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Statin Drug Use Is Not Associated with Prostate Cancer Risk in Men who are Regularly Screened

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Abstract

Purpose—Prospective cohort studies support that statin drug users have a lower risk of aggressive prostate cancer. Whether statin drug use influences risk of screen-detected disease is less clear, possibly because of complex detection biases. Thus, we investigated this association in a setting in which men had low baseline serum PSA concentration and were screened annually

Methods—We conducted a cohort study of 9,457 men aged 55 years old at randomization to the placebo arm of the Prostate Cancer Prevention Trial. The men reported new use of medications quarterly. We estimated the multivariable-adjusted hazard ratio (HR) of prostate cancer (N=574 in 62,192 person-years) for use of a statin drug and duration of use during the trial using Cox proportional hazards regression.

Results—Over seven years of follow up, use of a statin drug during the trial was not associated with risk of total (HR=1.03, 95% CI 0.82–1.30), lower- (HR=0.96, 95% CI 0.71–1.29), or higher-

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grade (HR=1.27, 95% CI 0.85–1.90) prostate cancer. Duration of use during follow-up also was not associated with risk of total (P-trend=0.7), lower- (P-trend=0.5), or higher- (P-trend=0.2) grade disease.

Conclusion—These prospective results do not support the hypothesis that statin drugs protect against prostate cancer in the setting of regular prostate cancer screening.

Keywords

statin; prostate cancer; risk; cohort

Introduction

Several prospective cohort studies support that men who use cholesterol-lowering statin drugs (HMG-CoA reductase inhibitors), especially for a longer duration, have a lower risk of prostate cancer with a more aggressive phenotype (1–3), or of prostate cancer diagnosed at a more advanced stage in the absence of screening (4). In contrast, the association between statin use and prostate cancer overall, and especially early-stage disease, has not been consistent (1). The lack of consistency may have arisen from differences in the extent to which a complex set of detection biases are operating. Detection bias in these studies could result from the possible influence of statins on serum PSA (5, 6) and from the tendency for men seeking medical care to receive regular screening for both elevated cholesterol and PSA (7).

To evaluate whether statins influence prostate cancer risk in the setting of regular screening for the disease, and in which detection bias is less likely to be operating, we conducted a prospective cohort study in the placebo arm of the Prostate Cancer Prevention Trial. Unlike standard cohorts, the PCPT protocol called for annual PSA screening and prostate digital-rectal examination during the seven years of the trial (8). Thus, the opportunity to detect prostate cancer was less influenced by factors (e.g., medical care uptake) that may be correlated with statin use than in other studies.

Methods

Study design and population

We included in this prospective cohort study all men randomized to the placebo arm of the multi-center SWOG-coordinated PCPT (N=9,457) (8). The PCPT tested whether the 5 α -reductase type II inhibitor, finasteride, prevents prostate cancer in 18,882 men aged 55 years old with a normal DRE and serum PSA $\leq$ 3.0 ng/mL. To be eligible, the men could not have had a diagnosis of cancer, aside from nonmelanoma skin cancer. The Institutional Review Boards at the participating centers approved the PCPT. Approval for this secondary analysis was received from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Assessment of statin use, PSA, and other factors

The men were asked to complete a survey about demographic characteristics, lifestyle, and medical history during the entry visit. At most study centers, the men were asked to

complete a food frequency questionnaire during the next annual visit. At the entry visit, height and weight were measured using standardized protocols. Weight was measured at each annual visit. Waist and hip circumferences were measured at the first annual visit after the entry visit.

At entry, current medication use was assessed by interview using both closed (e.g., aspirin, hypertension drugs) and open-ended questions. At each 6-month and annual clinic visit, and on every 3- and 9-month telephone call between clinic visits, the men were asked, "Have you started any new medications since we last talked with you?". We coded as a statin any of the following brand or generic medication names: Lescol (fluvastatin), Lipitor (atorvastatin), Altoprev (lovastatin), Mevacor (lovastatin), Pravachol (pravastatin), Zocor (simvastatin), Baycol (cerivastatin), Advicor (lovastatin), or statin. Other cholesterol-lowering drugs (i.e., Gemcor (gemfibrozil), Lopid (gemfibrozil), Tricor (fenofibrate), Cholestid (colestipol)) and nonspecific drugs (i.e., cholesterol drug, cholesterol lowering drug, high-cholesterol drug) were not included. Because the interviews requested new medication use, to determine statin use during the trial and to calculate duration of use during the trial, we assumed that once a man reported taking a statin he continued taking it until the end of the trial. We also assumed that the date a man reported first use of a drug was the date he began taking it. We did not have information on use prior to baseline in 1993–1997. The earliest possible statin use was 1987, the year first available on the market (9, 10).

As a component of the trial protocol, serum PSA was measured in a central laboratory (Esoterix, Inc, Calabasas Hills, CA) in samples collected at the entry visit and then annually. Serum total cholesterol was measured in the sample collected at the entry visit (11).

Ascertainment of prostate cancer cases

We included as cases those that were detected on a prostate biopsy performed for clinical indication, usually an elevated PSA and/or an abnormal DRE. We did not include as cases those detected on the end-of-study biopsy performed without clinical indication per PCPT protocol (8) as these cases otherwise would not have been detected during the trial. The biopsies were reviewed by pathologists at the study center and confirmed by the Prostate Diagnostic Laboratory, University of Colorado. We used the Gleason score that was determined by central review.

Statistical analysis

We calculated age-adjusted means and prevalences of baseline characteristics by statin use during the trial using linear regression. We estimated percent difference in serum PSA (repeated measures) between use and never use of a statin during the trial (updated, but truncated at date of prostate cancer diagnosis) using generalized estimating equations with an autoregressive correlation structure.

We estimated the hazard ratio and 95% confidence interval of total, localized (T1 or T2, and N0 and M0; N=507), Gleason 2–6 (lower-grade; N=351), and 7–10 (higher-grade; N=156) prostate cancer detected on a biopsy performed for clinical indication using Cox

proportional hazards regression. Few men were diagnosed with advanced-stage disease (5 T3N0M0, 3 N+M0, and 6 M+) because of the trial eligibility criteria and screening protocol, precluding its analysis. We evaluated statin use during the trial (use versus never) and duration of statin use during the trial (never, 0 to <4 years, ≥4 years) as time-dependent variables. Time at risk began accruing at the trial entry date and ended on the date of diagnosis or censor, whichever came first. Men diagnosed with prostate cancer on an end-of-study biopsy that was performed without clinical indication per trial protocol (8) were censored at their date of diagnosis. Men not diagnosed with prostate cancer were censored at the date of the end of study (7 years) or at the date of their last trial contact.

We report age- and multivariable-adjusted results. The final multivariable models included factors selected *a priori* based on their likely associations with prostate cancer and/or use of a statin: age (year, continuous), race (nonwhite versus white), first-degree family history of prostate cancer, body mass index (BMI, kg/m², continuous), and self-reported diagnosis of diabetes mellitus, regular aspirin use and use of other NSAIDs, and history of myocardial infarction. Attained education, alcohol consumption, physical activity, cigarette smoking history, and intake of energy, saturated fat, fish, tomatoes, calcium, and vitamin E were not confounders based on the change in the estimate approach, and thus were not included in the multivariable models.

We stratified by baseline serum cholesterol (cutpoint at 200 mg/dL, borderline high) and baseline serum PSA (cutpoint at the median, 1.1 ng/mL). We tested for effect modification by entering the product of use of a statin during the trial and baseline cholesterol or PSA in the model, the coefficient for which we evaluated using the Wald test.

We performed the statistical analyses using SAS release 9.2 (SAS Institute, Cary, NC) and report two-sided P-values.

Results

23.8% of men used a statin during the trial. Compared with never users, users were more likely to be white, were slightly shorter and had slightly higher BMI, were more likely to have a history of diabetes mellitus and myocardial infarction, had a higher serum cholesterol, and were more likely to be aspirin users (Table 1).

Statin use and serum PSA

Adjusting for age, ever users of a statin during the trial (mean 1.19 ng/mL) had a slightly lower baseline serum PSA than never users (mean 1.24 ng/mL; $P<0.01$). When considering repeated measures of PSA concentration and updating statin use during the trial, PSA was 2.7% higher in ever than never users after adjusting for age and race ($P=0.0002$). However, this difference was attenuated after multivariable adjustment (1.3% higher, $P=0.09$).

Association between statin use and prostate cancer

Statin use during the trial and duration of use were not associated with total, localized, lower- or higher-grade prostate cancer after age- or multivariable-adjustment (Table 2). The association between use and prostate cancer risk did not statistically significantly differ

between men with serum cholesterol <200 and 200 mg/dL at trial entry (Table 3) or between men with serum PSA below the median (1.1 ng/mL) or at or above the median at trial entry (Table 4).

Discussion

In this prospective study in the setting of regular screening for the disease and in which detection bias is less likely to be operating, use of a statin and duration of use during the trial were not associated with prostate cancer risk. Also, the percent difference in PSA concentration between statin users and never users was very small, a finding that helps to rule out a possible source of detection bias. We also did not observe evidence of effect modification by serum cholesterol or PSA measured at entry.

In the setting of *ad hoc* prostate cancer screening, detection bias can result when men who seek medical care are more likely to be screened for both elevated cholesterol and PSA than men who do not seek care. These screenings increase the opportunity that a man will be prescribed a statin and be recommended to undergo a prostate biopsy. This source of detection bias would tend to produce a positive association between use and risk of prostate cancer overall, especially screen-detected, early-stage disease (7). Indeed, some studies have observed possible, very slight to moderate, positive associations between statin use and prostate cancer overall, and early-stage disease (12–15). Murtola et al. were the first to address this source of detection bias in depth by conducting a large prospective study in the screening arm of the Finnish component of the European Randomized Study of Prostate Cancer Screening (16). In the Finnish component, men were screened for elevated PSA every four years; the maximum number of PSA tests was three. In the screened men, statin use was not positively associated with prostate cancer as would be seen with this source of detection bias. Instead, use was inversely associated with prostate cancer overall, and with early-stage disease, in a cumulative dose-dependent manner (16). In the PCPT, we also did not observe a positive association between statin use and prostate cancer. In contrast to Murtola et al., use was not associated with prostate cancer detected on a biopsy performed for clinical indication, and risk did not decrease with duration of use, suggesting that statins are unlikely to protect against screen-detected, early prostate cancer. Differences between the two studies that might explain differences in findings include population (Finns vs Americans), background of regular PSA screening in the population (Finland–no, US–yes), screening interval (Finland–4 years, US–1 year), trial entry criteria (e.g., Finnish study–no restriction on PSA, PCPT–restricted to PSA ≤ 3.0 ng/mL), sample size (Finnish study–23,320 men, PCPT–9,457 men), and source of information on statin use (Finland–national drug reimbursement database, PCPT–self reported medications use).

Another possible source of detection bias in the association between statin use and prostate cancer is the influence of these drugs on serum PSA. In small randomized trials, serum PSA has been shown to decline in hypercholesterolemic men after starting on a statin (17). Likewise, several observational studies conducted cross-sectionally (18, 19) or longitudinally (5, 6) found that statin users have lower PSA than nonusers and that serum PSA declines after starting to use a statin. An inverse association between statin use and PSA concentration would tend to produce an inverse association between use and prostate

cancer, including aggressive disease. While Murtola et al. did not find a difference in the age-adjusted geometric mean PSA concentration between current statin users and did not find an association between the cumulative number of doses received over time, they did observe that in men who later were diagnosed with prostate cancer, statin users had a lower prediagnostic PSA than nonusers (16). In our study, which used repeated measures of both statins and PSA over the course of the trial, users had a slightly higher PSA than never users during the trial. This difference was attenuated and not statistically significant after taking into account factors associated with both use and PSA concentration, supporting that this possible source of bias in the association between statin use and prostate cancer, is unlikely to be playing a role in low PSA settings (e.g., those with regular screening).

We stratified by serum cholesterol to determine whether statins may be differently associated with prostate cancer among those with and without elevated cholesterol. We previously observed in the PCPT that lower concentration (<200 mg/dL) was associated with a lower risk of high-grade prostate cancer (20), indicating possibly that low cholesterol rather than cholesterol lowering may be more important. However, statin use was not associated with risk, including risk of high-grade disease, either in men with lower or with elevated serum cholesterol.

Several features of our prospective study require discussion. The PCPT inclusion/exclusion criteria yielded a study population that may differ from the general US population. Nevertheless, the men included in the PCPT would reflect healthy men who are regularly screened, and thus have lower PSA. We relied on self-reported statin use in response to in-person and telephone interviews conducted quarterly, and assumed that once a man reported taking a statin he continued taking it and that the date he reported first use of a statin was the date he began taking it. The prevalence of use at trial entry was low (2.9%), although during the trial the prevalence increased substantially and we were able to capture use and duration of use during the trial. Information was not collected to address the influence of duration of use prior to trial entry (i.e., between 1987, date of first approval, and 1993), or dose, or brand of statin used on risk. Any misclassification of statin use due to our ascertainment methods are unlikely to be differential with respect to future prostate cancer risk, and thus any resulting bias would tend to attenuate any association. We could not address statin use and advanced disease because so few of these highly screened men were diagnosed at a late stage. Prior prospective studies suggest that statin users, especially long term, have a lower risk of being diagnosed with prostate cancer that is already advanced. Because the trial's duration was only 7 years, we could have missed the minimum etiologically-relevant duration of use. Nevertheless, the study goals were to address the link between statin use and early-stage disease in a setting in which the potential for differential detection of prostate cancer between users and nonusers could be minimized. In addition, for some analyses, the precision of the HRs is such that we cannot rule out the possibility of modest to moderate associations. We could not separately study Gleason 8+ disease, the outcome most clearly associated with low serum cholesterol in the PCPT (20), because the number of statin users with very high-grade disease was small.

Conclusion

Statin use does not appear to influence prostate cancer risk in a setting of annual screening and in which detection bias was less likely to be operating.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics^a of the 9,457 men by use of a statin drug during the trial, placebo arm of the Prostate Cancer Prevention Trial

	Use of a statin drug during the trial ^b		P
	Never	Use	
Number of men	7,208	2,249	
Mean age in years	63.3	63.3	
Nonwhite (%)	8.2	6.2	<0.01
Education (%)			
<High school	1.5	1.2	
High school	17.3	17.1	0.44
>High school	81.2	81.8	
Mean height in inches	69.9	69.6	<0.0001
Mean body mass index in kg/m ²	27.5	27.7	0.01
History of diabetes (%)	5.0	8.1	<0.0001
History of myocardial infarction (%)	3.2	10.7	<0.0001
Family history of prostate cancer (%)	15.6	14.5	0.20
Mean serum PSA concentration (ng/mL)	1.24	1.19	<0.01
Mean serum cholesterol concentration (mg/dL)	206.8	224.5	<0.0001
Cigarette smoking (%)			
Never	34.1	31.6	
Former	57.6	62.0	0.66
Current	8.3	6.4	
Physical activity (%)			
Sedentary	17.8	16.8	
Light	42.1	42.2	0.07
Moderate	30.2	29.4	
Active	9.3	11.2	
Mean alcohol intake (g/day)	9.78	9.59	0.57
Mean red meat intake (servings/day)	0.60	0.59	0.18
Mean calcium intake from food and supplements	914.2	902.2	0.23
Regular aspirin use (%)	38.6	51.9	<0.0001

Use of a statin drug during the trial ^a		
	Never	Use
P		
Regular use of other nonsteroidal anti-inflammatory drugs (%)	3.2	3.6
		0.47

^a All means (except age) and prevalences are least-square means adjusted for age.

Association^a of use of a statin drug and duration of use during the trial with risk of prostate cancer, placebo arm of the Prostate Cancer Prevention Trial

Table 2

	Use of a statin drug ^b		Duration of use of a statin drug ^b			P-trend
	Never use	Use	Never use	>0 to < 4 years	4 years	
Person-years at risk	54,284	7,908	54,284	6,407	1,501	
Total prostate cancer (N)	479	95	479	69	26	
Age-adjusted HR	ref	1.03 (0.82–1.29)	ref	1.03 (0.79–1.34)	1.05 (0.64–1.72)	0.7
Multivariable-adjusted HR	ref	1.03 (0.82–1.30)	ref	1.03 (0.79–1.34)	1.05 (0.64–1.72)	0.7
Localized (N)	422	85	422	60	25	
Age-adjusted HR	ref	1.04 (0.82–1.32)	ref	1.01 (0.77–1.34)	1.14 (0.68–1.91)	0.6
Multivariable-adjusted HR	ref	1.04 (0.81–1.32)	ref	1.01 (0.76–1.34)	1.14 (0.68–1.91)	0.6
Gleason score 2–6 (N)	297	54	297	43	11	
Age-adjusted HR	ref	0.98 (0.73–1.32)	ref	1.07 (0.77–1.50)	0.65 (0.30–1.39)	0.6
Multivariable-adjusted HR	ref	0.96 (0.71–1.29)	ref	1.05 (0.75–1.47)	0.64 (0.30–1.37)	0.5
Gleason score 7–10 (N)	124	32	124	21	11	
Age-adjusted HR	ref	1.24 (0.84–1.84)	ref	1.07 (0.66–1.74)	1.51 (0.68–3.36)	0.2
Multivariable-adjusted HR	ref	1.27 (0.85–1.90)	ref	1.10 (0.67–1.80)	1.52 (0.68–3.40)	0.2

^a Hazard ratio (HR) adjusted for age (year, continuous), race (nonwhite versus white), first-degree family history of prostate cancer, BMI (kg/m², continuous), histories of diabetes mellitus and myocardial infarction, and regular aspirin and regular NSAIDs use.

^b Use and duration of use of a statin drug during the trial were modeled as time-dependent variables.

Association^a between use of a statin drug during the trial and risk of prostate cancer by serum cholesterol concentration at trial entry, placebo arm of the Prostate Cancer Prevention Trial

Table 3

	Serum cholesterol concentration ^c					
	<200 mg/dL			200 mg/dL		
	Never use of a statin drug	Use of a statin drug	Never use of a statin drug	Use of a statin drug	Use of a statin drug	P-interaction
Person-years at risk	22,198	1,980	31,832	5,905		
Total prostate cancer (N)	214	19	262	76		
Age-adjusted HR	ref	0.79 (0.49–1.26)	ref	1.16 (0.89–1.50)		0.2
Multivariable-adjusted HR	ref	0.83 (0.51–1.36)	ref	1.14 (0.87–1.48)		0.1
Localized (N)	185	17	235	68		
Age-adjusted HR	ref	0.80 (0.48–1.32)	ref	1.16 (0.88–1.53)		0.2
Multivariable-adjusted HR	ref	0.83 (0.49–1.39)	ref	1.14 (0.86–1.51)		0.2
Gleason score 2–6 (N)	137	12	158	42		
Age-adjusted HR	ref	0.81 (0.45–1.47)	ref	1.10 (0.78–1.57)		0.4
Multivariable-adjusted HR	ref	0.86 (0.46–1.59)	ref	1.04 (0.73–1.48)		0.3
Gleason score 7–10 (N)	47	7	77	25		
Age-adjusted HR	ref	1.22 (0.55–2.71)	ref	1.18 (0.75–1.87)		1.0
Multivariable-adjusted HR	ref	1.30 (0.57–2.97)	ref	1.20 (0.75–1.92)		1.0

^a Hazard ratio (HR) adjusted age (year, continuous), race (nonwhite versus white), first-degree family history of prostate cancer, BMI (kg/m², continuous), histories of diabetes mellitus and myocardial infarction, and regular aspirin and regular NSAIDs use.

^b Use of a statin drug during the trial was modeled as a time-dependent variable.

^c Serum cholesterol concentration was missing for 44 men.

Association^a between use of a statin drug during the trial and risk of prostate cancer by serum PSA concentration at trial entry, placebo arm of the Prostate Cancer Prevention Trial

Table 4

Serum PSA concentration at trial entry					
	<1.1 ng/mL		1.1 ng/mL		
	Never use of a statin drug	Use of a statin drug	Never use of a statin drug	Use of a statin drug	P-interaction
Person-years at risk	26,851	4,050	27,433	3,858	
Total prostate cancer (N)	77	21	402	74	
Age-adjusted HR	ref	1.33 (0.81–2.18)	ref	1.00 (0.77–1.28)	0.3
Multivariable-adjusted HR	ref	1.39 (0.84–2.29)	ref	0.96 (0.75–1.25)	0.2
Localized (N)	64	19	358	66	
Age-adjusted HR	ref	1.43 (0.85–2.41)	ref	0.99 (0.76–1.30)	0.2
Multivariable-adjusted HR	ref	1.47 (0.86–2.50)	ref	0.96 (0.73–1.26)	0.2
Gleason score 2–6 (N)	50	14	247	40	
Age-adjusted HR	ref	1.45 (0.79–2.66)	ref	0.91 (0.65–1.28)	0.2
Multivariable-adjusted HR	ref	1.53 (0.83–2.83)	ref	0.85 (0.60–1.20)	0.2
Gleason score 7–10 (N)	16	5	108	27	
Age-adjusted HR	ref	1.32 (0.48–3.65)	ref	1.26 (0.82–1.93)	0.8
Multivariable-adjusted HR	ref	1.38 (0.49–3.86)	ref	1.26 (0.81–1.96)	0.8

^a Hazard ratio (HR) adjusted for age (year, continuous), race (nonwhite versus white), first-degree family history of prostate cancer, BMI (kg/m², continuous), histories of diabetes mellitus and myocardial infarction, and regular aspirin and regular NSAIDs use.

^b Use of a statin drug during the trial was modeled as a time-dependent variable.