Preoperative Statin Use Associated with Lower PSA But Similar Prostate Size and Histopathologic Outcomes: Implications for Active Surveillance?

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Purpose: The potential effects of statins on clinical and histopathologic variables, prostate size, or PSA density (PSAD) and resulting influences on active surveillance eligibility have not been adequately explored. This study examines the effect of statins on prostate specimens following prostatectomy.

Materials and Methods: Patients that received robotic-assisted laparoscopic prostatectomy (RALP) (n = 2,632) were dichotomized according to preoperative statin use. Logistic regression was used to evaluate associations between statin use and patient clinical and pathological characteristics.

Results: Men using statins at the time of prostatectomy were older (61.6 ± 6.4 versus 58.8 ± 7.2 years, $P < .001$), and had poorer health status ($P < .001$). Biopsy Gleason grade, clinical stage and prostate size were similar among the two groups, although statin users had lower diagnostic PSA levels (5.5 ± 3.6 versus 6.3 ± 4.9 ng/mL, $P < .001$) and PSAD (.12 versus .13, $P = .001$).

Conclusion: Men taking statins at the time of prostatectomy had similar histopathologic characteristics to non-users, despite having significantly lower serum PSA, being older and having similar sized prostates. This supports prior studies suggesting a PSA reduction effect of statins may warrant consideration of statin usage in decision algorithms for active surveillance.

Keywords: active surveillance; neoplasm; PSA; robotic prostatectomy; prostate; Statins.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are one of the most-prescribed classes of medications worldwide.(1) They have long been used in the management of cholesterol related conditions, but their potential role as a chemopreventive agent is the subject of recent debate. Many investigations have focused specifically on their relationship to prostate cancer. Though evidence are equivocal on the link between statin use and prostate cancer incidence(2,3). Several studies have shown decreased rates of aggressive disease(4,5) and disease recurrence(6-8) with statin use, potentially due to either the anti-inflammatory properties or nascent anti-neoplastic effects of the statins themselves. Statins were not related to recurrence rate in other studies.(9,10)

In contradistinction, one recent report demonstrated increased rates of aggressive disease and higher risk of biochemical recurrence in patients on statins.(11) It is possible that the varied findings in aggressive and recurrent outcomes may be due to the lower serum PSA concentrations found among patients taking statins confounding referral and biopsy/treatment patterns. (12-14) The use of statins have been clearly shown to reduce serum PSA concentration but to our knowledge has not yet been fully evaluated in the context of active surveillance (AS) for low-risk prostate cancer. AS protocols are largely based on parameters that include biopsy Gleason score and PSA concentration, with some protocols also incorporating other factors such as PSA density (PSAD: PSA concentration divided by prostate volume).(15)

Other drugs, such as 5-alpha reductase inhibitors, have been shown to lower both PSA and prostate size.(16) Similarly, statins have been shown to lower PSA to a greater degree than prostate size, potentially leading to an "artificially" lowered PSAD.(17) Thus, it is possible that statin use may affect the qualification of certain patients for AS protocols based on an "artificially low" PSA and/or PSAD. In this context we sought to investigate the effects of statins on preoperative PSA, prostate size, and the resulting implications for AS eligibility.

MATERIALS AND METHODS

Under institutional review board approval at Lenox Hill Hospital, 2,632 patients were considered for enrollment in this study who underwent robotic assisted laparoscopic prostatectomy (RALP) at our institution between May 2004 and July 2012. This is a retrospective analysis on a database of patients diagnosed with prostate cancer. Patients' diagnosis was based on pathology proven presence of prostate adenocarcinoma. No patient was considered for surgery based on an abnormal PSA level per se. Investigated variables included demographic information, American Society of Anesthesiology score, preoperative diagnosis of diabetes, preoperative

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Table 1. Demographic and clinical characteristic of patients in the study

		No Statin Use N = 1283 (67%)	Statin Use N = 630 (33%)	*p* value
Age, years; mean ± SD		58.8 ± 7.2	61.6 ± 6.4	< .001
Race; N(%)	White	990 (77%)	543 (86%)	< .001
	Black	176 (14%)	42 (7%)	
	Other	117 (9%)	45 (7%)	
BMI Categories; N(%)	< 24.9	318 (25%)	129 (21%)	.11
	25.0-29.9	680 (53%)	349 (55%)	
	> 30	285 (22%)	152 (24%)	
Diabetes; N(%)	No	1225 (96%)	554 (88%)	< .001
	Yes	58 (4%)	76 (12%)	
ASA; N(%)	1	71 (6%)	5 (1%)	< .001
	2	974 (75%)	375 (59%)	
	3	234 (18%)	243 (39%)	
	4	4 (1%)	7 (1%)	

5-alpha reductase inhibitor usage, statin use, body mass index (BMI), and standard histopathologic outcomes (pathologic Gleason score, prostate weight, pathologic stage, margin status, extracapsular extension, perineural invasion, seminal vesicle involvement, lymphovascular invasion). Prostatectomy specimens were sectioned in quadrants and mounted in standard fashion. All radical prostatectomy specimens were examined by dedicated genitourinary pathologists.

Statin use was defined as any hMG-CoA reductase inhibitor taken by the patient prior to surgery. This information was driven from the patient chart at the hospital and self-reported list of drugs at office visit. Positive surgical margins on pathologic examination were categorized as either focal or extensive (< 3 or ≥ 3 mm, respectively).[18] Biochemical recurrence was defined as a single serum PSA measurement greater than .2 ng/mL beyond 6 weeks after surgery.

Pathologic weight was used as a surrogate for prostate volume, which has been validated as the preferred measurement of prostate size in RALP cohorts in previous studies.[19] PSA density was then approximated by dividing preoperative PSA by this surrogate volume.

Baseline characteristics and histopathologic outcomes were reported using means for continuous variables and proportions for categorical variables. A logistic regression was performed utilizing log-transformed values for PSA. T-tests or ANOVA were used to compare continuous variables and chi-square tests were used to compare categorical variables between statin users and non-users. A Cox proportional hazards model was created to assess predictors of biochemical recurrence using enter method. Age at diagnosis, race, ASA scale, pathologic Gleason score, pathologic stage, clinical stage, prostate weight, statin use and preoperative PSA level were used in the analysis. Significance was defined as a two-sided p value < .05. Analyses were performed using SPSS version 20 (IBM Inc., Armonk, NY).

RESULTS

In total, 1,913 of 2,632 patients had complete clinical and medication records and were included in analysis. Whites comprised 77% of the cohort, blacks comprised 11%, and all other races comprised 9%. Of all patients, 630 (33%) were taking statins preoperatively. Demographics of the two groups are presented in **Table 1**. The group of statin users were older (61.6 ± 6.4 versus 58.8±7.2 years, $P < .001$), more likely to be diabetic (12% vs. 4%, P=.001), had fewer blacks (7% vs. 14%, $P < .001$), and had slightly higher, but not significantly different, BMI (27.8 vs 27.5, $P = .09$). The statin group also had more comorbidities as measured by the proportion with ASA scores >2 (40% vs. 19%, $P < .001$). Forty-nine patients (23 statin users, 26 non-users, $P = .03$) were taking 5-alpha reductase inhibitors preoperatively. Patients taking 5-alpha reductase inhibitors were excluded from the analysis in PSA level.

Preoperative disease characteristics of the two groups are presented in **Table 2**, and histopathologic outcomes among the two groups are presented in **Table 3**. Preoperative clinical staging and D'Amico risk were similar with the vast majority of both groups having a clinical stage of T1c or below, and low or intermediate risk prostate cancer. Proportions of biopsy Gleason sums were also similar between the groups.

The mean preoperative PSA was significantly lower among the statin group than among the non-statin group (5.6 vs. 6.4 ng/mL, $P < .001$). This finding persisted in multiple subanalyses that divided patients into groups of similar ages, prostate weights, tumor volumes and pathologic stages. Statin users were also more likely to have presented with initial PSA values less than 4 ng/mL (32% vs. 24%, $P < .001$) and less likely to have presented with initial PSA values ≥ 10 ng/mL (7% vs. 11%, $P < .001$). There were no differences in clinical stage between statin users and non-users who were above and below each respective PSA threshold.

Additionally, the mean prostate weight was similar be-

Table 1. Preoperative characteristics of patients in the study

		No Statin Use N = 1283	Statin Use N = 630	*p* value
PSA Density; mean ± SD*		0.13 ± 0.10	0.11 ± 0.08	.001
PSA; mean ± SD □		6.3 ± 4.9	5.5 ± 3.6	< .001
PSA Categories; N(%)	< 2.5	64 (5%)	51 (8%)	< .001
	2.5-4.0	246 (19%)	149 (24%)	
	4.1-9.9	828 (65%)	387 (61%)	
	> 10	145 (11%)	43 (7%)	
Biopsy Gleason Sum; N(%)	< 6	696 (54%)	333 (53%)	.84
	7	476 (37%)	240 (38%)	
	> 8	111 (9%)	57 (9%)	
Clinical Stage; N(%)	T1c and Below	1092 (85%)	530 (84%)	.57
	T2 and Above	191 (15%)	100 (16%)	
D'Amico Risk; N(%)	Low	649 (51%)	313 (50%)	.88
	Intermediate	498 (39%)	252 (40%)	
	High	136 (11%)	65 (10%)	

* Patients taking 5-alpha reductase are not included in the analysis

tween both groups (51.0 g vs. 51.6 g, $P = .52$). PSA density, calculated using preoperative PSA divided by pathologic weight, was significantly lower among statin users compared to non-statin users (.12 vs. .13, $P = .001$). Further, the range of PSAD was much smaller among statin users (.02-.75) than non-statin users (0 - 1.31).

There were no significant differences in pathologic staging, tumor volume or pathologic Gleason scores between statin users and non-users. Median and mean follow-up were similar between the two groups (median 16.4 and 14.4 months for statin users and non-users, respectively ($P = .19$), both with a mean of 20 months). Biochemical disease-free survival (BDFS) rates 2 years post-operatively were also similar (94% vs. 92% for statin users and non-users, respectively, $P = .23$). In logistic regression models (**Table 4**), preoperative statin usage was a significant predictor of PSA concentration (95% confidence interval (CI) = -.069 - -.023), $P < .001$), along with age (95% CI = .002 - .005, $P < .001$), Gleason score on biopsy (95% CI = .081 - .113, $P < .001$), and prostate weight (CI 95% = .002 - .003, $P < .001$). In cox regression analysis, pathologic Gleason score (hazard ratio (HR) = 9.3, 95% CI = 2.2 - 38.8, $P = .002$), pathologic stage (HR = 3.2, 95% CI = 2.1 - 4.9, $P < .001$) and preoperative PSA level (HR = 4.9, 95% CI = 2.5 - 9.5, $P < .001$) but not statin usage (HR = .77, 95% CI = .48 - 1.08, $P = .11$) were predictive of biochemical recurrence.

DISCUSSION

Statins are the most commonly prescribed medications for hypercholesterolemia, and are currently used by over 24 million Americans,[20] a number that continues to rise.[21] Aside from their use in primary, secondary and tertiary prevention of cardiovascular morbidity and mortality, many studies have focused on possible antineoplastic effects as they relate to prostate cancer prognosis and PSA screening.[22] Despite early studies that demonstrated an inverse relationship between prostate cancer incidence and statin use, recent reviews and meta-analyses have not shown conclusive evidence to support such an association.[2,3] However, a recent meta-analyses on 13 paper with 100,536 patients conclude that statin use is associated with better overall and prostate cancer specific survival.[23] Some studies have suggested that statins decrease the likelihood of advanced or aggressive disease, rather than preventing de novo prostate cancer incidence.[4,5] Possible mechanisms proposed include statins' effect on inflammation and angiogenesis.[24] It has also been postulated that statins' reduction of cholesterol-based lipid rafts, which regulate certain apoptotic signaling pathways such as Akt, may be an important mechanism behind these findings.[25] Loss of low density Lipoprotein receptor regulation with a possible role for statins has been proposed in prostate cancer cells as well.[26] In our study we could not find any difference in pathologic characteristics and pathologic stage of the prostate cancer between statin users and non-users.

Aside from a potential therapeutic benefit, statins' effect on clinical parameters may have an impact on screening and treatment options for prostate cancer. Statins have been consistently shown to reduce serum levels of PSA.[12-14] In this higher PSA population, in whom prostate cancer is heavily screened, the impact of lowered PSA values in relation to delayed diagnosis remains to be defined. Our study demonstrated that patients using statins had lower PSA level at all stages of the disease. Though the effects of statins on screening and surgically treated populations have been described, the influence on eligibility for AS protocols, and the po-

Table 3. Surgical pathology characteristics of patients in the study

		Non-Statin Users N = 1283	Statin Users N = 630	*p* value
Gleason Sum; N(%)	< 6	308 (24%)	152 (24%)	.40
	7	905 (71%)	434 (69%)	
	> 8	70 (6%)	44 (7%)	
Prostate Weight (g): mean		51.6 (20.3)	50.9 (17.6)	.52
Pathological Staging; N(%)	< T2	993 (77%)	493 (78%)	.67
	> T3	290 (23%)	137 (22%)	
Lymph node involvement; N(%)		9 (0.9%)	1 (0.2%)	.12
Margins; N(%)	Negative	1021 (80%)	516 (82%)	.43
	Focal	182 (14%)	82 (13%)	
	Extensive	80 (6%)	32 (5%)	
Extracapsular Extensions; N(%)	No	1000 (78%)	503 (80%)	.34
	Yes	283 (22%)	127 (20%)	
Tumor in Seminal Vesicles; N(%)	No	1204 (94%)	592 (94%)	.91
	Yes	79 (6%)	38 (6%)	
Perineural Invasion; N(%)	No	277 (22%)	132 (21%)	.75
	Yes	1006 (78%)	498 (79%)	
Lymphovascular Invasion; N(%)	No	1230 (96%)	612 (97%)	.17
	Yes	53 (4%)	18 (3%)	

tential treatment benefit for patients on such protocols, has not yet been explored. The ability to forego or defer treatment in active surveillance hinges on prognostication: the ability to identify parameters that will predict low-risk disease with an acceptable degree of certainty. These protocols tend to be based on biopsy Gleason score, clinical stage, total PSA, and often PSA density in addition to other factors.[15] Imaging studies including multiparametric magnetic resonance imaging (mpMRI) are under investigation to provide sound information in patients undergoing AS protocols. Although primary investigations have provided promising results, the role

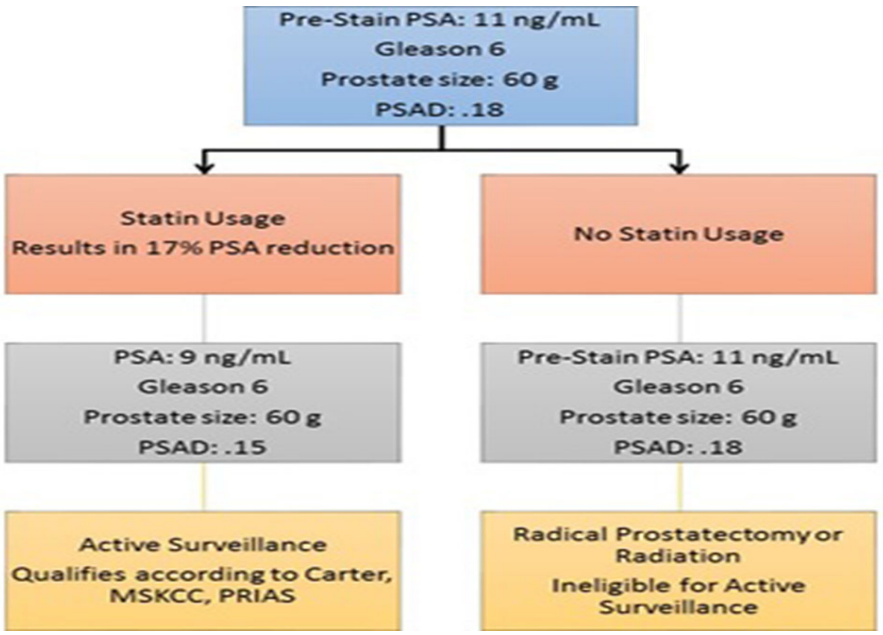

Figure 1. Hypothetical influence of statin use in patient eligibility for active surveillance protocols

Table 4. Clinical Features Predicting Log Transformed PSA*

	Beta	95% CI	*p* value
Statin Usage	-.046	-.069, -.023	< .001
Age	.004	.002, .005	< .001
Race	.026	.009, 0.044	.004
Year of Surgery	.002	-.005, 0.009	.57
Biopsy Gleason	.097	.081, 0.113	< .001
Clinical Stage	-.020	-.050, 0.011	.20
BMI	-.001	-.017, 0.015	.87
ASA	.008	-.013, 0.029	.45
Diabetes Status	.013	-.029, 0.056	.54
Path Weight	.003	.002, 0.003	< .001

*Patients taking 5-alpha reductase inhibitors are not included in the analysis

of imaging in AS is still to be determined.[27]

As statins lower PSA levels, patients may "inappropriately" qualify for active surveillance protocols that are driven by PSA thresholds. This may shift some patients from a higher risk into a lower risk group based on the AS protocol cut-offs. Studies have shown that higher PSA values are more affected by statin use than lower values. Hamilton et al. reported that in men with a pre-statin PSA above 4 ng/mL, median PSA declined by 12.5%, but when analyzed in men with pre-statin PSA above 2.5 ng/mL this decline was only 9.5%.[28] Notably, they also reported that in men with baseline PSA between 2.5 and 10 ng/mL, those receiving robust LDL responses with statin usage experienced median PSA declines of 17%.[29] In our study population, statin users had an average 8.7% lower PSA levels. While studies have not yet directly described the effect of statins on men with PSA above 10 ng/mL, the trend at lower levels potentially makes it more likely that a patient with a PSA value around the AS protocol eligibility cutoffs (i.e. a PSA of 10 or 15 ng/mL) may have their PSA lowered below the cutoff. For example, a PSA of 11 ng/mL would render a man ineligible for many AS protocols, but a reduction as reported by Hamilton et al. brings him to 9 ng/mL and would not exclude eligibility for any protocol based on PSA alone. (**Figure 1**)

Further, our study demonstrated that while PSA was lower among statin users, prostate size was similar between the two groups. As a result, PSA Density was lower among statin users compared to non-statin users. The use of a PSAD cutoff as a common inclusion criterion in AS protocols, combined with the increasing prevalence of statin use in this population, raises the concern that a common pharmacologic intervention may distort a standard prognostic biomarker. The extent to which statins mask the true PSA level, without offering any actual reduction in risk, could result in a non-trivial number of statin users enrolled in AS trials having a disproportionately higher risk profile at entry, as well as worse survival outcomes. The unclear nature of the relationship between statins and prostate cancer risk underscores the need for more careful monitoring of statin use in these study populations.

While the effect of statins on PSA is clear, the explanatory mechanism remains elusive. One possible explanation for our results involves the previously reported anti-inflammatory effects of statins.[12] Prostatic inflammation is a known cause of elevated serum PSA in men without prostate cancer.[30] Decreased inflammation could thus theoretically lower PSA while not affecting prostate size or tumor characteristics, a scenario that would be consistent with our findings.

The observed demographic differences in ASA, BMI, age and history of diabetes are expected, as hyperlipidemia shares a pathophysiologic relationship associated with other comorbid conditions such as diabetes and obesity. It has been postulated that statins' lowering effect on PSA may be influenced by hemodilution in obese, statin-using cohorts.[31] Drugs such as 5-alpha reductase inhibitors can also directly decrease serum PSA.[32] However, in our cohort, differences in BMI were minimal and not statistically significant, and after controlling for BMI and use of 5-alpha reductase inhibitors our results were unaffected.

While some studies support our histopathologic findings,[2,17] others studies have reported a protective benefit of statins against prostate cancer, in contrast to our findings.[4,6,33] Similarly, lower prostate cancer recurrence rates have been reported for statin users, and attributed variously to statins' purported anti-neoplastic activity, protective effects against aggressive disease or a reduction in prostate cancer cells' ability to produce PSA.[6-8] These studies used clinical staging and biopsy characteristics to determine histopathologic risk, which is known to be suboptimal given the inaccuracies of clinical prostate cancer staging.[34] Additionally, Ritch and colleagues[11] observed a higher recurrence rate 5 years after surgery among statin users, and suggested this may be due the masking of aggressive disease by an artificially lowered PSA, as is suggested by our results. While our follow-up may be too short (median 14.7 months) to reveal true differences in biochemical recurrence, no differences in early BCR were noted. Similar findings were noted in the study of Cattarino et al. with a medial follow up time of 42.3 months.[10]

The similarity of histopathologic outcomes between groups despite disparate PSA and PSAD values appears to imply the necessity for inclusion of PSA and PSA density modulation by statins in clinical decision making. As higher PSA values are generally associated with both a higher Gleason score and poorer prognosis,[33] an artificially lowered PSA and/or PSAD as observed in our cohort of patients on statins may lead to an underestimation of risk of high-grade disease, recurrence or subsequently higher-grade disease on pathologic specimen. In this sense, it may be important to weigh other arms of protocols (e.g. Gleason sum, number of positive cores) more highly in prognosticating patients on statins, or account for their lower PSA concentration.

Our study does have additional notable findings. Our patient cohort was 11% black, a higher proportion than most published studies of statins and PSA or prostate cancer.[35] Our cohort in this sense may better represent the American population than other published studies. Additionally, our findings of a reduced PSA density in the setting of prognosticating patients and selecting treatment plans underscore the current debate on prostate cancer treatment selection and suggest the

importance of further studies into both the selection of patients for treatment options and the potential for chemoprevention of prostate cancer.

We lacked specific data regarding the duration of preoperative statin treatment, which has previously been shown to impact statins' overall effect on PSA.[4,35] We recognize that our cohort was comprised entirely of patients who underwent surgical extirpation for prostate cancer following prostate biopsy. The inherent biases of such study design prevent screening-based epidemiologic conclusions from being drawn from such a cohort. Further, there may be variations in some measures between a RALP cohort and actual active surveillance cohort, such as prostate size between the TRUS calculated values and pathologic weight, though previous studies have shown prostate weight to be the best measure of prostate size for use in PSAD corrections.[19] These measure must of course be taken under consideration and validated in a cohort considering active surveillance. However, given the large number of patients with standardized histopathologic analysis by dedicated genitourinary pathologists, our findings are interesting and hypothesis-generating. Prospective studies involving larger cohorts are needed to confirm our findings with detailed information of the type, dosage and duration of statin usage.

CONCLUSIONS

PSA levels were lower in statin users than non-statin users among men presenting for robotic-assisted laparoscopic prostatectomy. Despite this difference, prostate size, histopathologic outcomes and short term biochemical recurrence were similar between the two groups. Further investigation is needed to test causal hypotheses for these findings, to establish whether differential active surveillance criteria are warranted for statin users, and to explore the potential therapeutic benefits of statins in the active surveillance population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to state.

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