous studies of the association between statin use and risk of recurrence have been inconsistent in their findings. Among 691 men treated with radiation therapy, statin use (median follow-up time of 50 months) was associated with improved freedom from biochemical failure and improved survival.(8) However, Ritch et al.(9) found an increased risk of BCR after post-operative statin use after a median follow-up time of six months. Park et al., conducted a meta-analysis of 13 studies assessing the association between statin medications and risk of recurrence after various treatments for prostate cancer and found that statins conferred a reduced risk in men treated with radiation therapy but not in those treated with RRP. (10) Among 1,319 men undergoing RRP, Hamilton et al. (11)found that statin use was associated with a 30% decreased risk of BCR and the associations occurred in a dose-dependent manner. Since we did not collect data on statin medication dose, we were prohibited from observing such a relationship. Further, a recent meta-analysis of 19 studies concluded that statins are not associated with the risk of prostate cancer incidence, but may be protective with respect to advanced prostate cancer.(4) Our study found that recurrence was strongly associated with pre-diagnostic PSA and high Gleason grade (7=4+3, 8–10), which are consistent predictors of BCR.(12, 13)

In this study, BMI was not associated with the risk of BCR in crude analysis or in an analysis adjusted for other clinical covariates. The association between BMI and prostate cancer has not been consistently reported in the literature. BMI has been hypothesized to decrease PSA levels and therefore, may complicate diagnosis.(14) In a study of over 3,000 patients who underwent RRP, obesity (BMI ≥30 kg/m^2) was associated with increased

disease grade, PSA levels and rates of positive surgical margins, however, these unfavorable prognostic factors did not translate into decreased biochemical recurrence-free survival.(15)

In both crude and adjusted models Gleason grade of 7=4+3 pattern and higher was significantly associated with BCR. In stratified models, comparing participants with high Gleason grade cancers with participants with low Gleason grade cancers (Gleason grade 6 and below), we did not observe any associations between statin use and the risk of BCR. However, if the true effect of statin use in reducing prostate cancer risk is specific to high-grade cancers, we may have been underpowered to detect such an association. The inconsistent results among studies of statin use and recurrence could be linked to residual confounding after attempting to control for clinical or pathologic characteristics that may be indicative of advanced prostate cancer. As none of the studies of prostate cancer recurrence and statins have been performed prospectively, we cannot conclude that the associations between statin use and prostate cancer risk or recurrence are not being driven by high-grade cancers with poorer pathologic features.

However, despite the conflicting results from observational studies, the findings from *in vitro* studies that statins may inhibit cancer cell growth, induce apoptosis(16) and cell cycle arrest (17) continue to fuel interest in exploring statin therapy as a potential chemopreventive agent in prostate cancer. Currently there are no guidelines as to the use of statin medications in cancer risk or prevention. Studying these agents in men with a family history may provide a motivated group of men to focus preventative strategies. Men with a family history of prostate cancer have demonstrated their willingness to use chemopreventive agents to decrease risk. (18)Further, BMI may be mediating the relationship between prostate cancer and statin use. This study may also be difficult to interpret in light of a study assessing men who were statin-users at the time prior to and during the time their RRP was performed and found that pre-operative PSA was lower in statin users and compared to non-statin users. (19) Whether the observed decrease in PSA measurements leads to a detection bias or to actual changes in cancer progression is unknown. However, if the effect of statin medication use was solely to lower PSA but not to decrease risk, we would expect studies to find increased prostate cancer-specific or cancer-specific mortality and after a long-follow period. However, in a matched case-control study, statin use was associated with a decrease in prostate cancer mortality (OR=0.37, p value <0.0001).(20)Further, a study of both PSA and prostate cancer risk among statin users concluded that although PSA was lower among statin users, the relative risk decrease in prostate cancer risk was not accounted for by the decrease in PSA. (21)These scenarios highlight the notion that there may potentially be biologic effects of statin use on the progression of prostate cancer, other than to lower PSA and induce a detection bias.

The strengths of this study include a long follow up period (mean=94.9 months) and a unique cohort of men with inherited forms of prostate cancer/early onset prostate cancer. Statin medication use was high among survey respondents. The PCGP cohort has been previously reported to have higher education and income levels.(22) The high statin use reported in this study may indicate a healthy user bias. Participants may be more likely to be screened frequently, possibly leading to less differential in PSA screening practices between statin and non-statin users. Men enrolled in this study do so voluntarily and may be more

likely to accurately report health updates, statin use and PSA testing history. This group represents a motivated group and is likely to have accurate recollection of PSA tests and medication use. In addition to statin use and recent PSA testing information asked on the 2009 HUS, participants were also asked to recall the date and treatment they received related to their initial prostate cancer diagnosis in the same survey. Among survey respondents, the concordance between information reported on the 2009 HUS and information previously confirmed through medical record review was very high (>98%). The mean follow-up period (post-surgery) was significantly longer in ever-statin users as compared to non-statin users (101.5 months vs. 88.8 months, *p* value =0.009). The longer follow-up period observed among statin users may indicate that there is a differential loss to follow-up by exposure in our study population.

This study has some limitations. Statin medication dose information was not collected from subjects and we were not able to examine a dose effect other than what we could characterize by the potency of the statin. We did not collect information on co-morbidities, cholesterol levels or other indicators of overall health. Confounding could have resulted from not controlling for other factors associated with statin use and risk factors for recurrence. Studies have shown that cholesterol levels may be associated with cancer risk.(23) Diabetes (treated or untreated) has been associated with an increased risk of BCR after prostatectomy.(24). Further, even in subjectsusing statins, we did not measure cholesterol levels and there is also a complex interplay between cholesterol and prostate cancer malignancy. A review of prostate cancer and cholesterol found that hypercholesterolemia is likely a risk factor for prostate cancer progression.(25)Such potential unmeasured confounders could have altered our association between statin use and BCR risk.

Our eligibility criteria specific response rate was low (41%). Given that our study sample consists of men who responded to the 2009 HUS, there is likely a response bias. We were unable to collect statin medication use data on men who were deceased, or were in poor health. However, we found that known prognostic factors (pre-diagnostic PSA, Gleason grade and pathologic stage) for BCR did not differ significantly between subjects who responded and subjects who did not respond (*p* value =0.76, 0.64, 0.41, respectively), indicating that response bias with respect to risk of disease may have not been considerable. Conclusions from this retrospective study based on self-report are limited by the nature of the study design.

Prostate cancer's high incidence and treatment-related morbidities make this disease an ideal target for chemoprevention. This is particularly true in the secondary prevention setting as the 20–30% recurrence rate among men treated with RRP presents a significant public health issue. This study did not identify an association between statin use and BCR in this population of men with inherited and/or early-onset prostate cancer.

Conclusions

Statins are a potential prostate cancer chemopreventive agent. In this study of men with inherited and/or early-onset prostate cancer, statin use was not associated with the risk of biochemical recurrence after prostatectomy. However, due to the limited number of men in

this study, this association may warrant further investigation, particularly in men with high-grade cancers who are known to be at risk for recurrence.

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Table 1

Demographic, Clinical and Pathological Characteristics of Study Participants according to Statin Use

Characteristic	All participants (n=539)	Statin Users * (n=258, 47.9%)	Non-Statin Users (n=281, 52.1%)	*a* value
Age at survey, Mean (SD)	64.5 (9.4)	66.5 (9.1)	62.6 (9.3)	<0.001 *c*
Age at surgery, Mean (SD)	56.5 (7.6)	58.0 (7.4)	55.2 (7.6)	<0.001 *c*
Follow-Up Time (months), Mean (SD)	94.9 (56.6)	101.5 (56.5)	88.8 (56.2)	0.009 *c*
Most Recent PSA Test Value, Mean (SD)	2.1 (19.1)	1.37 (13.4)	2.8 (23.0)	0.44 *c*
Race, No. (%)				
White	523 (97.0)	249 (96.5)	274 (97.5)	0.83 *b*
African-American	13 (2.4)	7 (2.5)	6 (2.1)	
Other	3 (0.56)	2 (1.0)	1 (0.4)	
PC affected relatives, No (%)				
0	46 (8.6)			
1	212 (39.3)			
2	261 (48.4)			
≥3	20 (3.7)			
BMI < 25.0 kg/m^2, No. (%)	148 (27.5)	53 (20.5)	95 (33.8)	0.003 *a*
BMI 25.0–29.9 kg/m^2	305 (56.6)	159 (61.6)	146 (52.0)	
BMI ≥ 30 kg/m^2	86 (16.0)	46 (17.8)	40 (14.2)	
Lipophilic Statin Users, No. (%)		196 (36.4)	n/a	----
Hyrdrophilic Statin Users		51 (9.5)	n/a	
Current NSAID User, No. (%)	270 (50.1)	156 (60.5)	114 (40.6)	<0.001 *a*
Non-user	269 (49.9)	102 (39.5)	167 (59.4)	
Gleason Grade**, No (%)				
≤6	240 (44.5)	116 (45.0)	124 (44.1)	0.87 *a*
7	180 (33.4)	83 (32.2)	97 (34.5)	
8–10	94 (17.4)	47 (18.2)	47 (16.8)	
Unknown	25 (4.7)	12 (4.6)	13 (4.6)	
Pre-Operative PSA, Mean (SD)§	7.5 (9.7)	7.9 (10.2)	7.1 (9.1)	0.38 *c*
Prostatectomy Year categories, No (%)				
< 2000	190 (35.2)	107 (41.5)	83 (29.5)	0.004 *a*
2000 – 2009	349 (64.8)	151 (58.5)	198 (70.5)	
Pathologic Stage, No. (%)				
T2a	74 (13.7)	25 (9.7)	49 (17.4)	0.05 *a*
T2b	294 (54.5)	145 (56.2)	149 (53.0)	
T3	113 (21.0)	54 (20.9)	59 (21.0)	
Unknown	58 (10.8)	34 (13.2)	24 (8.5)	
Duration of Statin Use, months, Mean (SD)		86.5 (57.5)	n/a	---

* Ever users

** Pathological Gleason Grade except 20 observations where pathological Gleason was missing and biopsy Gleason was substituted

*** Refers to male relatives enrolled in PCGP

§ Pre-diagnostic PSA missing for 58 subjects

[a] *P* value obtained using the Chi-square test,

[b] p value obtained using Fisher's exact test,

[c] *p* value obtained from Student's t test

Table 2

Crude and Adjusted Proportional Hazards Model for Statin Use and Risk of BCR

	Crude HR (95% C.I.)	Crude *p* value	Adjusted HR (95% C.I.)+	Adjusted *p* value
Current Statin Use (n=226)	0.96 (0.66–1.39)	0.82		
Ever User (n=258)	1.04 (0.72–1.49)	0.86	1.06 (0.68–1.64)	0.81
Age at time of surgery, yrs	0.99 (0.96–1.01)	0.23	0.97 (0.95–1.00)	0.07
BMI (kg/m^2), <25	ref			
BMI (kg/m^2), ≥25–30	1.25 (0.86–1.82)	0.25	1.31 (0.78–2.20)	0.31
BMI (kg/m^2), >30	1.20 (0.74–1.97)	0.46	1.35 (0.70–2.63)	0.37
NSAID Use	0.94 (0.65–1.35)	0.72	0.96 (0.62–1.48)	0.73
Pathological Gleason				
6	ref		ref	
7 (3+4)	1.07 (0.72–1.60)	0.74	1.62 (0.95–2.77)	0.08
7 (4+3) & 8–10	3.78 (2.59 – 5.55)	<0.01	3.63 (2.07–6.37)	<0.001
Pre-Diagnostic PSA* (ng/mL)	1.45 (1.14–1.84)	0.01	1.32 (1.02–1.70)	0.03
Clinical Stage				
T2a	ref		ref	
T2b	0.39 (0.26–0.59)	<0.01	0.58 (0.32–1.07)	0.08
T3	2.86 (1.94–4.22)	<0.001	1.26 (0.65–2.42)	0.50
Decade of Surgery				
<1999	ref		ref	
2000–2009	1.99 (1.26–3.13)	0.003	2.27 (1.36–3.80)	0.002

*Pre-Diagnostic PSA was log transformed

+Models adjusted for age at time of surgery, BMI, NSAID use, Gleason grade, pre-diagnostic PSA, clinical stage and decade of surgery

Table 3

Cox Proportional Hazards Models of association between a) Lipophilic statin use and BCR and b)Hydrophilic statin use and risk of BCR

	No.	Crude HR (95% C.I.)	Unadjusted p value	No.	Adjusted HR * (95% C.I.)	Adjusted p value
Lipophilic Statin User	196	1.16 (0.80–1.68)	0.43	169	1.20 (0.80–1.81)	0.37
Hydrophilic Statin Use	81	0.75 (0.38–1.48)	0.41	51	0.74 (0.35 – 1.54)	0.42

* Multivariate models adjusted for decade of prostatectomy, Gleason 7=3+4 pattern, Gleason ≥7 =4+3, log transformed pre-diagnostic PSA

Table 4

Cox Proportional Hazards Models of association between statin use and BCR comparing high Gleason grade cancers to low Gleason grade cancers

	No.	Adjusted HR * (95% C.I.)	Adjusted *p* value
Gleason 7=4+3, 8=10	87	1.01 (0.51–1.99)	0.98
Gleason 7=3+4	255	1.15 (0.72–1.83)	0.57
Gleason ≤ 6	197	Ref	

* Multivariate models adjusted for decade of prostatectomy, log transformed pre-diagnostic PSA, NSAID use and BMI