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Original Contribution

Statin Use and Risk of Prostate Cancer: Results from a Population-based Epidemiologic Study

Ilir Agalliu[1,2], Claudia A. Salinas[1,3], Philip D. Hansten[4], Elaine A. Ostrander[5], and Janet L. Stanford[1,3]

[1] Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA.
[2] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY.
[3] Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA.
[4] Department of Pharmacy, School of Pharmacy, University of Washington, Seattle, WA.
[5] National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

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Epidemiologic studies of statin use in relation to prostate cancer risk have been inconclusive. Recent evidence, however, suggests that longer-term use may reduce risk of more advanced disease. The authors conducted a population-based study of 1,001 incident prostate cancer cases diagnosed in 2002–2005 and 942 age-matched controls from King County, Washington, to evaluate risk associated with statin use. Logistic regression was used to generate odds ratios for ever use, current use, and duration of use. No overall association was found between statin use and prostate cancer risk (odds ratio (OR) = 1.0, 95% confidence interval (CI): 0.8, 1.2 for current use; OR = 1.1, 95% CI: 0.7, 1.8 for >10 years' use), even for cases with more advanced disease. Risk related to statin use, however, was modified by body mass index (interaction $p = 0.04$). Obese men (BMI $\geq$30 kg/m^2) who used statins had an increased risk (OR = 1.5, 95% CI: 1.0, 2.2) relative to obese nonusers, with a stronger association for longer-term use (OR = 1.8, 95% CI: 1.1, 3.0 for $\geq$5 years' use). Although statin use was not associated with overall prostate cancer risk, the finding of an increased risk associated with statin use among obese men, particularly use for extended durations, warrants further investigation.

case-control studies; hydroxymethylglutaryl-CoA reductase inhibitors; obesity; odds ratio; prostatic neoplasms

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

Statin drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme that controls conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an essential precursor of cholesterol (1–3). Statins are used to treat hypercholesterolemia and have been shown to reduce cardiovascular disease incidence and mortality (4–7). Thus, use of statins has increased exponentially in the United States over the last decade (8).

Statin use in relation to prostate cancer etiology is of interest because 1) these drugs inhibit the synthesis of cholesterol, a precursor of androgens that also plays a role in cell signaling pathways (9); 2) mevalonate is necessary for the prenylation of proteins involved in signal transduction cascades downstream of membrane receptors that are crucial in cell growth and apoptosis (10, 11); and 3) in experimental models, statins inhibit cell proliferation, inflammation, oxidative stress, angiogenesis, and metastasis (2, 3, 11, 12).

Some studies suggest that statins may alter prostate cancer risk. Randomized clinical trials of statin use to prevent cardiovascular disease reported no associations with prostate cancer incidence (13–15), but such trials were limited by the short durations of use and brief follow-up periods (16, 17).

Correspondence to Dr. Janet L. Stanford, Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, 1100 Fairview Avenue N, M4-B874, Seattle, WA 98109-1024 (e-mail: jstanfor@fhcrc.org).

Several observational studies showed an inverse association between statin use and risk of prostate cancer (18–23), although others found no association (24–27). The inverse association observed in some studies was limited to subgroups of men with advanced-stage disease (20, 23); current, more-than-5-year users with advanced disease (21); or regular users of nonsteroidal antiinflammatory drugs (22). An increase in overall prostate cancer risk was observed for statin users in two studies (23, 28). To further examine the potential relation between these widely used medications and risk of prostate cancer, we conducted a population-based case-control study.

MATERIALS AND METHODS

Study population

Subjects were Caucasian and African-American men residing in King County, Washington, aged 35–74 years. Incident cases were diagnosed with histologically confirmed adenocarcinoma of the prostate from January 1, 2002, through December 31, 2005, and were identified via the Seattle-Puget Sound Surveillance, Epidemiology, and End Results Program cancer registry. Caucasian cases aged 50–74 years were randomly sampled (30 percent of cases); 100 percent of eligible Caucasian cases aged 35–49 years and 100 percent of African-American cases aged 35–74 years were selected. This registry provided information on Gleason score, tumor stage, and serum prostate-specific antigen (PSA) level at diagnosis. Of the 1,327 eligible cases ascertained, 1,001 (75.4 percent) were interviewed. Reasons for nonresponse were patient refused (14.9 percent), physician refused to allow patient contact (1.8 percent), patient could not be located (2.3 percent), patient moved (1.3 percent), patient was too ill or had other problems (2.6 percent), or patient had died (1.7 percent).

Controls without a history of prostate cancer were identified via random digit dialing, frequency matched to cases by 5-year age groups, and were recruited evenly throughout the ascertainment period for cases (29). Household census information was obtained for 81.4 percent of the 24,106 residential telephone numbers contacted. Of the 1,507 eligible controls identified, 942 (62.5 percent) were interviewed. Reasons for nonparticipation included the following: the person providing the household census data refused to provide information needed to send a recruitment letter to the eligible man in the household (10.5 percent), refusal (21.7 percent), illness (1.7 percent), language problem, moved or lost to follow-up (3.3 percent), or death (0.3 percent).

Subjects completed a structured, in-person interview administered by a trained male interviewer. The questionnaire collected demographic and lifestyle information, family history of cancer, medical history, medication use, and prostate cancer screening history prior to the reference date (i.e., date of diagnosis for cases and a similar, randomly preassigned date for controls that approximated the distribution of diagnosis dates for cases). Participants were also asked to complete a self-administered food frequency questionnaire and to provide a blood sample and consent for access to medical records. The study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center, and written informed consent was obtained from all study participants.

Use of statin medications

Information about statin use was obtained during the in-person interview, including ever use (use at least once a week for 3 months or longer), type of statin used (a show card listing all brand names and generic names for statin drugs approved by the US Food and Drug Administration was used to assist recall), dates of first and last use, and total duration of use for each episode. Current use was defined as use within the year prior to the reference date. Total duration of statin use was calculated as the sum of all episodes of use. Time since first use of a statin was defined as years elapsed from date of first use until the reference date. In addition, statins were grouped into two classes: 1) lipophilic or fat soluble (lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin), which may be distributed at low levels throughout the body; and 2) hydrophilic (pravastatin, rosuvastatin), which act primarily in the liver. Because all statins undergo hepatic first-pass metabolism, systemic bioavailability is limited (30, 31).

Genotyping

Germline DNA was used to genotype variants in two cytochrome P-450 genes, *CYP3A4* (rs2740574) and *CYP3A5* (rs776746). These single nucleotide polymorphisms were selected because they affect statin metabolism (32) and thereby may influence the statin–prostate cancer relation. The SNPlex Genotyping System from Applied Biosystems (Foster City, California) was used for genotyping (www.appliedbiosystems.com). Quality control included genotyping 84 blind duplicate samples, which showed 100 percent agreement. Both single nucleotide polymorphisms were in Hardy-Weinberg equilibrium in controls (exact $p > 0.05$).

Statistical analyses

Unconditional logistic regression was used to compute odds ratios and 95 percent confidence intervals (33). Potential confounding was assessed by fitting models including each main effect and then evaluating the change in parameter estimates when other variables entered the models one at a time. Covariates that changed the parameter estimates for statin use by more than 10 percent were incorporated into the final model and included age, race, and prostate cancer screening history (none, digital rectal examination only, PSA test) within the 5-year period prior to the reference date. Further adjustment for family history of prostate cancer, smoking status, body mass index (BMI; weight (kg)/height $(m)^2$), alcohol consumption, income, education, physical activity, and dietary intake (calories, fat) did not change risk estimates associated with statin use. Goodness of fit of statistical models was assessed by comparing the -2

TABLE 1. Selected demographic, lifestyle, and clinical characteristics of population-based prostate cancer cases and controls, King County, Washington, 2002–2005

Characteristic	Cases ($n = 1,001$)		Controls ($n = 942$)		OR*,†	95% CI*
	No.‡	%	No.‡	%		
Age (years)						
35–49	93	9.3	96	10.2		
50–54	108	10.8	113	12.0		
55–59	184	18.4	174	18.5		
60–64	218	21.8	187	19.9		
65–69	210	21.0	202	21.4		
70–74	188	18.8	170	18.0		
Race						
Caucasian	843	84.2	844	89.6	1.00	
African American	158	15.8	98	10.4	1.68	1.28, 2.21
First-degree family history of prostate cancer						
No	775	77.4	833	88.4	1.00	
Yes	226	22.6	109	11.6	2.24	1.75, 2.87
Body mass index (kg/m^2)						
<25	287	28.7	259	27.5	1.00	
25.0–29.9	492	49.2	444	47.1	1.00	0.81, 1.24
≥ 30	222	22.2	239	25.4	0.84	0.66, 1.08
Smoking status						
Nonsmoker	428	42.8	429	45.6	1.00	
Former smoker	462	46.2	394	41.9	0.95	0.71, 1.27
Current smoker	111	11.1	118	12.5	1.16	0.96, 1.40
Lifetime alcohol consumption (drinks/week)						
Nondrinker or <1	222	22.2	234	24.8	1.00	
Low (1–7)	354	35.4	316	33.5	1.18	0.93, 1.50
Moderate (8–14)	222	22.2	205	21.8	1.15	0.88, 1.49
High (≥ 15)	203	20.3	187	19.9	1.16	0.88, 1.52
Recent exercise (times/week)						
None	262	26.2	246	26.1	1.00	
1–2	315	31.5	283	30.0	1.06	0.84, 1.35
3–4	251	25.1	244	25.9	0.98	0.76, 1.26
≥ 5	172	17.2	168	17.9	0.96	0.73, 1.26
Education						
High school or less	196	19.6	181	19.2	1.00	
Some college	241	24.1	210	22.3	1.08	0.82, 1.42
College degree	262	26.2	261	27.7	0.95	0.72, 1.24
Graduate degree	301	30.1	289	30.7	0.98	0.75, 1.27
Prostate cancer screening§						
None	133	13.3	136	14.4	1.00	
Digital rectal examination only	159	15.9	263	27.9	0.62	0.45, 0.84
PSA*	709	70.8	543	57.6	1.34	1.02, 1.75

Table continues

log-likelihood difference between nested models. Tests for trend were used to assess linear trends in risk estimates by duration of statin use.

We also examined the association between statin use and prostate cancer by stratifying cases on clinical characteristics such as Gleason score (≤ 7, $3 + 4$, vs. ≥ 7, $4 + 3$),

TABLE 1. Continued

Characteristic	Cases ($n = 1,001$)		Controls ($n = 942$)		OR†	95% CI
	No.‡	%	No.‡	%		
NSAIDs* use						
None	792	79.1	746	79.1	1.00	
Former use	78	7.8	70	7.4	1.07	0.76, 1.51
Current use	131	13.1	126	13.4	0.98	0.75, 1.28
CYP3A4 (rs2740574) genotype						
AA	665	82.4	663	85.3	1.00¶	
AG	100	12.4	94	12.1	0.83	0.58, 1.19
GG	42	5.2	20	2.6	1.19	0.59, 2.43
CYP3A5 (rs776746) genotype						
GG	624	76.2	623	79.5	1.00¶	
GA	143	17.5	134	17.1	0.95	0.71, 1.26
AA	52	6.3	27	3.4	1.17	0.62, 2.21
Hypercholesterolemia						
No	572	57.1	556	59.0	1.00	
Yes	425	42.5	380	40.3	1.07	0.89, 1.29
Gleason score						
2–6	525	52.4				
7 (3 + 4)	294	29.4				
7 (4 + 3)	78	7.8				
8–10	99	9.9				
Unknown	5	0.5				
Stage of cancer						
Local	818	81.7				
Regional	159	15.9				
Distant	22	2.2				
Unknown	2	0.2				
PSA value (ng/ml) at diagnosis						
<4.0	134	13.4				
4.0–9.9	592	59.1				
10.0–19.9	143	14.3				
≥20.0	69	6.9				
Unknown	63	6.3				
Prostate cancer aggressiveness#						
Less aggressive	686	68.5				
More aggressive	315	31.5				

* OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; NSAIDs, nonsteroidal antiinflammatory drugs.

† Adjusted for age.

‡ Numbers may not add to total because of missing data.

§ Prostate cancer screening within the 5-year period before the reference date.

¶ Adjusted for age and race.

More aggressive: Gleason score 7 (4 + 3) or 8–10 or regional or distant stage or a diagnostic PSA ≥20 ng/ml; less aggressive: Gleason score 2–6 or 7 (3 + 4) and localized stage and a diagnostic PSA <20 ng/ml.

stage (localized vs. regional/distant), and a composite measure of disease aggressiveness (i.e., more aggressive: Gleason score ≥7, 4 + 3 or regional/distant stage or PSA ≥20 ng/ml at diagnosis; less aggressive: Gleason score ≤7, 3 + 4 and localized stage and PSA level <20 ng/ml). For these analyses, statin use in each group of cases was

TABLE 2. Distribution of selected demographic and lifestyle characteristics and medical conditions between users and nonusers of statins among population-based controls, King County, Washington, 2002–2005

Characteristic	Statin users ($n = 265$)		Statin nonusers ($n = 677$)		Chi-square p value
	No.*	%	No.*	%	
Age (years)					
35–49	11	4.2	85	12.6	<0.0001
50–54	15	5.7	98	14.5	
55–59	41	15.5	133	19.6	
60–64	65	24.5	122	18.0	
65–69	65	24.5	137	20.2	
70–74	68	25.7	102	15.1	
Race					
Caucasian	246	92.8	598	88.3	0.04
African American	19	7.2	79	11.7	
First-degree family history of prostate cancer					
No	231	87.2	602	88.9	0.45
Yes	34	12.8	75	11.1	
Body mass index (kg/m^2)					
<25.0	55	20.8	204	30.1	0.01
25.0–29.9	134	50.6	310	45.8	
≥30.0	76	28.7	163	24.1	
Smoking status					
Nonsmoker	104	39.2	325	48.0	0.01
Former smoker	132	49.8	262	38.8	
Current smoker	29	10.9	89	13.2	
Lifetime alcohol consumption (drinks/week)					
Nondrinker or <1	74	27.9	160	23.6	0.33
Low (1–7)	87	32.8	229	33.8	
Moderate (8–14)	49	18.5	156	23.0	
High (≥15)	55	20.8	132	19.5	

Table continues

compared with that for controls by using polytomous logistic regression. Lastly, we examined whether associations differed by age (<60 vs. ≥60 years), race (Caucasian vs. African American), first-degree family history of prostate cancer (yes vs. no), BMI (<30 vs. >30 kg/m^2), use of nonsteroidal antiinflammatory drugs, and *CYP3A4* and *CYP3A5* gene variants. SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses.

RESULTS

Demographic and lifestyle characteristics of cases and controls are presented in table 1. Cases were more likely than controls to report a first-degree family history of prostate cancer (23 percent vs. 12 percent) and to have had PSA screening in the 5 years before the reference date (71 percent vs. 58 percent). Cases and controls were similar with respect to BMI, smoking status, alcohol consumption, education, and recent exercise frequency. The prevalence of hypercholesterolemia for which statins are primarily prescribed was similar between cases and controls, 43 percent versus 40 percent (age-adjusted odds ratio (OR) = 1.07, 95 percent confidence interval (CI): 0.89, 1.29). With respect to clinical characteristics of prostate cancer, 31 percent of the cases were classified as having ''more aggressive'' disease.

The prevalence of any statin use among controls was 28 percent. Table 2 shows comparisons between users and nonusers in the control group. Statin users were older and more likely to be Caucasian, have a higher BMI, be former smokers, and have undergone PSA screening. There were no differences, however, with respect to first-degree family

TABLE 2. Continued

Characteristic	Statin users ($n = 265$)		Statin nonusers ($n = 677$)		Chi-square p value
	No.*	%	No.*	%	
Recent exercise (times/week)					
None	71	26.8	175	25.9	0.63
1–2	77	29.1	206	30.5	
3–4	63	23.8	181	26.8	
≥5	54	20.4	114	16.8	
Education					
High school or less	47	17.7	134	19.8	0.15
Some college	73	27.5	137	20.2	
College degree	65	24.5	196	29.0	
Graduate degree	80	30.2	209	30.9	
Prostate cancer screening†					
None	19	7.2	117	17.3	<0.0001
Digital rectal examination only	59	22.3	204	30.1	
PSA‡	187	70.6	356	52.6	
Hypercholesterolemia					
No	19	7.2	537	79.9	<0.0001
Yes	245	92.8	135	20.1	
Diabetes mellitus					
No	209	78.9	632	93.4	<0.0001
Yes	56	21.1	45	6.6	
Hypertension					
No	109	41.1	491	72.5	<0.0001
Yes	156	58.9	186	27.5	
Myocardial infarction					
No	202	76.2	660	97.5	<0.0001
Yes	63	23.8	17	2.5	
Stroke					
No	249	94.0	658	97.6	<0.0001
Yes	16	6.0	16	2.4	

* Numbers may not add to total because of missing data.
† Prostate cancer screening within the 5-year period before the reference date.
‡ PSA, prostate-specific antigen.

history of prostate cancer. Users of statin medications had a higher prevalence of self-reported hypercholesterolemia, diabetes mellitus, hypertension, myocardial infarction, or stroke in comparison to nonusers (all $p < 0.0001$).

The prevalence of statin use was similar in prostate cancer cases and controls (OR = 0.98, 95 percent CI: 0.80, 1.21) (table 3). No associations were observed with other measures of statin use (current use, duration of use, age at first use, time since first use). In relation to the type of statin used, most cases and controls, respectively, reported using atorvastatin (18.3 percent and 17.8 percent), followed by simvastatin (9.1 percent and 9.2 percent) and pravastatin and lovastatin (4.2 percent and 4.0 percent for each drug). The prevalence of use of other types of statins was low (<2 percent). Statins were also grouped as hydrophilic or lipophilic, but no association was found for either group.

Next, we examined statin use and prostate cancer risk according to clinical features (table 4). No associations were found between statin use and Gleason score (≤ 7, $3 + 4$ vs. ≥ 7, $4 + 3$), tumor stage (local vs. regional/distant), or prostate cancer aggressiveness status (less vs. more). In a subset analysis of metastatic or fatal prostate cancer ($n = 27$ cases), we found an odds ratio of 0.24 (95 percent CI: 0.05, 1.02) for ever use; however, only two cases who used a statin for less than 12 months contributed to this observation.

Lastly, we examined statin use in relation to prostate cancer in analyses stratified by age (<60 vs. ≥60 years), race (Caucasian vs. African American), first-degree family

TABLE 3. Associations between statin use and prostate cancer risk in a population-based case-control study, King County, Washington, 2002–2005

	Cases ($n = 1,001$)		Controls ($n = 942$)		OR*,†	95% CI*
	No.	%	No.	%		
Statin use						
None	712	71.1	677	71.9	1.00	
Ever use	289	28.9	265	28.1	0.98	0.80, 1.21
Current use	272	27.2	244	25.9	1.00	0.81, 1.24
Duration of use (years)						
<5.0	154	15.4	146	15.5	0.96	0.74, 1.23
5.0–9.9	90	9.0	81	8.6	0.97	0.70, 1.34
≥10	45	4.5	38	4.0	1.11	0.70, 1.75
Continuous					1.01	0.98, 1.03
Age at first use (years)						
<59‡	166	16.6	138	14.6	1.11	0.86, 1.43
≥59	123	12.3	127	13.5	0.81	0.60, 1.07
Time since first use (years)						
<5	145	14.5	133	14.1	0.96	0.74, 1.24
≥5	144	14.4	132	14.0	0.97	0.75, 1.27
Type of statin used§						
Hydrophilic	42	4.2	42	4.5	0.91	0.58, 1.44
Lipophilic	274	27.4	246	26.1	1.02	0.83, 1.27

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, race, and prostate cancer screening within the 5-year period before the reference date.

‡ Age 59 years was the median age at first use of a statin medication among controls.

§ Hydrophilic statins: pravastatin, rosuvastatin; lipophilic statins: lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin. Some cases ($n = 27$) and controls ($n = 24$) reported use of both types, so the analysis was also adjusted for the other type used.

history of prostate cancer (yes vs. no), BMI (<30 vs. ≥30 kg/m^2), use of nonsteroidal antiinflammatory drugs, and *CYP3A4* and *CYP3A5* gene variants. No differences in risk estimates were observed for any of these other factors, except for BMI (table 5). A statistically significant interaction between statin use and BMI was observed for ever use (interaction $p = 0.03$) and for duration of use (interaction $p = 0.04$). No association was observed among nonobese men, but, for obese men (BMI ≥30 kg/m^2), statin use relative to no use increased risk (OR = 1.5). The odds ratio was higher among obese, long-term users (OR = 1.8, 95 percent CI: 1.1, 3.0 for ≥5 years of use).

DISCUSSION

In this study, there were no associations between detailed measures of statin use and risk of either prostate cancer overall or more aggressive disease. Interestingly, analyses stratified by BMI showed that obese men (BMI ≥30 kg/m^2) who reported current use of a statin had an increased odds ratio of prostate cancer (OR = 1.5, 95 percent CI: 1.0, 2.1), which was stronger for those with extended durations of use (OR = 1.8 for >5 years of use).

Several randomized clinical trials of cardiovascular disease (13–15), as well as observational studies (19–28), have examined risk of prostate cancer in relation to statin use. The randomized trials data revealed no associations (13–15), but the trials were not designed to test the statin–prostate cancer hypothesis. Moreover, these trials involved short durations of statin use and limited periods of follow-up, which are likely inadequate for assessing statin use in relation to cancer occurrence (16).

Several observational studies have examined the association between statin use and prostate cancer (19–28). Most utilized hospital- or clinic-based populations or computerized pharmacy data for analyses. The prevalence of statin use varied widely across studies, ranging from 5 percent to 49 percent, and in some studies increased over time. Two studies reported an overall inverse association between any statin use and prostate cancer risk (18, 19), while others reported no association (24–27) or a positive association (23, 28). Shannon et al. (19) conducted a study within a Veterans Administration hospital population and reported an odds ratio of 0.4 (95 percent CI: 0.2, 0.7) for prostate cancer in relation to ever use of a statin and an odds ratio of 0.3 for more than 2 years' duration of use. Graaf et al. (18)

TABLE 4. Associations between statin use and clinical characteristics of prostate cancer in a population-based case-control study, King County, Washington, 2002–2005

Statin use	Controls ($n = 942$)		Cases, Gleason score ≤7 (3 + 4) ($n = 816$)				Cases, Gleason score ≥7 (4 + 3) ($n = 177$)			
	No.	%	No.	%	OR*,†	95% CI*	No.	%	OR†	95% CI
Gleason score										
None	677	71.9	584	71.6	1.00		120	67.8	1.00	
Ever use	265	28.1	232	28.4	0.96	0.77, 1.19	57	32.2	1.14	0.80, 1.63
Current use	244	25.9	220	27.0	0.99	0.79, 1.23	52	29.4	1.12	0.78, 1.62
Duration of use (years)										
<5	146	15.5	127	15.6	0.96	0.73, 1.26	27	15.3	1.00	0.63, 1.58
≥5	119	12.6	105	12.9	0.97	0.72, 1.29	30	16.9	1.31	0.83, 2.07
Continuous					0.99	0.97, 1.03			1.02	0.98, 1.07
	Controls ($n = 942$)		Cases, localized stage ($n = 818$)				Cases, regional/distant stage ($n = 181$)			
	No.	%	No.	%	OR†	95% CI	No.	%	OR†	95% CI
Tumor stage										
None	677	71.9	568	69.4	1.00		142	78.5	1.00	
Ever use	265	28.1	250	30.6	1.03	0.83, 1.27	39	21.5	0.79	0.53, 1.17
Current use	244	25.9	239	29.2	1.07	0.86, 1.33	33	18.2	0.73	0.48, 1.10
Duration of use (years)										
<5	146	15.5	136	16.6	1.03	0.79, 1.34	18	9.9	0.65	0.38, 1.11
≥5	119	12.6	114	13.9	1.03	0.77, 1.37	21	11.6	0.96	0.58, 1.60
Continuous					1.00	0.97, 1.03			0.99	0.94, 1.04
	Controls ($n = 942$)		Cases, less aggressive ($n = 686$)				Cases, more aggressive ($n = 315$)			
	No.	%	No.	%	OR†	95% CI	No.	%	OR†	95% CI
Disease aggressiveness‡										
None	677	71.9	478	69.7	1.00		234	74.2	1.00	
Ever use	265	28.1	208	30.3	1.01	0.81, 1.27	81	25.8	0.92	0.68, 1.23
Current use	244	25.9	199	29.0	1.05	0.83, 1.32	73	23.2	0.89	0.66, 1.22
Duration of use (years)										
<5	146	15.5	116	16.9	1.04	0.78, 1.37	38	12.1	0.78	0.53, 1.15
≥5	119	12.6	92	13.4	0.98	0.73, 1.34	43	13.7	1.08	0.73, 1.59
Continuous					1.00	0.97, 1.04			1.00	0.96, 1.04

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, race, and prostate cancer screening within the 5-year period before the reference date; respective analyses excluded cases for whom Gleason score ($n = 8$) or tumor stage ($n = 2$) was missing.

‡ More aggressive: Gleason score 7 (4 + 3) or 8–10 or regional or distant stage or a diagnostic PSA ≥20 ng/ml; less aggressive: Gleason score 2–6 or 7 (3 + 4) and localized stage and a diagnostic PSA <20 ng/ml.

used a pharmacy database to define exposure and observed a similar reduction in risk (OR = 0.4) of prostate cancer in relation to statin prescriptions. However, both of these studies had small sample sizes. Recently, Flick et al. (22) used data from the California Men's Health Study cohort to evaluate statin exposure and also reported an inverse association between 5 or more years of statin use and overall prostate cancer risk (relative risk = 0.72, 95 percent CI: 0.53, 0.99). The remaining studies reported no associations with overall prostate cancer risk, with the exception of two studies. Data from the United Kingdom General Practice Research Database (28) revealed a modest increase in prostate cancer risk (OR = 1.3, 95 percent CI: 1.0, 1.9) associated with use of a statin drug, and a large population-based study from Finland (23) also reported an elevated risk estimate for statin users (OR = 1.07, 95 percent CI: 1.0, 1.2).

With respect to clinical features of prostate cancer, Shannon et al. (19) reported an odds ratio of 0.3 (95 percent CI: 0.1, 0.5) for men with a Gleason score of higher than 7 in relation to ever use of a statin. In another recent analysis based on the Health Professionals Follow-up Study, Platz et al. (20) reported a significant reduction in risk of advanced-stage disease (relative risk = 0.5, 95 percent CI: 0.3, 0.9) and metastatic or fatal prostate cancer (relative risk =

TABLE 5. Associations between statin use and prostate cancer risk stratified by body mass index in a population-based case-control study, King County, Washington, 2002–2005

Statin use	Cases ($n = 779$)		Controls ($n = 703$)		OR*,†	95% CI*
	No.	%	No.	%		
Body mass index <30 kg/m^2						
None	582	74.7	514	73.1	1.00	
Ever use	197	25.3	189	26.9	0.87	0.68, 1.11
Current use	187	24.0	176	25.0	0.89	0.69, 1.14
Duration of use (years)						
<5	108	13.9	101	14.4	0.91	0.67, 1.23
≥5	89	11.4	88	12.5	0.83	0.59, 1.15
Continuous					0.99	0.96, 1.02
	Cases ($n = 222$)		Controls ($n = 239$)		OR†	95% CI
	No.	%	No.	%		
Body mass index ≥30 kg/m^2						
None	130	58.6	163	68.2	1.00	
Ever use	92	41.4	76	31.8	1.45	0.99, 2.13
Current use	85	38.3	68	28.5	1.50	1.00, 2.24
Duration of use (years)						
<5	46	20.7	45	18.8	1.21	0.75, 1.96
≥5	46	20.7	31	13.0	1.80	1.06, 3.03
Continuous					1.05	1.00, 1.10

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, race, and prostate cancer screening within the 5-year period before the reference date.

0.4, 95 percent CI: 0.2, 0.8) among users of cholesterol-lowering medications. An inverse association between statin use and advanced prostate cancer was also noted in some other studies (21–23). In the Cancer Prevention Study II Nutrition Cohort, long-term (≥5 years) statin use was associated with a reduction in risk of advanced prostate cancer (stage III, IV, or fatal; relative risk = 0.60, 95 percent CI: 0.36, 1.00) (21). Similar findings were observed in the California Men's Health Study Cohort regarding risk of regional/distant-stage disease in relation to statin use of 5 or more years (relative risk = 0.57, 95 percent CI: 0.2, 1.4), although this result was not statistically significant. In a third study that included 24,723 prostate cancer cases identified via the Finnish Cancer Registry, Murtola et al. (23) also reported an inverse association between statin use that was limited to advanced-stage disease (OR = 0.75, 95 percent CI: 0.62, 0.91), with a dose-response relation (p trend = 0.001).

In our study, we evaluated several measures of statin use (ever use, current use, duration of use) in relation to clinical features of prostate cancer such as Gleason score, tumor stage, and a composite measure of more aggressive disease, but we found no associations. In the subset of cases with regional or distant-stage disease, we found a nonsignificant reduction in risk for current statin users relative to nonusers (OR = 0.73, 95 percent CI: 0.5, 1.1). We also analyzed data according to distant-stage or fatal prostate cancer and found an inverse association between ever use of a statin medication (OR = 0.24, 95 percent CI: 0.05, 1.02) and metastatic or fatal disease, but there were only two exposed cases in this analysis, and both had used a statin for less than 1 year. These findings, however, are consistent with the hypothesized antimetastatic activity of statins (3, 11).

In relation to BMI, the Cancer Prevention Study II Nutrition Cohort investigators reported an interaction between long-term use of cholesterol-lowering drugs and BMI ($p = 0.02$) for advanced prostate cancer, but not for overall prostate cancer (21). However, in that study, there were no obese cases with advanced disease among long-term users of cholesterol-lowering drugs. Our study included 74 obese cases with more aggressive disease features; of these, 13 (18 percent) had used a statin for 5 or more years. The prevalence of long-term (≥5 years) statin use in the obese, more-aggressive-disease subgroup was not markedly different in comparison to the prevalence of long-term use (22 percent, $p = 0.3$) among obese men with less-aggressive disease. No clear biologic mechanism explains why statin use may preferentially increase risk of prostate cancer in obese men. Data from our control group show that statin users have higher BMIs and are more likely to have comorbid

conditions that may be indications for statin use. These medical conditions may also be associated with altered hormone levels that could affect prostate cancer risk. Of interest in this regard is a recently published study that found no difference in circulating levels of androgens between statin users compared with nonusers (34), but levels of sex hormone-binding globulin were significantly lower in statin users. With respect to the latter finding, a recent meta-analysis of studies of endogenous sex hormones and prostate cancer revealed that men with lower levels of sex hormone-binding globulin are at higher risk of developing prostate cancer (35). Another potential mechanism described by Goldstein et al. (36) is the ability of statin medications to increase the level of regulatory T cells, which may suppress antitumor T-cell response and thereby enhance cancer risk.

Our study has several strengths and limitations that should be considered when interpreting these results. Strengths are its population-based approach, sample size, and the fact that it was designed to test the association between statin use and risk of prostate cancer. In addition, we had detailed information about statin use that enabled us to evaluate duration of use, time since first use, time since last use, age at first use, and type of statin used. One concern in observational studies is the accuracy of self-reported exposures. In an attempt to address this issue, we compared self-reported use of statins (162 cases, 162 controls) with data from a computerized pharmacy database maintained by Group Health Cooperative of Puget Sound. There was 87 percent agreement for any use of a statin (90 percent and 85 percent agreement for cases and controls, respectively).

Another issue is that of potential confounding by prostate cancer screening, which is correlated with statin use and prostate cancer diagnosis. We evaluated the statin–prostate cancer relation after adjusting for various measures of prostate cancer screening: 1) any tests (none, digital rectal examination only, PSA) conducted within the 5-year period before the reference date; 2) the number of PSA tests (0, 1–2, 3–4, $\geq$5) performed within the 5-year period before the reference date; and 3) the time interval since the most recent PSA test and the reference date. Prostate cancer screening questions were asked in such a way so as to exclude diagnostic tests, and only 25 cases and 38 controls reported having a PSA screening test within 4 months of the reference date. We also analyzed our data by excluding men (84 cases, 46 controls) who reported that they ''had a problem or symptom'' at the time of the most recent PSA test prior to the reference date, and we performed separate analyses of men who reported having a PSA screening test within the 5 years before the reference date and of men who reported no such screening. Results from these analyses were similar to the risk estimates presented, which are adjusted for any prostate cancer screening tests within the 5 years prior to the reference date.

Other concerns include potential selection bias and recall bias. There is a possibility that men who did not participate had a different prevalence of statin use than those who joined the study. Although we had no data on nonparticipants, it is reassuring that the prevalence of statin use in our control group (28 percent) is similar to the prevalence estimates of 25 percent (21) and 27 percent (22) for statin use reported in other recently conducted studies. Standardized interviews, medication show cards, and trained interviewers were used to enhance reporting of drug use. Lastly, the prevalence of long-term statin use (>10 years) is low (4 percent in controls) since these medications became available in the United States only in 1987. Thus, our study, as well as other studies reported to date, was underpowered to address the relation between extended periods of statin use (>10 years) and risk of developing prostate cancer.

In conclusion, results of this study suggest that statin use is not associated with overall prostate cancer risk. However, obese men who use statin medications, particularly for longer durations, have an increased risk of prostate cancer relative to obese nonusers. This latter observation warrants further investigation, particularly given the high prevalence of both statin use and of obesity in the general population.

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