Statin Use and Risk of Prostate Cancer in the California Men's Health Study Cohort

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Abstract

Statins have known anticarcinogenic effects, however, evidence for long-term statin use as effective chemoprevention for prostate cancer is inconsistent. We examined the association between statin use and risk of prostate cancer among 69,047 eligible participants in the California Men's Health Study, a prospective cohort of Northern and Southern California Kaiser Permanente (KP) members, ages 45 to 69 years, initiated in 2002. Prostate cancer cases were identified by linkage to the KP California Cancer Registries. Statin exposure, estimated from automated KP outpatient pharmacy records (available since 1991 in Southern California and since 1994 in Northern California), was treated as time-varying and defined as the cumulative days dispensed of any statin from the first dispensing until a prostate cancer diagnosis, radical prostatectomy, termination of membership, or end of study (December 31, 2004). Cox proportional hazards models with age as the time scale were used to estimate rate ratios, while controlling for confounding variables. During follow-up, 888 prostate cancer cases, including 131 advanced cases, were identified. There was no association between ever statin use or <5 years use and prostate cancer. Conversely, ≥5 years use was associated with a 28% lower risk for prostate cancer compared with nonuse (adjusted rate ratio, 0.72; 95% confidence interval, 0.53-0.99). This association did not differ markedly for advanced disease. However, the association did seem to be restricted to those who regularly take nonsteroidal anti-inflammatory drugs. Our findings suggest that long-term statin use might be associated with a reduced risk of prostate cancer but perhaps only among regular nonsteroidal anti-inflammatory drug users. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2218–25)

Introduction

Prostate cancer is the most common cancer diagnosis in men in the United States, with 218,890 new cancer cases and 27,050 cancer deaths estimated to be attributable to this disease in 2007 (1). Despite substantial research efforts, few risk factors for prostate cancer have been identified. A higher risk has been consistently reported among older persons, those of African American ethnicity, and those with a family history of prostate cancer (1). The effects of body mass index and diet remain controversial, but generally, the data suggest that obesity may be inversely associated with risk in middle-aged men (2-4), and a diet high in saturated fat might be positively associated with risk (1, 5). Additionally, diabetes may confer a lower risk, possibly due to lower circulating testosterone levels (6-9).

A class of pharmacologic agents potentially associated with prostate cancer is 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, or ''statins.'' Statins are the most commonly prescribed class of antihyperlipidemic drugs in the United States. Statin use accelerated during the mid to late 1990s after trials showed their safety and effectiveness in lowering cholesterol, and their ability to prevent adverse cardiovascular outcomes especially in those with higher baseline risk, such as persons with diabetes (10).

The interest regarding an association between statins and prostate cancer stems from experimental evidence of a positive association between cholesterol and prostate cancer (11-14). Additionally, substantial laboratory data indicate that statins may function as anticancer agents through proapoptotic, antiangiogenic, and antimetastatic processes (15-34). However, the results of individual randomized controlled trials (35-41), as well as those from systematic reviews of large trials (42-46), do not support an association between statins and cancer risk, although the number of cancers at any specific site, including the prostate, have been small and the follow-up time has been short. Results of observational studies of statin use and prostate cancer risk have been inconsistent (47-53).

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The inconclusive findings from trials and observational studies suggest a need for more studies of statin use and prostate cancer in larger, broader patient populations, considering the high prevalence of the disease and the ubiquitous use of these agents. Furthermore, the minimum duration of statin use that may be necessary to affect prostate cancer risk remains largely unexplored. To address these issues, we analyzed the association between statin use and risk of prostate cancer in a cohort of middle-aged men enrolled in a large health maintenance organization.

Materials and Methods

Study Population. A description of the California Men's Health Study (CMHS) cohort, recruitment, and data collection methods have been reported previously (54). Briefly, the cohort consists of 84,170 Northern and Southern California Kaiser Permanente (KP) members who completed mailed questionnaires in 2002 to 2003. Information was collected regarding baseline demographic characteristics, health status, and life-style behaviors using a two-stage mailed survey. Participants were ages 45 to 69 years at the time of the first mailing and had been members of Northern or Southern California KP for at least 1 year prior to study entry. The CMHS was approved by the Institutional Review Boards of KP Northern and Southern California. Study participants provided written informed consent.

For the current study, a participant was excluded from the analyses if at completion of the full questionnaire he either reported or had a KP cancer registry record of a prior cancer diagnosis with the exception of nonmelanoma skin cancer (n = 8,930); if he had a recorded prior radical prostatectomy (n = 17); or if he had no KP pharmacy benefit at baseline (n = 5,349). We further excluded those who were missing a prostate cancer diagnosis date (n = 4), information on race (n = 566), date of death (n = 29), or had no active KP membership on the date of the full questionnaire (n = 228). The remaining 69,047 men (82%) were included in the analysis.

Exposure Assessment. Automated outpatient pharmacy records were used to characterize statin use. Drug dispensing records include drug name, strength, quantity dispensed, date dispensed, and days supply. Complete outpatient pharmacy dispensing records are available from 1991 and 1994 onward for Southern and Northern California KP, respectively. Although all Food and Drug Administration–approved statins were dispensed by KP outpatient pharmacies, only lovastatin and simvastatin are on the formulary, and consequently, 94% of all dispensings were of one of these two agents (64% lovastatin, 30% simvastatin). Duration of statin exposure was estimated as the cumulative days dispensed of any statin from 1991 or 1994 until the end of follow-up. Because of apparent pill-cutting and changes in the strength and type of statin dispensed, we analyzed the total days dispensed of all statins combined for each patient, regardless of strength or type.

Exposure to statins was defined as more than a total of 100 days supply of one or more statins dispensed (henceforth referred to as ''ever use''). The 100-day cutpoint was used because KP plans often permit a 100-day supply of a chronic medication and thus restricting exposure to >100 days increased the likelihood that the medication was actually taken. Those who were never dispensed a statin from a KP pharmacy or who received a total of 100 days or less formed the reference group (henceforth referred to as ''nonusers'').

Prostate Cancer Case Ascertainment. Prostate cancer diagnoses were identified through the KP Northern and Southern California Cancer Registries, which provide data to the Surveillance, Epidemiology, and End Results program. These data are >99% complete for inpatient and outpatient admissions for the diagnosis of new and prevalent cancers from 1988 onward (55). The cancer registries provide information on disease stage at diagnosis based on the Surveillance, Epidemiology, and End Results staging system, which includes codes for *in situ* cancers, and for local, regional, or distant invasive disease. Cases were restricted to invasive prostate cancer.

Covariate Assessment. The following covariates were based on information obtained from the baseline questionnaire or from electronic medical or pharmacy records and were considered potential confounding variables: race (non-Hispanic White, Black/African American, Hispanic, Asian, other); family history of prostate cancer (yes/no); KP California region (North/South); education (less than high school, high school graduate, high school plus some college, and college graduate); body mass index (<18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m^2); high-fat diet (yes/no; yes >35% total calories from fat calories); regular nonsteroidal anti-inflammatory drug (NSAID) use (yes/no; yes = self-reported use of any NSAID for at least 3 to 4 days per week in the 3 months prior to questionnaire and/or >100 total days of prescription NSAIDs dispensed from a KP pharmacy prior to baseline); other antihyperlipidemic drug use at baseline [ever/never; ever = at least 1 dispensing prior to baseline of any of the following: fibric acid derivative, bile acid resin, niacin/nicotinic acid, ezetimibe, and miscellaneous (probucol, docosahexanoic acid)]; medical record of at least one prostate-specific antigen (PSA) test in the 5 years prior to baseline; history of diabetes (yes/no; recorded diagnosis in 2002 Northern or Southern California KP Diabetes Registry); histories of cardiovascular disease (including hypertension), hyperlipidemia, and benign prostatic hyperplasia (BPH) (self-report, yes/no). We also considered total number of months of KP membership at baseline, obtained from automated membership files, as a potential confounder.

Statistical Analysis. Data extraction and statistical analyses were performed using SAS 9.1 (SAS Institute, Inc.). Proportional hazards regression analyses with age as the time scale were used to estimate the rate ratios (RR) and 95% confidence intervals (CI) for prostate cancer incidence. Members of the study cohort were followed from the date of a completed CMHS questionnaire until the earliest occurrence of any of the following events: a prostate cancer diagnosis, a radical prostatectomy, a >90-day gap in KP membership, death, or the end of the study period (December 31, 2004). Cumulative use of statins was treated as a time-dependent variable in which the days supplies of each statin prescription dispensed were summed over time from the first recorded dispensing until the end of follow-up. Therefore, many exposed cohort members were prevalent

statin users at the start of follow-up. First, statin exposure was categorized as nonuse and ever use. Second, duration of statin use was evaluated, with use categorized as nonuser, 101 days to <5 years (henceforth referred to as ''short-term users''), and ≥5 years (henceforth referred to as ''long-term users''). All baseline covariates were entered into the models as categorical indicator variables, except for the continuous variable of months of KP membership. To maintain sample size throughout the evaluation of confounding, indicator variables for missing values were created for family history of prostate cancer, education, body mass index, regular NSAID use, and BPH.

All models were adjusted for race and KP California region. Any other covariate was considered a confounder if its inclusion in the multivariable model induced a 10% or greater change in the effect estimates. For the duration analyses, if the effect estimates in the final model decreased or increased linearly, dose-response was assessed through a test for linear trend.

To evaluate the association between statin use and the risk of advanced prostate cancer, the outcome was restricted to regional and distant disease (Surveillance, Epidemiology, and End Results summary stages II-V and VII, respectively), and men with local disease (stage I) or who were missing stage information were censored at their diagnosis date. Additionally, because statins are likely to be taken concurrently with NSAIDs to prevent cardiovascular disease and NSAIDs have inhibited prostate cancer growth in animal models (56), we examined whether regular NSAID use modified the statin-prostate cancer association through the inclusion of a cross-product term for regular NSAID use and ever statin use in the final adjusted Cox model. The Wald χ^2 P value for the interaction term provided a statistical assessment of effect measure modification.

We also attempted to ascertain whether differential rates of PSA screening in relation to statin use may have introduced a ''healthy screenee'' selection bias, especially among long-term users. Through stratification, we examined the association between statin use and prostate cancer risk among those with an electronic medical record of at least one PSA test within the 5 years prior to the questionnaire and among those with no record of a PSA test during this time period.

Results

Selected characteristics of the study cohort are provided in Table 1. The median length of membership from 1980 until baseline in the CMHS study cohort was 8.8 years and the majority of study participants (78%) had been KP members since before 1994. The cohort was primarily non-Hispanic White, however, Black/African Americans, Hispanics, Asians, and other races were well represented. The median age at the time of study enrollment was 58 years and 42% were age 60 or older. The majority of men were overweight or obese, were regular NSAID users, and had been tested for PSA within the 5 years prior to baseline (75%). Compared with the whole study population, long-term statin users were more commonly older, regular users of NSAIDs, and were more likely to have a history of cardiovascular disease, hyperlipidemia, diabetes, or BPH. They also were more likely to have had a PSA test (88%).

Of the whole study cohort, 37% (n = 25,470) had at least one statin-dispensing record, and of these men, 90% (n = 22,903) had received more than a total of 100 days supply and 19% (n = 4,770) were long-term users at or after start of follow-up. The majority (95%) of the exposed cohort either had a statin dispensing record within 1 year prior to baseline (68%) or initiated statin therapy after baseline (27%).

A total of 144,129 person-years were contributed by the 69,047 study cohort members. The maximum follow-up time after questionnaire completion was 3 years with a median of 2.3 years. During the follow-up period, 888 prostate cancer cases were diagnosed. Stage I or local disease accounted for 85% of the cases (n = 752). Only 131 cases were categorized as regional (stages II-IV, n = 118) or distant (stage VII, n = 13) disease at diagnosis and 5 cases had a stage that could not be determined. Among the 68,159 men without prostate cancer, 91% were followed until the end of the study period and 9% were censored because of a membership gap >90 days (n = 5,303), death (n = 585), or a radical prostatectomy (n = 16).

The following baseline covariates were positively associated with prostate cancer risk among those unexposed to statins at baseline: Black/African American race, family history of prostate cancer, membership in KP Southern California region, months of KP membership, and BPH. Obesity and diabetes were inversely associated. Having a medical record of a PSA test prior to baseline was not predictive of prostate cancer risk among the unexposed. Among the whole study population, ever statin use at baseline was positively associated with the majority of the covariates examined, but was inversely associated with family history of prostate cancer, college education, and high-fat diet and was not associated with BPH. The final multivariable Cox analyses were adjusted for race, KP California region, and diabetes. None of the other covariates appreciably changed the effect estimates with the exception of hyperlipidemia, whose inclusion in the analyses resulted in a 6% to 7% decrease in the effect estimates. This did not meet our criterion for confounding, so it was dropped from the final model.

There was no association between ever use of statins and prostate cancer risk (Table 2). The result for ever use was similar when the outcome was restricted to regional/distant disease. There also was no association between short-term use of statins and risk of prostate cancer. Conversely, use for 5 years or longer was associated with a 28% reduced risk. The test for linear trend was statistically significant (P_{trend} = 0.04). Although based on a small number of exposed cases, there was a suggestion that long-term use was associated with a slightly greater reduction in risk for regional/distant disease than for local disease (RRs 0.57 versus 0.72, respectively).

Because most prostate cancers have a long latency period, statin exposure shortly before diagnosis may have little effect on the development of the disease. When we excluded statin use within 1 year prior to the diagnosis date for each case and within 1 year prior to the corresponding date for the noncases in the risk set, the results changed negligibly: the adjusted RRs were 0.94 and 0.71 for short-term use and long-term use, respectively, compared with nonuse.

Table 1. Baseline characteristics by duration of statin drug use (CMHS 2002-2004)

Characteristic	Study population, n = 69,047 (%)	Duration of statin use*		
		0-100 d (n = 46,144)	101 d to <5 y (n = 18,133)	≥5 y (n = 4,770)
Age				
<50	10,697 (15.5)	19.0	9.4	4.2
50-59	29,421 (42.6)	45.7	38.2	29.5
60-69	28,082 (40.7)	34.3	50.8	63.9
≥70	847 (1.2)	1.0	1.6	2.4
Race				
Non-Hispanic White	43,138 (62.5)	63.5	59.6	63.6
Black/African American	5,076 (7.4)	6.9	8.4	7.7
Hispanic	9,209 (13.3)	13.4	13.8	10.9
Asian	5,370 (7.8)	7.9	7.7	7.3
Other	6,254 (9.1)	8.4	10.4	10.4
Family history of prostate cancer				
No	55,746 (80.7)	80.7	80.9	80.7
Yes	8,546 (12.4)	12.8	11.7	11.4
Missing	4,755 (6.9)	6.6	7.4	7.9
Membership, median (y)*	69,047 (8.8)	8.7	8.8	9.4
KP California region				
Southern	31,498 (45.6)	44.9	46.9	47.7
Northern	37,549 (54.4)	55.1	53.1	52.4
Education				
Less than high school	3,939 (5.7)	5.5	6.4	5.4
High school graduate	8,080 (11.7)	11.0	13.1	13.8
Some college	23,679 (34.3)	33.4	36.7	33.9
College graduate	33,071 (47.9)	49.8	43.4	46.6
Missing	278 (0.4)	0.4	0.4	0.3
Body mass index				
<18.5 kg/m^2	413 (0.6)	0.6	0.6	0.5
18.5 to <25 kg/m^2	17,726 (25.7)	28.5	20.1	19.5
25 to <30 kg/m^2	31,893 (46.2)	46.3	45.8	46.9
≥30 kg/m^2	17,913 (25.9)	23.0	31.9	31.5
Missing	1,102 (1.6)	1.6	1.6	1.6
High-fat diet†				
No	35,495 (51.4)	50.8	51.6	56.6
Yes	33,552 (48.6)	49.2	48.4	43.4
Regular NSAID use‡				
No	29,378 (42.6)	49.5	31.0	19.2
Yes	36,114 (52.3)	45.3	63.7	76.9
Missing	3,555 (5.2)	5.2	5.3	3.9
Other antihyperlipidemic drug dispensing§				
Never	63,554 (92.0)	97.4	85.7	64.4
Ever	5,493 (8.0)	2.6	14.3	35.6
History of PSA testing‖				
No	17,337 (25.1)	29.5	17.3	12.5
Yes	51,710 (74.9)	70.5	82.7	87.6
History of cardiovascular disease				
No	36,271 (52.5)	62.3	35.8	21.7
Yes	32,776 (47.5)	37.7	64.2	78.3
History of hyperlipidemia				
No	40,955 (59.3)	75.2	31.1	12.6
Yes	28,092 (40.7)	24.8	68.9	87.4
History of diabetes				
No	59,098 (85.6)	93.9	69.1	67.9
Yes	9,949 (14.4)	6.1	30.9	32.1
History of BPH				
No	52,840 (76.5)	78.2	73.9	70.2
Yes	13,533 (19.6)	18.2	21.7	24.9
Missing	2,674 (3.9)	3.6	4.4	5.0

NOTE: Baseline is the date of a completed CMHS questionnaire.
*Duration of use defined as the total days dispensed of statin drug(s) from the first recorded dispensing until the end of follow-up. All frequencies expressed as percentages, except for membership, which is median years(y) of Kaiser Permanente membership from 1980 until baseline.
†High-fat diet defined as having >35% of total daily calories come from fat calories.
‡Regular NSAID use defined as those who reported taking NSAIDs ≥3 to 4 d per week within the 3 mo prior to baseline and/or had >100 d total prescription NSAIDs dispensed from a Kaiser pharmacy prior to baseline.
§Other antihyperlipidemic drugs include fibric acid derivatives, bile acid resins, niacin/nicotinic acid, ezetimibe, and miscellaneous (probucol, docosahexanoic acid).
‖History of at least one medical record of a PSA test within 5 y prior to baseline.

Table 2. RRs for prostate cancer incidence associated with statin drug use (CMHS 2002-2004)

	Statin drug use*				
	Nonuse	Ever use	101 d to <5 y	≥5 y	*P* for trend
All prostate cancer (*n* = 888)					
No. of cases/total no. of person-years	618/104,596	270/39,534	228/32,606	42/6,928	
Multivariable RR (95% CI)†	1.0	0.92 (0.79-1.07)	0.97 (0.83-1.13)	0.72 (0.53-0.99)	0.04
Regional/distant prostate cancer (*n* = 131)					
No. of cases/total no. of person-years	95/104,596	36/39,534	31/32,606	5/6,928	
Multivariable RR (95% CI)†	1.0	0.80 (0.53-1.19)	0.85 (0.56-1.30)	0.57 (0.23-1.40)	0.50

*Total statin use from first recorded dispensing until the end of follow-up. Ever use defined as having been dispensed >100 total days of statins; nonuse defined as having been dispensed ≤100 total days.
†RR and 95% CI estimated from proportional hazards regression models with age as the time scale. Models adjusted for race, diabetes, and Kaiser Permanente California region. Statin use categories entered into the models as time-dependent variables.

The test of interaction provided some weak evidence of effect modification by regular NSAID use ($P_{interaction}$ = 0.10). Based on this result, we looked at risk associated with long-term statin use stratified by regular NSAID use (Table 3). Regular NSAID users who were long-term statin users had a lower risk of prostate cancer compared with the whole cohort analysis (RR, 0.64). However, long-term statin use was not associated with prostate cancer among never or episodic NSAID users (RR, 1.05).

Among those who had at least one statin dispensing prior to baseline, 85% had a record of a PSA test compared with 71% of those who were never users at baseline. The findings were similar for KP members who joined prior to 1994 (86% versus 73%) and for those who joined later (82% versus 66%), and was also similar for long-term users compared with nonusers (88% versus 71%). In the regression analyses, an inverse association between long-term statin use and prostate cancer risk was observed among those with and among those without a history of PSA testing (Table 4), although estimates for those without a PSA test were imprecise.

Discussion

Our findings suggest that use of statins for 5 years or longer may be associated with a lower risk of prostate cancer and the association may be more pronounced in patients with advanced disease, although our findings were imprecise due to small numbers. Our data also suggest that the effect of long-term use might be restricted to those who are regular users of NSAIDs.

Statin therapy as chemoprevention for prostate cancer is biologically plausible. Statins decrease cholesterol production through the inhibition of 3-hydroxy-3-methylglutaryl CoA reductase. This enzyme converts 3-hydroxy-3-methylglutaryl CoA to mevalonate, a precursor to cholesterol as well as numerous, potentially tumorigenic molecules (57). Statins have shown proapoptotic, antiangiogenic, and antimetastatic effects primarily through the decreased production of geranylgeranylated proteins, which are end-products of mevalonate conversion that are essential to the G_1-S transition in the cell cycle, regulation of bcl-2 expression, and factors associated with vascularization (57, 58). Additionally, cell signaling pathways that are essential for tumor cell adhesion and metastasis have been attenuated by statin administration, primarily through inactivation of RhoA (57). Statins also have shown immunomodulatory effects through both 3-hydroxy-3-methylglutaryl CoA reductase–dependent and -independent pathways, such as effects on leukocyte adhesion and migration, T cell activation, and the production of inflammatory mediators (58). Another mechanism by which statin use may be preventive of prostate cancer is by lowering PSA levels over time, which was observed in a retrospective cohort study of airline pilots (59).

Our data are consistent with a possible synergistic relation between statins and NSAIDs in prostate cancer chemoprevention (56). This hypothesis is based on laboratory data showing that either of these agents alone could inhibit prostate cancer growth primarily via apoptotic mechanisms and hence coadministration of these agents may augment their proapoptotic effects, as

Table 3. RRs for prostate cancer incidence associated with statin drug use by history of regular NSAID use (CMHS 2002-2004)

	Duration of statin drug use			
	0-100 d	101 d to <5 y	≥5 y	*P* for trend
Regular NSAID use (*n* = 36,114)				
No. of cases/total no. of person-years	317/48,215	147/21,356	30/5,379	
Multivariable RR (95% CI)*	1.0	0.89 (0.73-1.09)	0.64 (0.44-0.93)	0.04
Never or episodic NSAID use (*n* = 29,378)				
No. of cases/total no. of person-years	259/50,661	65/9,519	10/1,280	
Multivariable RR (95% CI)*	1.0	1.11 (0.84-1.47)	1.05 (0.55-1.98)	0.93

NOTE: Regular NSAID use was defined as having had reported taking NSAIDs ≥3 to 4 d/wk within the 3 mo prior to baseline and/or had >100 d total prescription NSAIDs dispensed from a Kaiser pharmacy prior to baseline (3,555 missing).
*RRs and 95% CI estimated from proportional hazards regression models with age as the time scale. Models adjusted for race, diabetes and Kaiser Permanente California region. Statin use categories entered into the models as time-dependent variables.

Table 4. RRs for prostate cancer incidence associated with statin drug use by baseline history of PSA testing (CMHS 2002-2004)

	Duration of statin drug use		
	0-100 d	101 d to <5 y	≥5 y
Men with ≥1 PSA test in the 5 y prior to baseline (n = 51,710)			
No. of cases/total no. of person-years	511/74,029	202/27,325	40/6,067
Multivariable RR (95% CI)*	1.0	0.95 (0.81-1.13)	0.74 (0.54-1.03)
Men with no PSA test record in the 5 y prior to baseline (n = 17,337)			
No. of cases/total no. of person-years	107/30,567	26/5,281	2/861
Multivariable RR (95% CI)*	1.0	1.05 (0.66-1.65)	0.39 (0.10-1.61)

*RR and 95% CI estimated from proportional hazards regression models with age as the time scale. Models adjusted for race, diabetes and Kaiser Permanente California region. Statin use categories were entered into the models as time-dependent variables.

has been shown in colon cancer cells (26, 56, 60, 61). Furthermore, regular NSAID use, particularly aspirin, has been associated with a lower risk of prostate cancer in many observational studies (62-72). Although the majority of observational studies of statin use and prostate cancer risk have considered potential confounding or effect modification by NSAID use (47, 48, 50, 51), it is not apparent that statin use was considered in the NSAID-prostate cancer studies. Therefore, future studies may want to consider examining whether the prevention of prostate tumorigenesis is dependent upon concomitant use of both agents.

Our results concur with the findings from several earlier observational studies. In the Health Professionals Follow-up Study (47) current statin use, assessed through self-report, was associated with a decreased risk of advanced prostate cancer [16 exposed cases; adjusted relative risk, 0.51; 95% CI, 0.30-0.86] and use for 5 years or longer was associated with an even lower risk (3 exposed cases; adjusted relative risk, 0.26, 95% CI, 0.08-0.83). The observed inverse association remained after adjusting for PSA screening history. However, in contrast to our findings, there was no association between statin use and organ-confined or total prostate cancer (47). A case-control study (48) conducted in Oregon using automated pharmacy data reported a 65% reduction in prostate cancer risk associated with ever use of statins compared with never use [30 exposed cases; adjusted odds ratio, 0.35; 95% CI, 0.20-0.64]. Among those with advanced disease (Gleason score ≥7), the adjusted odds ratio was 0.24 (95% CI, 0.11-0.53). Although based on a small number of exposed cases (n = 8), the study findings also suggest that use of any statins for at least 2 to 3 years was associated with an ~75% reduction in prostate cancer risk (48). In Quebec, a nested case-control study found a possible 26% lower risk of being diagnosed with prostate cancer in statin users compared with users of bile acid–binding resins (78 cases; adjusted relative risk, 0.74; 95% CI, 0.36-1.51; ref. 49). Data from a population-based, nested case-control study conducted in the Netherlands (50) suggested a decreased risk of prostate cancer associated with 6 months or longer statin use compared with no use (186 cases; adjusted relative risk, 0.37; 95% CI, 0.11-1.25). In Denmark, a population-based cohort study using automated exposure data reported a modest reduction in prostate cancer risk comparing those who had at least two statin dispensings to those with fewer dispensings (34 exposed cases; adjusted relative risk, 0.87; 95% CI, 0.61-1.23; ref. 51).

In contrast, at least two epidemiologic studies have reported an increased risk of prostate cancer associated with statin use. A matched case-control study using the General Practice Research Database in the United Kingdom reported a 30% increase in risk of prostate cancer among current users of statins compared with nonusers of any antihyperlipidemic drugs who had no history of hyperlipidemia (62 exposed cases; adjusted relative risk, 1.3; 95% CI, 1.0-1.9). However, those with untreated hyperlipidemia had a 50% increase in risk compared with normolipidemics (52). Findings from a hospital-based case-control study suggested a mildly elevated risk of early stage prostate cancer among users of statins for at least 3 years relative to never statin users (10 exposed cases; adjusted odds ratio, 1.3; 95% CI, 0.6-3.0); however, the findings were attributed to detection bias (53).

The CMHS cohort offers several advantages to examining the association between statin use and prostate cancer risk. First, the large size and age range of the cohort afforded a high prevalence of statin exposure and a sufficient number of prostate cancer cases to observe the effect of statin use while controlling for a number of potential confounders. The covariate data were rich with self-reported and automated medical record information on race/ethnicity, personal and family histories of cancer, and numerous behavioral and clinical factors. Second, a prospective study design and the use of automated pharmacy data minimized the potential for information bias. Third, we were assured of nearly 100% capture of all statin dispensings since 1991 or 1994 because the study cohort consisted of KP members who had pharmacy coverage at baseline, and historically, nearly 100% of KP members with pharmacy coverage fill all prescriptions at KP pharmacies (73). Fourth, exposure misclassification was reduced by defining a statin user as a person who had been dispensed >100 days of statins, thereby moving episodic and true never users to the unexposed group. Furthermore, both KP California regions periodically audit the days supply variable and systematically remove duplicate prescriptions. We expect, therefore, that any exposure misclassification should have been minimal and towards the null.

Although we did not conduct subanalyses of statin type because of a high prevalence of statin switching, exposure was homogenous in terms of statin lipophilicity. More

than 99% of the statin dispensings were of lovastatin, simvastatin, atorvastatin, or fluvastatin which are lipophilic. It has been hypothesized that lipophilic statins, unlike hydrophilic statins, act chemopreventively by preventing mevalonate synthesis both hepatically and extrahepatically (74).

There were also some limitations that should be considered when interpreting our findings. It is possible that the inverse association found between long-term statin use and risk of prostate cancer was due to the long-term statin users being ''healthier'' at baseline with respect to risk of prostate cancer because long-term users would have been PSA-screened more frequently prior to baseline than short-term users or nonusers. However, we believe that healthy screenee selection bias is unlikely to explain the results for the following reasons: (*a*) in the stratified analyses, the inverse association between long-term statin use and prostate cancer remained in both the PSA-tested and untested strata, although the latter was limited by small numbers; (*b*) the magnitude of such bias would be small because the prevalence of PSA testing was high in the study population (75% tested within 5 years before baseline) and the frequency of PSA testing was only 14% higher in baseline statin users than never users, and the relative difference between the PSA-testing histories for long-term users and nonusers was only 11.1% (using frequencies standardized to the age distribution in the CMHS cohort: 82.2% and 73.1% for long-term users and nonusers, respectively). Nevertheless, it is possible that screening differences between long-term statin users and nonusers prior to baseline may explain at least part of the observed inverse association.

There was also the concern for residual confounding by screening PSA because we were unable to adjust for screening PSA after baseline. However, because length of follow-up was only 3 years and screening was more common among statin users, we would expect any confounding to be minimal and to attenuate a real inverse association.

Lastly, chance cannot be ruled out as an explanation for our findings because, despite a large cohort, follow-up time was relatively short and so our analyses were limited by a small number of cases who were long-term statin users, especially those with advanced disease.

In this prospective study, we found statin use for 5 years or longer to be associated with a 28% lower risk of prostate cancer and possibly an even lower risk of advanced disease. Our data also suggest that the inverse association may be restricted to those who regularly take NSAIDs. This study adds to a growing body of evidence that duration of statin use may be important when investigating the chemopreventive or carcinogenic effects of these agents. Therefore, future studies of the relation between statins and cancer may benefit from both the assessment of length of statin use and the collection of detailed NSAID information.

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