Postoperative statin use and risk of biochemical recurrence following radical prostatectomy: Results from the SEARCH database.

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Abstract

Objective

- To investigate the effect of postoperative statin use on biochemical recurrence (BCR) in PC patients treated with radical prostatectomy (RP) who never used statins before surgery.

Patients and Methods

- We conducted a retrospective analysis of 1,146 RP patients within the Shared Equal Access Regional Cancer Hospital (SEARCH) database.
- Multivariable Cox proportional hazards analyses were used to examine differences in risk of BCR between postoperative statin users versus nonusers.
- To account for varying start dates and duration of statin use during follow-up, postoperative statin use was treated as a time-dependent variable.
- In secondary analysis, models were stratified by race to examine the association of postoperative statin use with BCR among black and non-black men.

Results

- After adjusting for clinical and pathological characteristics, postoperative statin use was significantly associated with 36% reduced risk of BCR (HR 0.64; 95%CI 0.47-0.87; p=0.004).

- Postoperative statin use remained associated with reduced risk of BCR after adjusting for preoperative serum cholesterol levels.

- In secondary analysis, following stratification by race, this protective association was significant in non-black (HR 0.49; 95%CI 0.32-0.75; p=0.001) but not black men (HR 0.82; 95%CI 0.53-1.28; p=0.384).

Conclusion

- In this retrospective cohort of men undergoing RP, postoperative statin use was significantly associated with reduced risk of BCR.

- Whether the association between postoperative statin use and BCR differs by race requires further study.

- Given these findings, coupled with other studies suggesting that statins may reduce risk of advanced PC, randomized controlled trials are warranted to formally test the hypothesis that statins slow PC progression.

Introduction

Worldwide, prostate cancer (PC) is the second most commonly diagnosed cancer type and the sixth most common cause of cancer death among men (1). In 2013, it is estimated there will be 238,590 new cases and 29,720 deaths from PC in the US alone (2). For men with localized disease, radical prostatectomy (RP) is a common treatment option. However, approximately 30% of men experience biochemical recurrence (BCR) within 10 years of RP (3, 4). These men are at increased risk of metastasis and PC-specific death, particularly those with high-grade disease and/or rapid PSA kinetics (5).

The impact of statin use on PC risk and progression is controversial. While there is mixed evidence for an association between statin use and total PC risk (6-11), two meta-analyses have reported a significant association between statin use and reduced risk of advanced PC (6, 9). Furthermore, there are conflicting results regarding PC progression after primary treatment; while one meta-analysis found a significant protective effect of statin use on BCR after radiotherapy (12), three meta-analyses have reported no association between statin use and BCR following RP (12-14). However, the studies contributing to these meta-analyses examined statin use at the time of treatment. Given the widespread use of statins, it is likely that many "nonusers" became statin users after treatment, which may bias the results of these previous studies towards the null. Moreover, in terms of translating findings to randomized controlled trials and ultimately to clinical practice, it would be informative to ascertain whether beginning statin therapy *after* primary treatment could influence PC progression.

In this study, we examined the impact of postoperative statin use on BCR in a retrospective cohort of RP patients who never received statins before surgery from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Given epidemiologic data supporting an antineoplastic role for statins, we hypothesized that postoperative statin use would be associated with reduced risk of BCR following RP. In addition, given the paucity of literature on statins and PC in black men, we tested in secondary analyses whether associations differed between black and non-black men.

Patients and Methods

Study Population and Design

After obtaining institutional review board approval from each institution, data from patients undergoing RP between 1996 and 2009 at five Veterans Administration (VA) Medical Centers (Palo Alto, CA; West Los Angeles, CA; Durham, NC; Asheville, NC; Augusta, GA) were combined into SEARCH (15). SEARCH does not include patients treated with preoperative androgen deprivation or radiation therapy. From a total cohort of 2,921 men we identified 1,337 men treated with RP during this time period who never received statins before surgery. We excluded patients with missing data on preoperative PSA (n=6), preoperative body mass index (BMI; n=146), pathological Gleason score (n=7), and pathological features (n=32), resulting in a study population of 1,146 men.

Exposure assessment

Postoperative statin use (yes/no), time in months from RP to first issue of a statin prescription, available for all 1,146 men, were ascertained from VA computerized medical records. Information on type and dose of statins was unavailable.

Follow-up

Follow-up protocols were at the discretion of the treating physicians. BCR was defined as a single PSA>0.2 ng/mL, two consecutive concentrations at 0.2 ng/mL, or secondary treatment for detectable postoperative PSA. Men receiving adjuvant therapy for undetectable PSA were

considered non-recurrent at the time of adjuvant therapy, and their follow-up was censored at that point.

Statistical Analysis

Differences in demographic and clinicopathological factors between postoperative statin users (n=400; men who started a statin at any time after RP but before BCR) and statin nonusers (n=746; men who were never prescribed a statin, or who began statin use after BCR) were examined using t-tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables.

Differences in risk of BCR between postoperative statin users and nonusers were analyzed using Cox proportional hazards analyses. Given that not all postoperative statin users began using statins immediately after RP, we treated postoperative statin use as a time-dependent variable, in order to account for varying start dates and duration of statin use during the follow-up period. Patients with missing follow-up (n=2) were excluded from Cox models. All assumptions for the Cox models were tested and met for all covariates. Cox models were adjusted for demographic information, clinical factors, and pathological factors. Baseline demographic information included age at surgery (continuous), surgery year (continuous), race (black vs. non-black), and BMI (continuous; log-transformed). Clinical factors included preoperative PSA (continuous; log-transformed). Pathological features included pathological Gleason score (2-6, 7, 8-10), extracapsular extension, seminal vesicle invasion, positive margins, and positive lymph nodes. Models were also adjusted for center.Secondary, stratified analyses were conducted to

examine whether the association between postoperative statin use and BCR differed between black (n=502) and non-black (n=644) men, adjusting for aforementioned demographic, clinical and pathological characteristics.

Statistical analyses were performed using Stata 13.0 (Stata, Corp., College Station, TX). Statistical significance was two-sided with $p<0.05$.

Results

Of 1,146 men that did not have exposure to statins prior to RP, 400 (35%) used statins after RP and before BCR and thus were classified as postoperative statin users. Overall, postoperative statin users had lower median preoperative PSA (5.9 vs. 7.1 ng/ml; p<0.001), higher median BMI (27.6 vs. 27.1 kg/m^2; p=0.029), lower biopsy and pathological Gleason scores (p<0.001 & p=0.001, respectively), fewer positive margins (40% vs. 50%; p=0.001) and less seminal vesicle invasion (5% vs. 11%; p=0.002). Postoperative statin users also had higher median pre-surgery serum cholesterol (202 vs. 185 mg/dl; p<0.001), relative to nonusers (Table 1). There was no association between postoperative statin use and age, race, clinical stage, extracapsular extension, or lymph node involvement.

The median follow-up time among men who did not recur was 76.2 months (IQR: 45.1-108.8). Postoperative statin users had earlier median year of surgery relative to nonusers (2002 vs. 2003; p<0.001) and significantly longer follow-up relative to nonusers (92.7 vs. 59.9 months; p<0.001). Sixty five postoperative statin users (16%) and 337 nonusers (45%) experienced BCR, giving rise to a total of 402 patients who experienced BCR during the follow up period (35% of the total patient cohort). Among postoperative statin users, median time from surgery to first issue of statins was 26.7 months (IQR: 12.4 – 47.3) and median time from first issue to BCR for those who recurred was 25.4 months (IQR: 13.5-54.9). There was a trend towards reduced risk of BCR among postoperative statin users versus nonusers, though this did not reach statistical significance (HR 0.75; 95%CI 0.56-1.00; p=0.051; Table 2). However, after adjusting for

demographic, clinical and pathological characteristics, postoperative statin use was significantly associated with 36% reduced risk of BCR (HR 0.64, 95%CI 0.47-0.87; p=0.004; Table 2).

Given that preoperative cholesterol levels differed by postoperative statin use, together with some epidemiologic data suggesting an association between lower cholesterol levels and improved clinical outcomes in PC (16), we adjusted for preoperative serum cholesterol levels in the subset of 704 patients for whom cholesterol levels within the year prior to surgery were available. When analysis was limited to only these patients and adjusted for pathological and clinical characteristics (but not cholesterol), the association between postoperative statin use and reduced risk of BCR persisted (HR 0.62; 95%CI 0.42-0.92; p=0.017). After adjusting for serum cholesterol in this subset, postoperative statin use remained significantly associated with reduced risk of BCR (HR 0.58; 95%CI 0.39-0.87; p=0.008).

In secondary analysis, we examined whether the protective association of postoperative statin use with BCR differed according to race by stratifying our cohort into black (n=502) and non-black men (n=644). Similar to our cohort as a whole, both black and non-black postoperative statin users had lower PSA levels, higher serum cholesterol, less recent year of surgery, longer follow-up time and lower biopsy Gleason score, relative to black and non-black statin nonusers, respectively (all $p<0.03$; data not shown). In addition non-black postoperative statin users had lower pathological Gleason score, fewer positive margins and less seminal vesicle invasion, relative to non-black statin nonusers (all $p<0.003$; data not shown). After adjusting for demographic, clinical and pathological characteristics, we found a significant association of postoperative statin use with reduced risk of BCR only among non-black men (HR 0.49; 95%CI

0.32-0.75; p=0.001), with no significant association among black men (HR 0.82; 95%CI 0.53-1.28; p=0.384) (Table 3).

Discussion

In this retrospective cohort of 1,146 men who never used statins prior to RP, we found that postoperative statin use was associated with a significant 36% decreased risk of BCR. Of note, we previously reported that *pre*operative statin use was associated with a significant 30% decreased risk of BCR within the SEARCH database (17). While this association did not differ by race in our previous study (17), in this study we found a significant association between postoperative statin use and reduced risk of BCR among non-black men, with no statistically significant association among black men. These results, which require confirmation in future studies, suggest that postoperative statin use may reduce risk of BCR among non-black PC patients undergoing RP.

Of a total of five meta-analyses published to date, four have reported a null association between statin use and total PC risk (6-8, 10). However, the largest and most recent meta-analysis of over 56,000 PC cases and nearly two million controls reported that statins had a significantly protective effect on total PC risk, albeit with a modest 7% reduction in PC incidence (9). Only two meta-analyses separated advanced from total PC and both found statin use was significantly associated with 20% (9) and 23% (6) reduced risk of advanced PC. Regarding PC outcomes after treatment, three meta-analyses examined the effect of statin use on BCR after definitive primary treatment. Of these, two reported no association between statin use and BCR following RP (13, 14), although the authors noted that substantial heterogeneity among studies may have contributed to this null finding (14). The third meta-analysis found a significant 32% reduction in risk of BCR after radiotherapy, but no association between statin

use and BCR after RP (12). The only study to our knowledge which specifically examined the impact of postoperative statin use on PC progression reported null findings (18). Despite similar numbers of PC patients, follow-up time was shorter than our study and there were less than half the number of BCR events. Thus, there may have been insufficient power to detect a modest association between post-RP statin use and BCR, though the prior study did not even suggest a trend for lower recurrence risk among statin users (18).

There are multiple biologic mechanisms by which statins may exert antineoplastic effects, both directly via mevalonate pathway inhibition and indirectly via cholesterol reduction (19). Cholesterol promotes PC cell growth both *in vitro* and in xenograft models via lipid raft-mediated Akt signaling (20). Moreover, cholesterol is the precursor for sex steroid synthesis and studies using xenograft models of human PC have demonstrated that pharmacologic lowering of serum cholesterol reduces tumor androgen levels and slows PC growth (21). Furthermore, direct inhibition of the mevalonate pathway by statins prevents prenylation of small G-proteins, Ras and Rho, thus inhibiting cellular proliferation and survival (22). Finally, statins have been shown to reduce inflammation and inhibit angiogenesis in both *in vitro* and *in vivo* models (22). Thus, the biological plausibility of our finding that postoperative statin use is associated with reduced risk of BCR is supported by multiple lines of evidence.

In addition to various detection biases and socioeconomic factors, there is some evidence that race-specific differences in tumor biology may contribute to the PC racial disparity (23, 24) and several of these pathways are known statin targets. For example, black race is associated with shorter androgen receptor (AR) CAG repeats resulting in enhanced AR signaling (25), potentially

contributing to resistance to the intra-prostatic androgen-lowering effects of statins (21). Additionally, black race has been associated with a greater degree of prostatic inflammation (23), leading us to speculate that the anti-inflammatory effects of the statins may not completely counteract this pro-tumor microenvironment. Moreover, a recent meta-analysis found that non-white individuals were less likely to adhere to statin therapy than white individuals (26) and thus, even if statins are equally efficacious at reducing PC progression in black and non-black men, lower compliance with statin use among black statin users during our follow-up period may bias our results for black patients towards the null. Indeed, we were unable to assess whether patients took statins continuously from their earliest issue date to end of follow-up. Finally, given our reduced sample size, it is possible that the lack of a statistically significant association between postoperative statin use and risk of BCR among black men could be attributable to type II error. Given this study is the first evidence of a possible race-specific effect of statins on PC progression, this finding requires further testing in future studies.

Several potential limitations of our study should be considered. First, we lacked sufficient data to examine postoperative statin dose and thus could not assess the presence of a dose-response relationship. Neither did we have access to statin type although a previous analysis of SEARCH revealed that simvastatin accounted for 72% of preoperative statin use (17), thus this figure is likely similar for postoperative statin use. Second, we had relatively few castrate-resistant PC, metastasis and PC-specific mortality events and thus could not examine differences in risk of these long-term PC outcomes between postoperative statin users and nonusers. Finally, as with all observational studies of retrospective design, treatment allocation

was not randomized. Despite adjusting for demographic, clinical and pathological features, it is likely statin users and nonusers differed in other ways that we could not control for. This may have given rise to residual confounding which could have impacted our results in ways that we were unable to assess. For example, men prescribed statins for cholesterol reduction may also have adopted a healthier lifestyle through dietary modification, weight loss and exercise, all of which have previously been suggested to contribute towards improved PC outcomes (27, 28).

These limitations are balanced by a key strength of the current study. Specifically, previous studies examining statin use and PC outcomes after treatment defined statin users according to use at time of treatment (12-14) and given the extremely widespread use of statins, it is likely that many "statin nonusers" began taking statins after treatment. This may bias the results of these studies towards the null and indeed the majority of existing studies reported a null association between statin use and PC outcome (13, 14). Since our cohort was based upon men who never used statins prior to RP, and subsequently categorized men according to *post*operative statin use or nonuse, this potentially important source of bias was avoided.

In summary, postoperative statin use was associated with 36% reduced risk of BCR in this retrospective cohort of RP patients, none of whom took statins prior to surgery. In secondary stratified analysis, this protective association was found to be significant only among non-black men. Together, these data provide support for conducting randomized controlled trials to assess the effect of postoperative statin use on BCR and longer-term PC outcomes including castrate-resistant PC, metastasis and PC-specific mortality. These future studies will help to determine whether these well-tolerated, cost-effective and widely-prescribed drugs may play a

beneficial role in PC treatment in addition to their proven role in preventing cardiovascular mortality.

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Table 1: Demographic, clinical, and pathological characteristics of postoperative statin users relative to nonusers

	Statin Nonusers (N=746; 65%)	**Statin Users** (N=400; 35%)	**P-value**[¤]
Age, mean ± SD	60.7 ± 6.5	60.6 ± 6.3	0.714[†]
Race, n (%)			0.244[‡]
White	378 (51)	205 (51)	
Black	334 (45)	168 (42)	
Other	34 (5)	27 (7)	
PSA (ng/ml), median (Q1–Q3)	7.1 (5.1-10.7)	5.9 (4.7-9.1)	<0.001[§]
BMI (kg/m^2), median (Q1–Q3)	27.1 (24.3-30.1)	27.6 (25.1-30.3)	0.029[§]
Cholesterol (mg/dl)*, median (Q1–Q3)	185 (165-208)	202 (181-224)	<0.001[§]
Year of surgery, median (Q1–Q3)	2003 (2000-2006)	2002 (1998-2004)	<0.001[§]
Follow-up months after RP**, median (Q1–Q3)	59.9 (31.0-90.4)	92.7 (68.7-124.2)	<0.001[§]
Biopsy Gleason score, n (%)			<0.001[‡]
2 – 6	439 (60)	281 (71)	
7	228 (31)	82 (21)	
8 – 10	68 (9)	33 (8)	
Clinical Stage*, n (%)			0.384[‡]
T1	456 (64)	236 (61)	
T2/T3	257 (36)	149 (39)	
Pathological Gleason score, n (%)			0.001[‡]
2 – 6	282 (38)	192 (48)	
7	374 (50)	178 (45)	
8 – 10	90 (12)	30 (8)	
Positive Margins, n (%)	373 (50)	160 (40)	0.001[‡]
Extracapsular Extension, n (%)	156 (21)	71 (18)	0.201[‡]
Seminal Vesicle Invasion, n (%)	80 (11)	21 (5)	0.002[‡]
Lymph Node Involvement, n (%)	12 (2)	3 (1)	0.476[‡]

RP=radical prostatectomy; SD=standard deviation; PSA=prostate specific antigen; BMI=body mass index; Q1=25th percentile; Q3=75th percentile

*Cholesterol data was only available on 704 patients, biopsy Gleason on 1,131 patients, and clinical stage on 1,098 patients

** Median follow-up time is among patients who did not recur

[¤] p-values computed using [†]t-test, [‡]chi-square, or [§]rank sum

Table 2: Risk of biochemical recurrence among postoperative statin users relative to nonusers

	Hazard Ratio	**95% CI**	**P-value**
Crude	0.75	(0.56-1.00)	0.051
Adjusted*	0.64	(0.47-0.87)	0.004

*Adjusted for age, race, PSA, BMI, pathological Gleason score, year of surgery, positive surgical margins, extracapsular extension, seminal vesicle invasion, lymph node involvement and center

Table 3: Risk of biochemical recurrence among postoperative statin users relative to nonusers stratified by race

	Hazard Ratio*	**95% CI**	**P-value**
Non-black men	0.49	(0.32-0.75)	0.001
Black men	0.82	(0.53-1.28)	0.384

* Adjusted for age, PSA, BMI, pathological Gleason score, year of surgery, positive surgical margins, extracapsular extension, seminal vesicle invasion, lymph node involvement and center