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Is statin use associated with prostate cancer aggressiveness?

Stacy Loeb, Donghui Kan*, Brian T. Helfand*, Robert B. Nadler*, and William J. Catalona*

Department of Urology, Johns Hopkins School of Medicine, Baltimore, MD

*Department of Urology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Abstract

OBJECTIVE—To further examine the association between statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) and pathological features in a large group of patients undergoing radical prostatectomy (RP), as epidemiological studies have suggested that statins, in addition to their beneficial cardiovascular effects, might reduce the risk of aggressive prostate cancer.

PATIENTS AND METHODS—From 2003 to 2009, 1351 men with data on preoperative statin use had RP by one surgeon. The clinical and pathological tumour features were compared between 504 users of statins and 847 who were not users.

RESULTS—Statin users were significantly older and had a higher mean body mass index than non-users. The preoperative serum prostate-specific antigen levels, tumour volume and percentage of cancer in the RP specimen were significantly lower in patients taking statins. Overall, statin users had a proportionately lower rate of adverse tumour pathology features, including a significantly lower risk of positive (cancerous) surgical margins.

CONCLUSION—Our results suggest that the use of statins might be associated with more favourable pathological features at RP. The long-term disease-specific outcomes and the underlying link between statins and prostate cancer require further investigation.

Keywords

statins; prostate cancer; prostatectomy; pathology; aggressive

INTRODUCTION

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, an important enzyme in the cholesterol synthesis pathway. The first statin received USA Food and Drug Administration approval for the treatment of hyperlipidaemia in 1987. Since then, the family of statin drugs has expanded, and they have become increasingly popular. According to data from the National Health and Nutrition Examination Survey (NHANES), ≈11.7% of adults in the USA were taking statins in 2003–2004, representing a significant increase from 9.3% in 2001–2002 and 6.5% in 1999–2000 (*P* trend <0.001) [1].

In addition to the well-documented reduction in cardiovascular events with statin therapy [2,3], emerging evidence suggests that statins might also be associated with a lower risk of aggressive prostate cancer. This is biologically plausible, given their known pro-apoptotic

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Correspondence: William J. Catalona, 600 N. St. Clair, Suite 20-150, Chicago IL, 60611, USA. wcatalona@nmff.org.

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and antiproliferative effects *in vitro* [4]. Moreover, due to the high prevalence of prostate cancer and lack of well-established chemoprevention strategies, a relationship between statins and risk of aggressive prostate cancer is a subject of considerable public health interest.

Much of the existing evidence relating to statins and prostate cancer is derived from *post hoc* analyses of clinical trials or prospective studies of statin therapy in which prostate cancer was not the primary endpoint. Therefore, our objective was to further characterize the relationship between preoperative statin use and pathological tumour features among men from an established cohort undergoing radical prostatectomy (RP).

PATIENTS AND METHODS

From February 2003 to May 2009, 1354 men had RP and bilateral pelvic lymphadenectomy at Northwestern University, undertaken by one surgeon (W.J.C.), with a cumulative experience of >5000 RPs. The surgical technique was described previously [5], and bilateral nerve-sparing was attempted when feasible.

The study protocol received institutional review board approval and all participants provided written informed consent. Demographics and clinical data were recorded in a prospective database, including age, race, clinical stage and prostate biopsy features. Because many patients were diagnosed at outside institutions and referred for treatment, PSA levels were measured at several laboratories using various assays.

Tumour grade was assigned using the standard Gleason grading system [6], and the TNM system was used for staging. Current statin use was assessed at the preoperative visit as part of the routine patient history, and this information was available for 1351 men (99.8%), who formed the study population.

After RP, we recorded information on the following pathological tumour features: pathological stage, surgical margin status, lymph node metastases, and RP Gleason score. Tumour volume and percentage of cancer were calculated by the hospital pathologist using visual estimates that have been shown to correlate well with the grid morphometric method [7].

Student's *t*-test (continuous variables) and the chi-square test (categorical variables) were used to compare clinicopathological features in relation to statin use. Multivariate logistic and linear regression models were used to examine the relationship between statin use with tumour pathology features after adjusting for clinical stage ($\geq T2$ vs $T1$) and Gleason score ($7-10$ vs ≤ 6).

RESULTS

Of the 1351 men, 1244 (92%) were white, 25 (2%) were African-American, 39 (3%) were from other ethnic backgrounds, and 43 (3%) were unknown. Table 1 shows the demographic features of the study population. The median age was 59 years, and the median preoperative serum PSA level was 4.9 ng/mL. The Gleason score was ≥ 7 in 433 (31.5%), and most (74.9%) had clinical stage $T1$ disease.

Overall, 504 (37.3%) men in the study population reported statin use. Statin users were significantly older and had a higher mean body mass index than non-users (Table 1). However, the preoperative PSA level was significantly lower among men taking statins. Biopsy Gleason score, clinical stage and PSA velocity were similar between the groups.

Table 1 also shows the pathology features in the study population; most patients (80.4%) had organ-confined disease, regardless of preoperative statin use. However, statin users had significantly fewer positive surgical margins ($P = 0.048$). In addition, statin use was associated with a significantly lower tumour volume and percentage of cancer in the RP specimen, despite a similar overall prostate size.

Table 2 shows the multivariate analysis for the prediction of positive surgical margins in the RP specimen. Adjusting for clinical stage and biopsy Gleason score, preoperative statin use had a statistically significant inverse relationship with positive surgical margins (odds ratio 0.71, 95% CI 0.51–0.98, $P = 0.034$). Statins also tended to have a protective association with tumour volume and percentage cancer in multivariable models that included tumour stage and grade (Table 2).

DISCUSSION

In the USA, ≈24 million adults are taking statin medications; this includes a considerable proportion of men undergoing prostate cancer screening. For example, in a population of men from the Prostate Cancer Prevention Trial, 27% were using lipid-lowering agents [8].

Numerous randomized controlled trials have established the utility of statins for preventing major coronary and cerebrovascular events [9]. Due to the role of cholesterol in numerous cellular pathways, there has also been considerable investigation into the association between statins and the risk of malignancy.

In the Health Professionals Follow-Up Study, Platz *et al.* [10] reported that current statin use was associated with a relative risk of 0.51 (95% CI 0.30–0.86) for advanced prostate cancer. There was also a significant reduction in the risk of metastatic or fatal prostate cancer with current statin use (relative risk 0.35, 95% CI 0.14–0.92).

In a recent meta-analysis of six randomized trials reporting on malignancy as a secondary endpoint, there was no association between statin use and overall prostate cancer risk (relative risk 1.06, 95% CI 0.93–1.20) [11]. The results were similar in a combined analysis of case-control and cohort studies, as well as in a separate meta-analysis using hierarchical quality-based methods [12]. However, in five studies evaluating prostate cancer aggressiveness, Bonovas *et al.* [11] reported a statistically significant inverse relationship between statin use and advanced disease (relative risk 0.77, 95% CI 0.64–0.93).

Consistent with these studies, statin use was associated with more favourable prostate cancer features in the present RP cohort. First, statin users had a significantly lower PSA level at diagnosis. Also, despite otherwise similar clinical characteristics, statin use was associated with a lower proportion of patients with positive (cancerous) surgical margins and lower tumour volume. Thus, our results concur with previous studies supporting an inverse relationship between statins and prostate cancer aggressiveness [10].

There are several possible explanations for these findings. One possibility is that statins alter prostate cancer pathogenesis through their cholesterol-lowering effects. Platz *et al.* [13] reported an inverse relationship between low plasma cholesterol levels and high-grade (odds ratio 0.61, 95% CI 0.39–0.98) or advanced prostate cancer.

Statins might also have indirect effects via androgen synthesis pathways. Interestingly, Hall *et al.* [14] did not find a significant association between statin use and serum levels of free testosterone. However, this does not exclude a relationship between statins and sex hormone concentrations at the tissue level. Notably, Locke *et al.* [15] recently reported the ability of castration-resistant prostate cancer cells to synthesize androgens *de novo* from cholesterol

precursors. Thus, it is possible that cholesterol metabolism might contribute to prostate cancer progression through an ‘endocrine’ mechanism.

Alternatively, statin use might simply represent a proxy for other important variables, such as socioeconomic status or race. Indeed, Mann *et al.* [1] reported that among individuals with elevated low-density lipoprotein cholesterol levels, statin use was significantly more common in those with private or public insurance than among the uninsured. Lower socioeconomic status has also been associated with higher rates of aggressive prostate cancer at diagnosis [16]. Similarly, race might represent a confounding factor. In the NHANES, non-Hispanic blacks with elevated low-density lipoprotein cholesterol levels were less likely to use statins than non-Hispanic whites [1]. These men also represent a high-risk group for aggressive prostate cancer [17].

Also, Hamilton *et al.* [18] reported significantly lower PSA levels among statin users, suggesting another possible mechanism. One explanation for the lower PSA levels at the diagnosis of prostate cancer among statin users in the present population is greater access to healthcare, leading to PSA screening and earlier diagnosis. Because our population was not derived from a formal screening study, data on the frequency of previous PSA screening were not available. Thus, further study is warranted on the association between statins and prostate cancer features, controlling for rates of PSA testing.

Our study is limited because all men were diagnosed with prostate cancer, precluding an analysis of the relationship between statins and the risk of prostate cancer. However, our specific objective was to examine differences in aggressive pathological features based on statin use, necessitating the use of a RP population. Because this induces a surgical selection bias, these results might not be generally applicable to other patient populations. Indeed, the prevalence of statin use was higher in our series than that reported in NHANES, further suggestive of the inherent selection bias. That notwithstanding, it is possible that more robust associations might be apparent in a more heterogeneous patient cohort.

In addition, because we focused on a contemporary population, the follow-up was relatively short. Pathological outcomes are an imperfect proxy for survival outcomes; as such, future studies are warranted to examine the relationship between statin use and long-term outcomes, such as cancer-specific survival.

Nor were data available on the dose or duration of statin use, which might modify its association with prostate cancer aggressiveness [10]. Only current statin use was addressed in this study, such that former users would have been classified as non-users. Depending upon the biologically relevant exposure period, the inclusion of some former users as non-users could potentially dilute any observed association between statins and tumour features. Similarly, it is possible that short-term statin use in the period immediately before RP might be less relevant than long-term exposure many years before the diagnosis.

Finally, it is possible that the observed association between statins and more favourable tumour features might be confounded by numerous unmeasured factors (e.g. concurrent medications, health-seeking behaviour, socioeconomic status, and other lifestyle factors). Also, data were not available for lipid profiles or testosterone levels, precluding an analysis of possible mediators.

Overall, it would be premature to base clinical recommendations on these observational results. A recent example of this pitfall was the use of selenium and vitamin E for prostate cancer prevention. Despite encouraging findings in numerous epidemiological studies [19,20], the randomized Selenium and Vitamin E Cancer Prevention Trial was closed prematurely when these agents failed to produce the anticipated reduction in the risk of

prostate cancer, and suggested possible adverse effects in relation to the rates of diabetes mellitus and prostate cancer [21]. Thus, carefully designed prospective trials are necessary to assess whether statins will be useful in prostate cancer chemoprevention.

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Abbreviations

RP	radical prostatectomy
NHANES	National Health and Nutrition Examination Survey

TABLE 1

The clinical characteristics and pathological features in the overall population and after stratification by statin use

Median (range) or <i>n</i> (%) variable (<i>n</i>)	Total	Statin	No statin	<i>P</i>
Age at surgery, years (1351)	59 (37–76)	61 (43–76)	58 (37–76)	<0.001
PSA level, ng/mL (1343)	4.9 (0.1–63.6)	4.8 (0.1–24)	5.0 (0.2–63.6)	0.002
Biopsy Gleason score ≥ 7 (1342)	433 (31.5)	157 (31.5)	265 (31.4)	1.000
Clinical stage <T2 (1348)	1009 (74.9)	379 (75.5)	630 (74.5)	0.700
PSA velocity, ng/mL/year (616)	1.32 (–251.4–41.5)	1.57 (–52.1–28.3)	1.25 (–251.4–41.5)	0.160
PSA velocity >2 ng/mL/year (616)	237 (38.5)	99 (40.6)	138 (37.1)	0.400
Body mass index, kg/m ² (1347)	27.0 (17.4–44.6)	27.3 (19.3–44.1)	26.6 (17.4–44.6)	0.001
Pathology at RP				
Organ-confined (1339)	1077 (80.4)	406 (81.2)	671 (80.0)	0.620
Positive margins (1349)	221 (16.4)	69 (13.7)	152 (18.0)	0.048
Extracapsular extension (1349)	251 (18.6)	87 (17.3)	164 (19.4)	0.350
Seminal vesicle invasion (1348)	57 (4.2)	15 (3.0)	42 (5.0)	0.093
Lymph node metastases (1348)	9 (0.7)	2 (0.4)	7 (0.8)	0.500
Gleason score ≥ 7 (1345)	653 (48.6)	234 (46.8)	419 (49.6)	0.340
Prostate weight, g (1340)	47.3 (16.0–557.3)	48.1 (18.5–254.7)	46.8 (16.0–557.3)	0.260
% cancer (1276)	8 (0.1–90)	7.0 (0.1–75.0)	9.0 (0.1–90.0)	0.049
Tumour volume, mL (1276)	3.7 (0.04–71.2)	3.5 (0.06–50.2)	3.7 (0.04–71.2)	0.032

TABLE 2

Multivariate models for the association between statins and positive surgical margins, tumour volume and percentage cancer at RP, adjusting for clinical stage and grade

Variables	Coefficient (SE)	P
Positive surgical margins		
Statin use	−0.35 (0.16)	0.034
Clinical stage ≥T2	0.23 (0.17)	0.162
Biopsy Gleason score 7–10	1.12 (0.15)	<0.001
Tumour volume		
Statin use	−0.66 (0.36)	0.061
Clinical stage ≥T2	0.66 (0.40)	0.098
Biopsy Gleason score 7–10	3.63 (0.38)	<0.001
% cancer at RP		
Statin use	−1.13 (0.66)	0.088
Clinical stage ≥T2	2.00 (0.74)	0.007
Biopsy Gleason score 7–10	7.36 (0.70)	<0.001