The Influence of Statin Medications on Prostate-Specific Antigen Levels

Robert J. Hamilton, Kenneth C. Goldberg, Elizabeth A. Platz, Stephen J. Freedland

Background
Recent data suggest that statin use may be associated with a reduced risk of advanced prostate cancer. However, the influence of statins on prostate-specific antigen (PSA) levels and what effect this could potentially have on prostate cancer diagnosis are unknown.

Methods
We conducted a longitudinal study of 1214 men who were prescribed a statin between 1990 and 2006 at the Durham Veterans Affairs Medical Center who were free of prostate cancer, had not undergone prostate surgery or taken medications known to alter androgen levels and who had at least one PSA value within 2 years before and at least one PSA value within 1 year after starting a statin. The change in PSA from before to after statin treatment was analyzed as a continuous variable using the Wilcoxon signed rank test. The association between change in PSA and change in cholesterol parameters (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol) was analyzed using multivariate linear regression. All statistical tests were two-sided.

Results
Mean (SD) age when starting statins was 60.3 (8.3) years; median prestatin PSA concentration was 0.9 (1.9) ng/mL; and mean prestatin LDL cholesterol concentration was 144 (34) mg/dL. After starting a statin, the median LDL decline was 27.5%, and the median PSA decline was 4.1% (P < .001, for both comparisons). Changes in PSA concentration were strongly associated with statin dose and changes in LDL levels. For every 10% decrease in LDL after starting a statin, PSA levels declined by 1.64 (95% confidence interval [CI] = 0.64% to 2.65%, p = .001). Among men most likely to be under consideration for prostate biopsy (prestatin PSA levels ≥2.5 ng/mL, n = 188), those with >41% declines in LDL (highest quartile) after starting a statin experienced a 17.4% (95% CI = 10.0% to 24.9%) decline in serum PSA.

Conclusions
PSA levels declined by a statistically significant extent after initiation of statin treatment. The reduction was most pronounced among men with the largest LDL declines and those with PSA levels that would make them candidates for prostate biopsy. By lowering PSA levels, statins may complicate cancer detection, although further studies are needed to quantify the clinical significance of this effect.

J Natl Cancer Inst 2008;100:1511–1518

The lipid-lowering agents known as statins are the most prescribed class of prescription drugs in the United States. In 2007, atorvastatin was the leading drug in terms of number of prescriptions dispensed (1). This popularity reflects the efficacy of statins in reducing cholesterol levels and the incidence of adverse cardiovascular outcomes, their safety profile and tolerability, the increasingly liberal guidelines for their use, and the increasing prevalence of hyperlipidemia (2–4).

Evidence suggests that statins may also prevent cancer. They inhibit many processes that are important in cancer development and growth (5–10), and several epidemiological studies found inverse associations of statin use with breast (11), lung (12), colorectal (13), renal (14), and all cancers combined (15–17). However, other studies (18–21) have not confirmed these associations.

Data on the preventative effects of statins on prostate cancer are encouraging but similarly conflicting. A small clinic-based case-control study (22), a case-control study within a pharmacy database (16), and a secondary analysis of a randomized controlled trial for prostate cancer screening reported reductions ranging from 50% to 65% in total prostate cancer risk among statin users vs nonusers (23). However, three meta-analyses (2,20,24) of trials or observational studies of statins and prostate cancer suggested that statins are associated with a reduced risk of advanced prostate cancer.

Correspondence to: Stephen J. Freedland, MD, Division of Urology, PO Box 2626 DUMC, Duke University School of Medicine, Durham, NC 27710 (e-mail: steve.freedland@duke.edu).

See “Funding” and “Notes” following “References.”

DOI: 10.1093/jnci/djn362

© The Author 2008. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.
studies of statins used for heart disease prevention reported no association between statin use and overall prostate cancer risk.

Recently, four large prospective cohort studies (25–28) observed that statin use, although not associated with overall prostate cancer, was associated with reductions in the risk of advanced prostate cancer that ranged from 25% to 75%. In these studies, the risk of total or advanced prostate cancer declined with higher doses and longer use.

Given the evidence that statins may be associated with lower prostate cancer risk, particularly of advanced prostate cancer, we sought to determine whether statin use was associated with changes in prostate-specific antigen (PSA) levels. In the only other study that to our knowledge directly examined this question, PSA declined by an average of 42% over 5 years among 15 healthy men starting statins (29). If confirmed in a substantially larger longitudinal study, these PSA declines could represent further evidence of a preventive biologic effect of statins on the prostate. Reduced PSA levels could also lead to fewer physician referrals for prostate biopsy, potentially entailing missed or delayed prostate cancer diagnoses. Although the clinical significance of missing cancers that without statin use might be detected is uncertain, given the prevalence of both PSA screening and statin use, the public health impact could be substantial (1,30).

Methods

Study Population

After obtaining Institutional Review Board approval, we used the computerized medical records at the Durham Veterans Affairs Medical Center (DVAMC) to identify all men from the DVAMC who filled an outpatient prescription for a statin between January 1, 1990, and September 10, 2006 (n = 23,428). Only men with at least one PSA value within 2 years before and at least one PSA value within 1 year after starting a statin were included (n = 2,991). This narrow time frame was chosen to minimize confounding due to the natural history of PSA to rise over time (31,32).

Figure 1 documents the sequence of exclusions in this study. Using the 9th revision of the International Classification of Disease codes (33), Current Procedural Terminology Codes (34), problem and visit lists from the computerized medical records, and outpatient pharmacy data, we excluded men with a diagnosis of prostate cancer, men having undergone a radical prostatectomy or cystoprostatectomy, and men treated with androgen deprivation therapy or bilateral orchiectomy (n = 745).

We also excluded the following categories of patients: men who at any point in the study period received finasteride, dutasteride, or androgen supplementation, underwent a transurethral resection of the prostate (TURP) or simple open prostatectomy, or were diagnosed with prostatitis (of these 435 men, 69 were excluded because of presumed prostatitis based on a subsequent drop in PSA of more than 40% from the first poststatin PSA to the next PSA value); men...
without evidence of remaining on a statin at least 1 month before their poststatin PSA or who were taking nonstatin lipid-lowering agents within the 3 years before they started a statin (n = 220); men in whom the prestatin PSA was >10 ng/mL, or undetectable (<0.1 ng/mL), or in whom the poststatin PSA value was undetectable (n = 39), this could have represented a missed case of prostate cancer and/or treatment; men without a prestatin or a poststatin low-density lipoprotein (LDL) cholesterol value within 2 years of starting a statin (n = 345). The latter exclusion was made because we were interested in the change in PSA relative to the change in LDL concentration after starting statins.

Assessment of Statin Prescription
For each eligible patient, using the pharmacy records from the DVAMC, the earliest statin prescription during the study period and the statin dose immediately before obtaining the poststatin PSA used in calculations was identified. The date the prescriptions were given, the specific drugs and doses prescribed were noted. These doses were translated into a dose equivalent based on published guidelines (35) with simvastatin 20 mg being assigned a value of 1. Because few patients were on very high (>4) or very low (<0.5) dose equivalents, dose equivalents were analyzed categorically as <1, 1, and >1.

Measurement of PSA Concentration
For each eligible subject, PSA concentrations before and after starting a statin were identified from the DVAMC computerized medical records. Generally, the Abbott (Abbott Park, IL) assay was used before 2000 and the Hybritech (Beckman Coulter Inc, Fullerton, CA) assay was used thereafter. We assessed the potential impact of the change in assay on our outcome by excluding men with pre- to poststatin comparisons that crossed the date of assay change. Excluding these men did not alter the observed changes in PSA (data not shown), and therefore all eligible men were included in the analyses regardless of the dates of PSA tests.

Statistical Analysis
The primary endpoint of this study was the percentage change in PSA after starting a statin, computed as follows: \[ \frac{(PSA_2 - PSA_1)}{PSA_1} \times 100 \]. PSA_1 represents the most recent PSA within 2 years before starting a statin and PSA_2 represents the earliest poststatin PSA at least 15 days but less than 1 year after starting the statin. P values pertaining to reported percentage change in PSA results are derived from Wilcoxon signed rank tests of differences between PSA_1 and PSA_2. Among men for whom a PSA value was available immediately before PSA_1 (n = 579) (ie, had at least two PSA tests in the 2 years before starting a statin), the change in PSA concentration in the period before starting statins was compared with the change in PSA after starting statins, also using the Wilcoxon signed rank test, thus providing an internal control for fluctuations in PSA values.

The percent changes in total, LDL, and high-density lipoprotein (HDL) cholesterol were computed using formulas analogous to the one used to calculate percent PSA change. The change in cholesterol parameters served as a marker for the biologic effect of statins on cholesterol synthesis in the individual patient and for patient compliance. The association between percent change in cholesterol parameters and percent change in PSA was analyzed by linear regression after ensuring that the data satisfied the assumptions of linear regression. To plot the association, locally weighted regression (LOWESS) without and with multivariable adjustment was used. Crude, age-adjusted, and multivariable-adjusted results are presented. Variables included in the multivariable model were age at the time of starting statins (continuous), statin dose equivalent at the time of PSA_1 (<1, 1, >1), race (black, white, other race), body mass index (BMI) at the time of starting statin (BMI in kg/m\(^2\): <25.0, 25.0–29.9, 30.0–34.9, ≥35), prestatin PSA concentration (continuous after log transformation), the year in which patients started a statin (continuous), the number of days between PSA, and PSA, (continuous), the time between starting a statin and PSA, (continuous), and whether the dose of statin was increased before poststatin PSA, (yes/no). Change in BMI after starting a statin was evaluated as a potential confounding factor. Because it was not correlated with PSA change and it did not substantially alter the association between PSA change and change in cholesterol levels in the multivariable model, and was only available for 801 (66%) patients, we did not adjust for this variable in the models.

All analyses were conducted using STATA 9.2 (College Station, TX), and all tests of statistical significance were two-sided.

Results
In total, 1214 patients were eligible for analysis (Table 1). Average age at the time of starting a statin was 60 years. Most patients were white (n = 726; 60%) and overweight (BMI 25.0–29.9 kg/m\(^2\); n = 457 [39%]) or obese (BMI ≥30.0 kg/m\(^2\); n = 538 [46%]). The most common statin used was simvastatin (used by 95% of patients), and the most common starting dose equivalent was 20 mg. Median prestatin PSA was 0.9 ng/mL, and median prestatin LDL was 144 mg/dL (Table 2). The median decline in LDL was 27.5%, and the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>726 (60)</td>
</tr>
<tr>
<td>Black</td>
<td>466 (39)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (1)</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>171 (15)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>457 (39)</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>340 (29)</td>
</tr>
<tr>
<td>≥35.0</td>
<td>198 (17)</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1151 (95)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>7 (&lt;1)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>37 (3)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>17 (1)</td>
</tr>
<tr>
<td><strong>Statin dose equivalent</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;simvastatin 20 mg</td>
<td>236 (19)</td>
</tr>
<tr>
<td>≈simvastatin 20 mg</td>
<td>404 (33)</td>
</tr>
<tr>
<td>&gt;simvastatin 20 mg</td>
<td>574 (47)</td>
</tr>
</tbody>
</table>

* Mean age ± SD of the cohort was 60.3 ± 8.1 years; median year of starting statin was 2003. BMI = body mass index.
average time between starting a statin and the poststatin LDL measurement was 227 days (Table 2).

The median change in PSA after starting a statin was a decline of 4.1% (interquartile range [IQR] −22.1% to +12.5%, P < .001 comparing poststatin to prestatin PSA, Table 2). The median time between the prestatin PSA (PSA1) and poststatin PSA (PSA2) measurements was 367 days, and the median time from starting a statin to the PSA2 was 214 days.

The PSA change in the period immediately before starting statins was determined for the 579 men for whom a PSA before the one used to compute the percent PSA change (PSA1) was available. The median time between these two PSA measurements was 396 days. During this time before starting a statin, median PSA change was 0% (IQR −16.7% to +21.2%), which was statistically significantly less than the change after starting a statin (P = .002). The median change in PSA after starting a statin for these 579 men was identical to the whole population (−4.1%).

The PSA decline after statin initiation was positively associated with LDL cholesterol decline in a near linear fashion (Figure 2; P = .003 from linear regression). After adjusting for multiple factors, for every 10% LDL cholesterol decline after statin initiation, PSA declined by 1.64% (95% confidence interval [CI] = 0.64% to 2.65%; P = .001; Figure 2; Table 3). Of note, men whose LDL cholesterol did not change after statin initiation (n = 22) experienced a 2.1% median PSA rise, whereas those who experienced an LDL cholesterol rise (n = 109) had an even greater PSA rise (Figure 2). The relationship between total cholesterol and PSA after statin initiation mimicked that of LDL in crude and multivariable-adjusted models (data not shown). The change in HDL after statin initiation was not associated with a change in PSA (P = .76, data not shown).

In the multivariable model, statin dose was associated with PSA decline above that accounted for by the LDL drop (Table 3). Doses equal to and greater than simvastatin 20 mg, respectively, were associated with an 8.5% (95% CI = 2.7% to 14.4%; P = .005) and 9.4% (95% CI = 3.3% to 15.5%, P = .003) greater decline in PSA than that observed with statin doses less than simvastatin 20 mg.

We evaluated the extent to which the observed PSA decline after statin initiation could potentially obscure prostate cancer detection. Given the low median prestatin PSA in our cohort, the 4.1% decline in PSA translated into only a modest median absolute change (IQR) in PSA overall, −0.03 ng/mL (−0.21 to +0.10 ng/mL). However, PSA declines were greater among men with higher prestatin PSA levels (Table 3). Thus, we examined men with prestatin PSA values above three commonly used PSA thresholds for consideration of prostate biopsy: Among men with PSA values ≥4.0, ≥3.0, and ≥2.5 ng/mL, the median absolute PSA decline was 0.6, 0.5, and 0.4 ng/mL, respectively, and the median percentage PSA decline was 12.5%, 11%, and 9.5%, respectively, with 39%, 26%, and 24%, respectively, of the men falling below the cut point after starting statins (Table 4).

Finally, we examined the association between LDL drop and PSA drop among men with prestatin PSA ≥2.5 ng/mL (n = 188). After adjustment for age, the median PSA change ranged from a 0.2% rise among those with rises or very small declines in LDL (lowest quartile of LDL decline), to a 17.4% (95% CI = 10.0% to

---

**Table 2. Lipid and PSA profile of study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prestatin concentration ± SD</th>
<th>Mean % change after statin ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>144 ± 34</td>
<td>−26.0 ± 20.6</td>
</tr>
<tr>
<td>HDL</td>
<td>39.9 ± 10.6</td>
<td>7.9 ± 19.8</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>216 ± 39</td>
<td>−23.8 ± 15.2</td>
</tr>
<tr>
<td>PSA</td>
<td>0.9 ng/mL (0.6–1.8 ng/mL)</td>
<td>−4.1% (−22.1% to +12.5%)</td>
</tr>
</tbody>
</table>

* LDL = low-density lipoprotein; HDL = high-density lipoprotein; PSA = prostate-specific antigen. LDL, HDL and Total cholesterol presented as mean ± SD; PSA presented as median (interquartile range).

**Table 3. Factors independently associated with change in PSA after starting a statin**

<table>
<thead>
<tr>
<th>Covariate parameter</th>
<th>% decline in PSA</th>
<th>95% CI</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% decline in LDL after starting statin</td>
<td>1.64</td>
<td>0.64 to 2.65</td>
<td>.001</td>
</tr>
<tr>
<td>Statin dose equivalent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;simvastin 20 mg</td>
<td>Ref</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>=simvastin 20 mg</td>
<td>8.53</td>
<td>2.65 to 14.41</td>
<td>.005</td>
</tr>
<tr>
<td>&gt;simvastin 20 mg</td>
<td>9.35</td>
<td>3.29 to 15.42</td>
<td>.003</td>
</tr>
<tr>
<td>Statin dose equivalent (two categories)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;simvastin 20 mg</td>
<td>Ref</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>≥simvastin 20 mg</td>
<td>8.90</td>
<td>3.40 to 14.40</td>
<td>.002</td>
</tr>
<tr>
<td>1 ng/mL increase in prestatin PSA§</td>
<td>2.87</td>
<td>1.96 to 3.80</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* PSA = prostate-specific antigen; LDL = low-density lipoprotein; CI = confidence interval. Model adjusted for age, race, body mass index, year started statin, statin dose equivalent, prestatin LDL, prestatin PSA, number of days between PSA, and PSA1, time between starting a statin and PSA1, and whether the dose of statin was increased during the time between PSA, and PSA1.† P values from linear regression.
‡ The full model depicted here was repeated with statin dose equivalent entered as a two category model given the nonlinear relationship observed when three categories of statin dose were used.
§ Entered in the model as natural log transformation of prestatin PSA; back transformed for ease of interpretation in the table.

---

**Figure 2.** Association between percent decline in prostate-specific antigen (PSA) concentration and percent decline in low-density lipoprotein (LDL) cholesterol concentration after starting a statin. Crude and multivariable-adjusted curves estimated using locally weighted regression are shown. P value is from the bivariate linear regression analysis.
Table 4. Decline in PSA with statin use among men with prestatin PSA levels above potential biopsy cut points of 2.5, 3.0, and 4.0 but ≤10.0 ng/mL*

<table>
<thead>
<tr>
<th>PSA cut point (ng/mL)</th>
<th>No. above cut point before statin use</th>
<th>Median PSA (ng/mL) before statin use</th>
<th>Median % PSA decline with statin use</th>
<th>Median absolute PSA decline after statin (ng/mL)</th>
<th>No. dropping below cut point after statin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4</td>
<td>70</td>
<td>5.1</td>
<td>12.5</td>
<td>0.6</td>
<td>27 (39%)</td>
</tr>
<tr>
<td>≥3</td>
<td>136</td>
<td>4.0</td>
<td>11.0</td>
<td>0.5</td>
<td>35 (26%)</td>
</tr>
<tr>
<td>≥2.5</td>
<td>188</td>
<td>3.6</td>
<td>9.5</td>
<td>0.4</td>
<td>45 (24%)</td>
</tr>
</tbody>
</table>

* PSA = prostate-specific antigen. Median time between the prestatin PSA (PSA) and poststatin PSA (PSA) was 367 days; median time from starting a statin to PSA, was 214 days.

24.9%) decline among those with a >41% (highest quartile) LDL decline (Figure 3).

Discussion

Statins are the most commonly used medication class in the United States (1). PSA screening, although controversial, is also very prevalent in the United States (30). Thus, an effect of statins on PSA levels could potentially complicate prostate cancer detection. We found PSA concentration declined by a median of 4.1% after starting statins, compared with no decline in the period immediately before starting statins. The PSA decline after starting statins was statistically significantly associated with the decline in LDL cholesterol concentrations. After adjusting for LDL changes, the statin dose remained associated with the PSA decline suggesting that there may be both cholesterol- and noncholesterol-mediated mechanisms by which statin treatment influences PSA. Men with PSA values ≥2.5 ng/mL and in the highest quartile decline in LDL (>41%) had a >17% PSA decline after starting statins. The PSA declines with statin use that we observed may represent objective evidence of statins influence on prostate biology in support of epidemiological studies suggesting statins reduce overall prostate cancer, yet no association with high-grade disease (37). If statins are most protective against aggressive tumors, this may explain why other observational studies and secondary analyses of randomized controlled trials that used overall prostate cancer incidence as the endpoint observed no association (21,25,20,24).

With some evidence suggesting that statin treatment prevents prostate cancer, particularly advanced prostate cancer, we thought it prudent to characterize the influence of statins on PSA, to obtain additional insight into the effects of statins on prostate biology as well as potential complications that changes in PSA levels might introduce into PSA screening. Previously, in a small study of 15 men with hyperlipidemia starting statins, PSA declined by 42% over 5 years (29). A randomized controlled trial of men with symptomatic benign prostatic hyperplasia treated with atorvastatin (n = 174) or placebo (n = 176) for 6 months found that PSA declined more in those receiving statins than placebo (−0.24 vs −0.14 ng/mL) (38). Given that baseline PSA values were 2.7 to 2.8 ng/mL, the difference in the rate of decline of 0.1 ng/mL represents ~3.6% greater decline in PSA in the statin arm. Although the difference in PSA decline was not statistically significant (P = .24), and thus must be interpreted with caution, it is consistent with the current results.

In our substantially larger cohort of men without prostate cancer, statin initiation was associated with a median 4.1% PSA decline (Figure 3).
or poor biologic activity, PSA rose by a median 2.1%.

Starting statins, an outcome possibly reflective of poor compliance group (31, 32). Because we limited analyses to men with relatively healthy prostates (ie, without cancer or prostatitis), the increase in PSA in our cohort may be less than the 3%–13% per year reported in other studies. In 579 men, we were able to compute the change in PSA concentration in the period immediately before starting statins, as an internal control for trends in PSA concentration not related to statin treatment. Among these men, the median PSA change over an average of 1 year before starting statins differed to a statistically significant extent from the PSA change over 1 year after starting statins (0% vs –4.1%, respectively, P = .002).

Moreover, among men who experienced no LDL decline after starting statins, an outcome possibly reflective of poor compliance or poor biologic activity, PSA rose by a median 2.1%.

We found that the PSA decline after starting statins was statistically significantly associated with the decline in LDL cholesterol consistent with prior evidence that through lowering cholesterol, statins may influence prostate biology. Prostate growth and cancer development have been linked to abnormal cholesterol metabolism. For example, it has been noted that increased cholesterol content in prostate tissue correlates with the presence of malignancy (39,40). Furthermore, reducing cholesterol bioavailability has been found to alter the composition of membrane-signaling domains and to induce apoptosis in prostate cells (41,42). Repleting cholesterol content reverses the apoptotic effects, implicating cholesterol reduction as a likely mechanism through which statins may influence prostate biology (42). Although cholesterol is an important precursor for androgen formation, statins do not lower serum androgens (43). However, it is conceivable that by influencing cholesterol metabolism, statins may lower levels of intraprostatic androgens, which could reduce PSA levels.

Even after adjusting for changes in cholesterol levels, statin dose was independently associated with PSA decline. This may suggest that there are additional noncholesterol-mediated effects of statins on prostate biology. In support of this possibility, there is evidence to suggest that by decreasing concentrations of mevalonate products downstream of HMG-CoA reductase, statins can inhibit inflammation (5,44), angiogenesis (6), cell proliferation (7), migration and adhesion (8), invasion (9), and affect intracellular survival signals such as Rho and Ras (45).

The anti-inflammatory effects of statins are well documented (5,44).

Although we excluded men with clinical prostatitis, higher PSA levels in our cohort may be indicative of men with low-grade subclinical inflammation. Thus, given the association between prostatic inflammation and elevated PSA levels (46), the fact that men with higher prestatin PSA levels achieved greater PSA declines after starting statins may provide evidence of the anti-inflammatory activity of statins on the prostate.

Regardless of the mechanism of statin action, if the PSA decline after starting statins is confirmed in other studies, the public health implications could be clinically significant given the prevalence of PSA testing in the United States (30). Men who would be influenced most by an unexpected PSA drop are those with PSA levels approaching a threshold for which a biopsy is considered. This threshold for biopsy is a subject of debate (47); however, for this study, we analyzed three potential PSA thresholds (≥2.5, ≥3.0, and ≥4.0 ng/mL) and observed that approximately one-third of men with PSA levels above each of these thresholds before starting statins dropped below the threshold after starting statins. Furthermore, among men with PSA ≥2.5 ng/mL, those with an LDL drop >41% (25% of those with PSA ≥2.5 ng/mL), experienced a 17% decline in PSA. With lower PSA levels, physicians may be less likely to perceive patients to be at risk for prostate cancer and thus less likely to recommend a prostate biopsy, potentially leading to diagnosis at later stages.

There is currently no level I evidence to suggest that PSA screening reduces prostate cancer mortality (48). Thus, it is premature to suggest lowering of PSA with statin treatment would translate into worse oncologic outcomes. However, most of the US public believes screening saves lives (49) and in a survey conducted in 2001, of men older than 50 years, 75% had at least one PSA test and 57% had a test within the past 12 months (30). Consequently, although our study did not address the risks and benefits of PSA-based prostate cancer screening, for men who do choose to be screened, the clinical relevance of the lower PSA values among statin users requires further study.

An effect of statins on PSA levels in the absence of any biologic effect on prostate cancer would not explain the inverse association between statins and advanced prostate cancer observed in some studies (25–28), as deferred biopsies would tend to translate into cancers being detected at more advanced stages. However, a lowering of PSA levels by statin treatment may represent evidence that statins prevent or delay prostate cancer progression, which could explain the reduced risk of advanced prostate cancer observed by others. Because our cohort excluded men diagnosed with prostate cancer during the study period, we cannot conclude whether statins lowering PSA represents a potential source of missed diagnoses or appropriate deferral of prostate biopsies because of a cancer-preventative mechanism.

Alternatively, it is possible that, like finasteride treatment, statin treatment could increase the sensitivity of PSA testing in identifying prostate cancer (50). Finasteride, a 5-alpha reductase inhibitor, reduces PSA by 50% and has proven prostate cancer-preventative actions (51). After correcting for the PSA decline among finasteride users in the Prostate Cancer Prevention Trial, the sensitivity and specificity of PSA in detecting prostate cancers improved by a statistically significant extent, especially for detection of high-grade disease (50). Our study did not address the influence of statins on the sensitivity and specificity of PSA. However, studies of statin use have shown a reduced risk of high-grade (22) or advanced disease (25–28). Thus, if statins do increase the sensitivity of detecting high-grade disease like finasteride, this would strengthen the findings of others that statins may prevent aggressive forms of prostate cancer. While the PSA decline among statin users is less than that observed among finasteride users, the influence of statins on the performance of PSA in detecting cancer warrants further study.

Our study had some limitations. We excluded men with prostatitis, or PSA values >10 ng/mL. Therefore, we cannot comment on the association between statin use and PSA decline in these subgroups. We were unable to capture information on possible lifestyle changes initiated by men who started statins, changes that could possibly explain the relationship between statins and PSA change. However, BMI change after starting a statin, which may
serve as a marker for lifestyle modifications, did not substantially confound the relationship between statin use and PSA. Because full demographic data were not available for all statin users, we are unable to assess if men included and excluded from analysis differed. However, because most men were excluded due to lack of PSA data, the importance of statin-associated PSA changes are not relevant among men not receiving PSA testing. Finally, medications prescribed outside the Veteran’s Administration system were not captured. Thus, men may have started medications (eg, finasteride) that potentially accounted for the observed PSA declines. However, given the strong correlation between PSA and LDL declines after starting statins, it is much more likely that the PSA declines we observed are due to the statin use and not non-VA use of drugs that lower PSA but not LDL (eg, finasteride).

Despite these limitations, we believe that our findings are likely to be accurate. By following a large sample of men without prostate cancer or prostatitis within a single, equal-access health care system, and in a longitudinal fashion where men were able to serve as their own controls, we were able to accurately measure the association between PSA levels and use of statins. In conclusion, in a group of men without prostate cancer, PSA levels declined by a statistically significant extent after they were treated with statins. The reduction was most pronounced among men with larger declines in LDL cholesterol, higher statin doses, and higher prestatin PSA levels. If confirmed in other studies, these findings would warrant investigation of the mechanism by which statins influence PSA and whether statins directly affect prostate biology. Most importantly, from a clinical standpoint, given the prevalence of both PSA testing and statin use, the potential influence a statin-mediated reduction in PSA could have on cancer detection must be further quantified.

References


**Funding**

Supported by the Department of Veterans Affairs, The Department of Defense Prostate Cancer Research Program (R.J.H., S.J.F.), and the American Urological Association Foundation/Astellas Rising Star in Urology Award (S.J.F.).

**Notes**

We thank Dr Girish Kulkarni, MD, PhD, for his statistical support.

The authors take full responsibility for the study design, data collection, analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Views and opinions of, and endorsements by the authors do not reflect those of the US Army or the Department of Defense.

Manuscript received March 24, 2008; revised August 10, 2008; accepted September 8, 2008.