

Statin Use, Serum Lipids, and Prostate Inflammation in Men with a Negative Prostate Biopsy: Results from the REDUCE Trial



Emma H. Allott¹, Lauren E. Howard², Adriana C. Vidal³, Daniel M. Moreira⁴, Ramiro Castro-Santamaria⁵, Gerald L. Andriole⁶, and Stephen J. Freedland^{3,7}

Abstract

Statin use is associated with lower advanced prostate cancer risk. In addition to cholesterol lowering, statins have systemic anti-inflammatory properties. However, their effect on histologic prostate inflammation is not well understood, particularly among men at increased prostate cancer risk but with a negative prostate biopsy. We examined associations between serum lipid levels, statin use, and histologic prostate inflammation using data from 6,655 men with a negative baseline prostate biopsy in the REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial. Statin use and lipid levels [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides] were assessed at baseline. Inflammation was assessed by central review. Logistic regression was used to examine the effects of lipids and statin use on presence and extent of chronic and acute prostate inflammation [none, moderate (<20%), severe (≥20% biopsy

cores)]. Chronic and acute inflammation affected 77% and 15% of men, respectively. Men with high HDL (≥60 vs. <40 mg/dL) had reduced presence of acute inflammation [OR, 0.79; 95% confidence interval (CI), 0.63–0.99] and were less likely to have severe acute inflammation (OR, 0.66; 95% CI, 0.45–0.97), but there were no other associations between lipids and inflammation. Statin users had reduced presence of chronic inflammation (OR, 0.81; 95% CI, 0.69–0.95) and were less likely to have severe chronic (OR, 0.80; 95% CI, 0.68–0.95) and severe acute inflammation (OR, 0.73; 95% CI, 0.53–1.00), relative to non-users. Given the possible role for inflammation in prostate cancer, the inverse association between statins and prostate inflammation suggests a mechanism linking statins with lower advanced prostate cancer risk. *Cancer Prev Res*; 10(6): 319–26. ©2017 AACR.

Introduction

Statin use is associated with reduced risk of advanced prostate cancer (1). Statins lower serum cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for cholesterol synthesis. High serum cholesterol drives tumor growth in mouse models of prostate cancer (2, 3), and results from epidemiologic studies show that high serum cholesterol is associated with increased risk of biochemical recurrence (4, 5) and prostate cancer-specific mortality (6–8). Together, these findings support a role for cholesterol, and cholesterol-lowering interventions, in prostate cancer (9). Beyond

cholesterol-lowering effects, statins may also have off-target effects on the prostate via non-cholesterol-mediated mechanisms (1). Clinical trials show that statins lower serum C-reactive protein (10, 11) and reduce cytokine production by circulating lymphocytes (12) independent of their cholesterol-lowering effects, demonstrating that statins lower systemic inflammation. Our group previously found that statin users had less histologic inflammation in their prostate tumors than non-users (13), suggesting that statins can also lower inflammation in the prostate tumor. However, no studies, to our knowledge, have examined the effect of statin use and serum lipid levels on prostate inflammation in men with a negative prostate biopsy.

Histologic evaluation of negative prostate biopsies from prostate cancer screening and prevention trials revealed prostate inflammation in approximately 60% to 80% of asymptomatic men undergoing biopsy due to elevated prostate-specific antigen (PSA) levels (14–16). However, factors contributing to prostate inflammation are largely unknown. Our group previously reported that smokers had higher levels of prostate inflammation (17), showing that lifestyle factors may influence prostate biology. Herein, we evaluated associations between serum lipid levels, statin use, and prostate inflammation in negative baseline prostate biopsies of men from the REDuction by DUtasteride of Prostate Cancer Events (REDUCE) trial (18). We hypothesized that high serum cholesterol would be associated with increased prostate inflammation, whereas statin use would be associated with reduced prostate inflammation.

¹Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. ²Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina. ³Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, California. ⁴Department of Urology, University of Illinois at Chicago, Chicago, Illinois. ⁵Research and Development, GlaxoSmithKline, Inc., King of Prussia, Pennsylvania. ⁶Washington University School of Medicine in St. Louis, St. Louis, Missouri. ⁷Division of Urology, Veterans Affairs Medical Center, Durham, North Carolina.

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Corresponding Author: Stephen J. Freedland, Cedars Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048. Phone: 310-423-3497; Fax: 310-423-4711; E-mail: stephen.freedland@cshs.org

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Materials and Methods

Study population

REDUCE was a 4-year, multicenter, double-blind and placebo-controlled study testing dutasteride for reducing incident prostate cancer (18). Only baseline data prior to randomization were used for the present analysis. Men were eligible for the study if they were between 50 and 75 years of age, had a serum PSA of 2.5 to 10 ng/mL (if 50–60 years of age) or 3 to 10 ng/mL (if 60 to 75 years of age) and a single, negative biopsy (6 to 12 cores) within 6 months before enrollment (independent of trial protocol). Baseline biopsies were centrally reviewed to confirm a negative prostate cancer diagnosis. Men were excluded if they had a history of prostate cancer, high-grade intraepithelial neoplasia, atypical small acinar proliferation, prostate volume > 80 mL, had undergone previous prostate surgery, or had an International Prostate Symptom Score ≥ 25 or ≥ 20 while receiving α -blockers for treatment of benign prostatic hyperplasia. The REDUCE protocol was approved by the Institutional Review Boards at each site and at the University of North Carolina at Chapel Hill (Chapel Hill, NC), and all participants provided written informed consent.

Exposure assessment

At baseline, a detailed medical history was obtained including smoking, medical comorbidities, medication use, and alcohol use. Total serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels were measured by Quest Diagnostic at baseline before randomization. The vast majority of lipid values were obtained in the fasting state (99.8%). Recommended cutoff points for normal, borderline, and abnormal serum levels (all in mg/dL) of total cholesterol (<200, 200–239, ≥ 240), LDL (<130, 130–159, ≥ 160), HDL (≥ 60 , 40–59, <40), and triglycerides (<150, 150–199, ≥ 200) were implemented according to National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP) III guidelines (19). Subjects reported all medications they were using at baseline, including lipid-lowering medications (statins, fibrates, and ezetimibe). Most men reporting lipid-lowering medication use were statin users ($n = 1,229$; 91%). Among statin users, most reported lipophilic statin use (simvastatin, lovastatin, fluvastatin, or atorvastatin; $n = 1,066$; 87%). Thus, we had insufficient numbers to conduct analysis stratified by statin type (i.e., lipophilic vs. hydrophilic) or by type of lipid-lowering medication (i.e., statin vs. non-statin). Data for dose and duration of statin use were unavailable. Therefore, we treated statin use versus statin non-use at baseline as our exposure variable, regardless of non-statin lipid-lowering medication use.

Outcome assessment

The presence and extent of histologic prostate inflammation was assessed by central review of baseline negative biopsies, as previously described (14). Chronic inflammation consisted mainly of lymphocytes and variable number of plasma cells and macrophages. Acute inflammation consisted of neutrophils. We calculated the extent of chronic and acute inflammation by dividing the number of biopsy cores with chronic and acute inflammation, respectively, by the total number of biopsy cores. The percentages of chronic and acute inflammation were each categorized as none, moderate (>0% to <20% of cores), and severe ($\geq 20\%$ of cores). Cutoff points were selected to ensure sufficient numbers in each category for analysis.

Statistical analysis

Of 8,122 men in the efficacy population, we excluded men with a baseline PSA <2.5 or >10 ng/mL ($n = 112$). We also excluded men with missing data for race ($n = 82$), body mass index (BMI; $n = 127$), smoking status ($n = 3$), and serum lipid levels ($n = 1,143$), resulting in $n = 6,655$ men. Men excluded because of missing lipid levels were less likely to be white, less likely to be North American, and less likely to use statins and nonsteroidal anti-inflammatory drugs (NSAID; Supplementary Table S1). However, age, BMI, diabetes status, alcohol use, or smoking status did not differ between groups. Men with and without lipid data had similar prevalence of chronic prostate inflammation, but men with missing lipid data were more likely to have acute prostate inflammation.

Differences in baseline characteristics by presence of chronic and acute prostate inflammation and by statin use were examined using the Student *t* tests and χ^2 tests for continuous and categorical variables, respectively, and Kruskal–Wallis tests for non-normally distributed continuous variables.

Logistic regression was used to estimate ORs and 95% confidence intervals (CI) for associations between serum lipids (borderline or abnormal vs. normal), statin use (vs. non-use), and the presence and extent of chronic and acute prostate inflammation. All models were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), and NSAID use. Models examining associations between serum lipids and prostate inflammation produced similar findings whether or not we further adjusted for statin use; thus, we chose to present findings adjusted for statin use. In sensitivity analyses, we explored further adjusting models examining associations between statin use and prostate inflammation for serum lipids. We also excluded men using any lipid-lowering medications (statins, fibrates, ezetimibe) from our analyses of associations between serum lipids and prostate inflammation. Finally, we explored excluding men using non-statin lipid-lowering medications ($n = 180$) from analysis of associations between statin use and inflammation. These sensitivity analyses produced similar findings and so these results are not presented.

Statistical analysis was performed using Stata, version 13.0 (Stata Corp.).

Results

Demographic characteristics of men with and without histologic prostate inflammation

Chronic and acute prostate inflammation was detected in negative baseline prostate biopsies in 5,151 (77%) and 1,005 (15%) men enrolled in REDUCE, respectively. Men with chronic prostate inflammation were older at the time of enrollment, less likely to be white, less likely to be European, and less likely to report heavy alcohol use relative to those without chronic prostate inflammation (Table 1). Men with acute prostate inflammation were younger at the time of enrollment, less likely to be European, and more likely to be current smokers than those without acute prostate inflammation. However, there were no differences in race or alcohol intake by acute inflammation status. Median BMI did not differ by either chronic or acute prostate inflammation status, and the prevalence of diabetes and NSAID use was similar in men with and without chronic and acute prostate inflammation (Table 1).

Table 1. Demographic characteristics of REDUCE participants according to the presence of chronic and acute prostate inflammation at baseline

	Chronic prostate inflammation			Acute prostate inflammation		
	Absent N = 1,504 (23%)	Present N = 5,151 (77%)	P	Absent N = 5,650 (85%)	Present N = 1,005 (15%)	P
Age, mean (SD), y	62.2 (6.1)	62.8 (6.0)	0.0006	62.8 (6.0)	62.1 (6.1)	0.0002
Race, n (%)						
White	1,400 (93)	4,698 (91)	0.021	5,177 (92)	921 (92)	0.989
Non-white	104 (7)	453 (9)		473 (8)	84 (8)	
Region, n (%)						
North America	336 (22)	1,562 (30)	<0.0001	1,496 (26)	402 (40)	<0.0001
Europe	990 (66)	2,947 (57)		3,405 (60)	532 (53)	
Other	178 (12)	642 (12)		749 (13)	71 (7)	
BMI, median (IQR), kg/m ²	26.8 (24.8–29.0)	26.9 (24.9–29.4)	0.277	26.9 (24.9–29.4)	26.9 (24.8–29.3)	0.766
Diabetes, n (%)						
No	1,369 (91)	4,726 (92)	0.373	5,174 (92)	921 (92)	0.944
Yes	135 (9)	425 (8)		476 (8)	84 (8)	
Statin use, n (%)						
No	1,212 (81)	4,226 (82)	0.198	4,632 (82)	806 (80)	0.178
Yes	292 (19)	925 (18)		1,018 (18)	199 (20)	
NSAID use, n (%)						
No	1,075 (71)	3,629 (70)	0.443	4,011 (71)	693 (69)	0.191
Yes	429 (29)	1,522 (30)		1,639 (29)	312 (31)	
Alcohol use, n (%) ^a						
None	360 (24)	1,372 (27)	0.040	1,472 (26)	260 (26)	0.693
Moderate	720 (48)	2,463 (48)		2,692 (48)	491 (49)	
Heavy	417 (28)	1,292 (25)		1,461 (26)	248 (25)	
Smoking status, n (%)						
Never	698 (46)	2,321 (45)	0.124	2,580 (46)	439 (44)	0.001
Former	604 (40)	2,028 (39)		2,257 (40)	375 (37)	
Current	202 (13)	802 (16)		813 (14)	191 (19)	

Abbreviation: IQR, interquartile range.

^aData for alcohol use was missing for n = 31 participants.**Demographic characteristics of men according to statin use**

Of a total of 6,655 participants in this analysis, 1,217 (18%) were statin users (Table 2). Relative to non-users, statin users were older at time of enrollment, more likely to be white, and more likely to be North American. Statin users also had higher BMI, a

higher prevalence of diabetes than non-users, and were more likely to also use NSAIDs. Smoking status differed by statin use, with statin users more likely to be former smokers and less likely to be never or current smokers than non-statin users. The prevalence of alcohol use did not differ significantly by statin use (Table 2).

Table 2. Demographic characteristics of REDUCE participants according to statin use

	Statin use		P
	No N = 5,438 (82%)	Yes N = 1,217 (18%)	
Age, mean (SD), y	62.6 (6.0)	63.1 (6.1)	0.005
Race, n (%)			
White	4,964 (91)	1,134 (93)	0.031
Non-white	474 (9)	83 (7)	
Region, n (%)			
North America	1,274 (23)	624 (51)	<0.0001
Europe	3,398 (62)	539 (44)	
Other	766 (14)	54 (4)	
BMI, median (IQR), kg/m ²	26.8 (24.7–29.1)	27.4 (25.4–30.1)	0.0001
Diabetes, n (%)			
No	5,063 (93)	1,032 (85)	<0.0001
Yes	375 (7)	185 (15)	
NSAID use, n (%)			
No	4,207 (77)	497 (41)	<0.0001
Yes	1,231 (23)	720 (59)	
Alcohol use, n (%) ^a			
None	1,383 (26)	349 (29)	0.054
Moderate	2,630 (49)	553 (46)	
Heavy	1,400 (26)	309 (26)	
Smoking status, n (%)			
Never	2,546 (47)	473 (39)	<0.0001
Former	2,052 (38)	580 (48)	
Current	840 (15)	164 (13)	

Abbreviation: IQR, interquartile range.

^aData for alcohol use was missing for n = 31 participants.

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Associations between serum lipid levels and prostate inflammation

Serum lipid levels were not associated with either the presence or extent of chronic prostate inflammation (Table 3). Neither were serum levels of total cholesterol, LDL, or triglycerides associated with the presence or extent of acute inflammation (Table 4). However, relative to men with low HDL levels (<40 ng/mL), those with high HDL (≥ 60 ng/mL) were less likely to have acute prostate inflammation (OR_{any vs. none} 0.79; 95% CI, 0.63–0.99), although the trend across HDL categories did not reach statistical significance ($P_{\text{trend}} = 0.071$). Men with high HDL were also less likely to have severe acute inflammation, defined as the presence of acute inflammation in $\geq 20\%$ of biopsy cores (OR_{severe vs. none} 0.66; 95% CI, 0.45–0.97; Table 4).

Associations between statin use and prostate inflammation

Relative to non-users, statin users were less likely to have chronic prostate inflammation (OR_{any vs. none} 0.81; 95% CI, 0.69–0.95), and the magnitude of this association was similar regardless of the extent of chronic inflammation (OR_{moderate vs. none} 0.82; 95% CI, 0.68–0.99 and OR_{severe vs. none} 0.80; 95% CI, 0.68–0.95; Table 5). Although statin use was not associated with the presence of acute inflammation (OR_{any vs. none} 0.97; 95% CI, 0.81–1.17), statin users were less likely to have severe acute inflammation than non-users (OR_{severe vs. none} 0.73; 95% CI, 0.53–1.00; $P = 0.052$), although this association was borderline significant.

Discussion

The prevalence of statin use has increased over the past few decades, and these medications are currently used by almost 30% of U.S. adults (20). In addition to their targeted cholesterol-lowering properties, statins reduce systemic inflammation (10) and have been associated with reduced inflammatory infiltrate in prostate tumors (13). However, direct effects of statins on histologic inflammation in benign prostate tissue have not been

described. Using data from 6,655 men with a negative baseline prostate biopsy participating in the REDUCE trial, we report that statin use was associated with reduced presence and extent of chronic prostate inflammation and reduced extent of acute prostate inflammation.

A state of chronic inflammation has been suggested to play a role in the development of many different cancer types, including prostate (21, 22). However, the clinical significance of histologic prostate inflammation remains controversial. Findings from the Prostate Cancer Prevention Trial (PCPT) showed that histologic inflammation in benign prostate tissue was positively associated with concomitant co-existence of high grade prostate cancer (16), with similar results seen in another small U.S. biopsy study (23). In contrast, data from REDUCE showed that the presence of histologic inflammation in benign prostate tissue was inversely associated with prostate cancer risk upon subsequent biopsy (14). An inverse association between benign prostate inflammation and prostate cancer risk has also been reported by a number of other epidemiologic studies (15, 24–26). With the exception of PCPT where histologic inflammation was assessed in PSA-independent prostate biopsies, all other studies evaluated the presence of histologic inflammation in PSA-driven prostate biopsies. Among men with an elevated PSA but a negative biopsy, elevated PSA may be due either to prostate inflammation or to undetected prostate cancer. Thus, men with an elevated PSA, caused by inflammation, may be at lower risk for prostate cancer detection upon re-biopsy, compared with their counterparts with elevated PSA caused by occult prostate cancer. As benign prostate tissue is difficult to obtain in the absence of a PSA-driven biopsy, the true direction of this association will be difficult to resolve. Given the null association between statin use and risk of either total or high-grade prostate cancer in REDUCE (27), the clinical implications of our observed inverse association between statin use and histologic prostate inflammation cannot be determined by the present study and require further investigation.

Table 3. ORs for associations between serum lipid levels and the presence and extent of baseline chronic prostate inflammation in REDUCE

	Presence of chronic inflammation			Extent of chronic inflammation				
	None	Any		None	Moderate; <20% of cores		Severe; $\geq 20\%$ of cores	
	n	n	OR (95% CI)	n	n	OR (95% CI)	n	OR (95% CI)
Total cholesterol								
<200 mg/dL	264	998	1	264	379	1	605	1
200–239 mg/dL	908	3,055	0.94 (0.80–1.09)	908	1,153	0.92 (0.77–1.10)	1,866	0.95 (0.80–1.12)
≥ 240 mg/dL	332	1,098	0.92 (0.76–1.11)	332	406	0.89 (0.71–1.10)	681	0.95 (0.77–1.16)
P_{trend}			0.657			0.501		0.854
LDL								
<130 mg/dL	733	2,591	1	733	969	1	1,583	1
130–159 mg/dL	424	1,496	1.03 (0.90–1.19)	424	568	1.04 (0.88–1.23)	917	1.05 (0.90–1.22)
≥ 160 mg/dL	347	1,064	0.94 (0.80–1.10)	347	401	0.93 (0.78–1.12)	652	0.95 (0.80–1.12)
P_{trend}			0.285			0.313		0.374
HDL								
<40 mg/dL	271	1,053	1	271	404	1	636	1
40–59 mg/dL	943	3,139	0.89 (0.77–1.04)	943	1,179	0.87 (0.73–1.04)	1,921	0.90 (0.77–1.07)
≥ 60 mg/dL	290	959	0.91 (0.75–1.11)	290	355	0.88 (0.70–1.11)	595	0.94 (0.76–1.15)
P_{trend}			0.993			0.857		0.848
Triglycerides								
<150 mg/dL	953	3,326	1	953	1,253	1	2,038	1
150–199 mg/dL	279	956	1.00 (0.86–1.17)	279	363	1.00 (0.84–1.20)	575	0.99 (0.84–1.17)
≥ 200 mg/dL	272	869	0.93 (0.79–1.09)	272	322	0.90 (0.75–1.09)	539	0.94 (0.80–1.12)
P_{trend}			0.329			0.276		0.508

NOTE: ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), statin use (no, yes), and NSAID use (no, yes).

Table 4. ORs for associations between serum lipid levels and presence and extent of baseline acute prostate inflammation in REDUCE

	Presence of acute inflammation			Extent of acute inflammation				
	None	Any		None	Moderate; <20% of cores		Severe; ≥20% of cores	
	n	n	OR (95% CI)	n	n	OR (95% CI)	n	OR (95% CI)
Total cholesterol								
<200 mg/dL	1,067	195	1	1,067	125	1	67	1
200–239 mg/dL	3,364	599	1.06 (0.89–1.27)	3,364	398	1.08 (0.87–1.34)	195	1.04 (0.78–1.39)
≥240 mg/dL	1,219	211	1.09 (0.87–1.35)	1,219	150	1.18 (0.91–1.52)	61	0.96 (0.67–1.39)
<i>P</i> _{trend}			0.669			0.313		0.655
LDL								
<130 mg/dL	2,802	522	1	2,802	352	1	165	1
130–159 mg/dL	1,645	275	0.97 (0.82–1.15)	1,645	181	0.95 (0.78–1.16)	91	1.00 (0.76–1.32)
≥160 mg/dL	1,203	208	1.04 (0.86–1.25)	1,203	140	1.04 (0.83–1.29)	67	1.07 (0.78–1.46)
<i>P</i> _{trend}			0.556			0.584		0.670
HDL								
<40 mg/dL	1,105	219	1	1,105	139	1	79	1
40–59 mg/dL	3,460	622	0.92 (0.78–1.09)	3,460	419	0.97 (0.79–1.19)	196	0.81 (0.62–1.07)
≥60 mg/dL	1,085	164	0.79 (0.63–0.99)	1,085	115	0.86 (0.66–1.13)	48	0.66 (0.45–0.97)
<i>P</i> _{trend}			0.071			0.248		0.120
Triglycerides								
<150 mg/dL	3,639	640	1	3,639	418	1	215	1
150–199 mg/dL	1,054	181	1.00 (0.84–1.20)	1,054	126	1.08 (0.87–1.34)	54	0.87 (0.64–1.19)
≥200 mg/dL	957	184	1.11 (0.92–1.33)	957	129	1.20 (0.97–1.49)	54	0.95 (0.69–1.30)
<i>P</i> _{trend}			0.268			0.118		0.884

NOTE: ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), statin use (no, yes), and NSAID use (no, yes).

Inflammation of benign prostate tissue is common, affecting 60% to 80% of men, but few lifestyle factors influencing prostate inflammation have been identified. Using REDUCE data, we previously reported a higher prevalence of histologic prostate inflammation in current versus former or never smokers (17), and a case-control study nested in the placebo arm of the PCPT reported that serum fatty acid levels were linked with prostate inflammation (28), showing that diet and lifestyle factors can impact prostate inflammation. Statins reduce PSA levels by 4% to 13% (29, 30), and the use of these medications has been inversely associated with benign prostatic enlargement and lower urinary tract symptoms (31, 32), suggesting that statins also directly influence prostate biology. Inflammation has been suggested as one potential mechanism contributing to these effects (33–35). Indeed, results from clinical trials have shown that statins have systemic anti-inflammatory properties over and above their cholesterol-lowering function (10, 11), and studies have also shown tissue-specific anti-inflammatory effects of statins, in adipose tissue (36) and in the vascular wall (37). However, this study is the first, to our knowledge, to show that statins may have anti-inflammatory effects in benign prostate tissue. With the exception of an inverse association between high HDL and acute prostate

inflammation, serum lipid levels were not associated with histologic prostate inflammation, suggesting that cholesterol-independent effects of statins may underlie the association with prostate inflammation.

Our findings should be considered in the context of the strengths and weaknesses of this study. First, although on-study biopsies in REDUCE occurred independent of PSA levels or PSA changes, the baseline biopsies, which were analyzed in this study, were largely carried out because of elevated PSA levels. As such, these results cannot be used to infer the relationship between statin use and histologic prostate inflammation in men without a PSA-driven biopsy. In addition, eligibility criteria for REDUCE ensured that all men had baseline PSA levels between 2.5 and 10 ng/mL. Thus, these data cannot be used to infer the association between statin use and inflammation in men with normal PSA values, and this may limit the generalizability of our findings to men with lower PSA levels. It is also possible that the prevalence of inflammation may differ in men with lower PSA levels, although prior studies have reported a similar prevalence of prostate inflammation across a range of PSA values (15, 16, 23). In addition, men with high-grade intraepithelial neoplasia, atypical small acinar proliferation, or those with a prostate volume >80 mL

Table 5. ORs for associations between statin use and presence and extent of baseline prostate inflammation in REDUCE

	Presence of chronic inflammation			Extent of chronic inflammation				
	None	Any		None	Moderate; <20% of cores		Severe; ≥20% of cores	
	n	n	OR (95% CI)	n	n	OR (95% CI)	n	OR (95% CI)
Statin use								
No	1,212	4,226	1	1,212	1,592	1	2,582	1
Yes	292	925	0.81 (0.69–0.95)	292	346	0.82 (0.68–0.99)	570	0.80 (0.68–0.95)
	Presence of acute inflammation			Extent of acute inflammation				
	None	Any		None	Moderate; <20% of cores		Severe; ≥20% of cores	
	n	n	OR (95% CI)	n	n	OR (95% CI)	n	OR (95% CI)
Statin use								
No	4,632	806	1	4,632	530	1	269	1
Yes	1,018	199	0.97 (0.81–1.17)	1,018	143	1.11 (0.90–1.38)	54	0.73 (0.53–1.00)

NOTE: ORs were adjusted for age at baseline (continuous), race (white, non-white), geographic region (North America, Europe, other), BMI (continuous, log-transformed), smoking status (never, former, current), and NSAID use (yes, no).

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or those who had undergone previous prostate surgery or those who had an International Prostate Symptom Score ≥ 25 or ≥ 20 while receiving α -blockers were excluded. Although these exclusions increase the homogeneity of the sample, they may limit the generalizability of our results. Finally, we lacked data for dose and duration of statin use, precluding dose–response analyses. We had access only to baseline data in REDUCE and therefore could not assess how patterns of statin use prior to baseline may have influenced PSA level and potentially affected trial eligibility. Study strengths include the large, multinational population in REDUCE. Moreover, histologic inflammation was centrally reviewed by a single pathologist using prostate biopsies confirmed to be negative for prostate cancer, whereas prior studies evaluated inflammation in benign regions of the prostate adjacent to prostate cancer (16, 24). Although it is possible that some men had prostate cancer that was missed in the baseline biopsy, the REDUCE study design better enables us to identify risk factors for histologic prostate inflammation while ruling out inflammation as a response to the tumor.

To conclude, epidemiologic and laboratory data strongly support an inverse association between statin use and risk of advanced prostate cancer, and improving our understanding of the mechanisms contributing to this inverse association will inform advanced prostate cancer prevention efforts (1). Using baseline data from the REDUCE trial, we report that statin use was associated with reduced presence and extent of histologic prostate inflammation among men with a negative prostate biopsy. The interpretation of these findings with respect to prostate cancer risk is somewhat challenging given the inverse association between histologic inflammation and prostate cancer risk in REDUCE that may be attributable, at least in part, to selection bias induced by PSA-driven baseline biopsies (14). The only study, to our knowledge, that avoided this potential source of bias by obtaining PSA-independent biopsies reported

a positive association between histologic prostate inflammation and prostate cancer risk (16). In the context of that study, in addition to a body of work linking inflammation with increased prostate cancer risk (38), our findings suggest that reduction of prostate inflammation could contribute to the inverse association between statin use and risk of advanced prostate cancer.

Disclosure of Potential Conflicts of Interest

R. Castro-Santamaria is the Vice President of R&D at GSK and has Ownership Interest (including patents) at GSK. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: E.H. Allott, G.L. Andriole, S.J. Freedland

Development of methodology: G.L. Andriole, S.J. Freedland

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.M. Moreira, R. Castro-Santamaria, G.L. Andriole, S.J. Freedland

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.H. Allott, L.E. Howard, D.M. Moreira, R. Castro-Santamaria, S.J. Freedland

Writing, review, and/or revision of the manuscript: E.H. Allott, L.E. Howard, A. C. Vidal, D.M. Moreira, R. Castro-Santamaria, G.L. Andriole, S.J. Freedland

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.E. Howard, D.M. Moreira, S.J. Freedland

Study supervision: S.J. Freedland

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Emma H. Allott, Lauren E. Howard, Adriana C. Vidal, et al.

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