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Authors

Chan, June M
Kenfield, Stacey A
Paciorek, Alan
et al.

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Postdiagnostic Statin Use and the Risk of Lethal Prostate Cancer in the Health Professionals Follow-up Study

June M. Chan[1,2], **Stacey A. Kenfield**[1], **Alan Paciorek**[2], **Elizabeth A. Platz**[3], **Edward L. Giovannucci**[4], and **Meir J. Stampfer**[4]

[1]Department of Urology, University of California San Francisco (UCSF), San Francisco, California [2]Department of Epidemiology and Biostatistics, UCSF, San Francisco, California [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [4]Departments of Epidemiology and Nutrition, Harvard TH Chan School of Public Health & Harvard Medical School, Boston, Massachusetts

Abstract

Background—Observational studies suggest potential chemopreventive benefits of statins on prostate cancer outcomes, but data on the impact of postdiagnostic use are sparse.

Methods—We examined the association of postdiagnostic statin use and risk of lethal prostate cancer (metastases or prostate cancer death, $N = 242$) among 3,949 men diagnosed with localized prostate cancer from the Health Professionals Follow-Up Study between 1992 and 2008 and followed through 2010 (33,302 person years). We used Cox proportional hazards regression models to estimate relative risks and 95% confidence intervals (CI), adjusting for age, time period, time from diagnosis to questionnaire, body mass index, vigorous physical activity, smoking, aspirin use, clinical stage, PSA at diagnosis, Gleason score, primary treatment, and comorbidities.

Results—We found no statistically significant association between postdiagnostic current use of statins or duration of statin usage and the outcome of lethal prostate cancer [$N = 242$ cases; multivariate HR = 0.97 (95% CI, 0.72–1.31) for current use yes/no; HR = 0.85 (95% CI, 0.59–1.22) for 1 to 5 years of use, 0.96 (95% CI, 0.66–1.38) for 6+ years of use vs. never use].

Corresponding Author: June M. Chan, University of California San Francisco, 1450 3rd Street, Box 3110 (Urology), San Francisco, CA 94158-9001. Phone: 415-514-4923; Fax: 415-476-5366; june.chan@ucsf.edu.

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Authors' Contributions: **Conception and design:** J.M. Chan, S.A. Kenfield
Development of methodology: J.M. Chan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.L. Giovannucci, M.J. Stampfer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Chan, S.A. Kenfield, A. Paciorek, E.A. Platz, E.L. Giovannucci
Writing, review, and/or revision of the manuscript: J.M. Chan, S.A. Kenfield, A. Paciorek, E.A. Platz, E.L. Giovannucci, M.J. Stampfer
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.A. Kenfield, M.J. Stampfer
Study supervision: J.M. Chan, M.J. Stampfer

Conclusions—We observed little evidence that statin usage after diagnosis of localized prostate cancer reduces risk of progression to metastatic disease or prostate cancer–specific death.

Impact—These results do not support statins as a chemopreventive agent for prostate cancer progression.

Introduction

Statin usage may offer chemoprotection against the development of advanced or lethal prostate cancer (1, 2). Hypothesized mechanisms of action, primarily based on preclinical studies, include effects on cholesterol lowering and lipid metabolism, which may in turn increase cell proliferation, inflammation, and intratumoral steroidogenesis, and decrease apoptosis (1, 2). Several studies (including our own; ref. 3) suggest an inverse relation between long-term prediagnostic statin use and incidence of advanced or lethal prostate cancer. A recent meta-analysis concluded that there was a nonstatistically significant inverse association between statin use after diagnosis and risk of recurrence among men with prostate cancer, although the benefit appeared limited to men treated with radiation (2). Several, but not all (4, 5), studies published later reported inverse associations of statin use after prostate cancer diagnosis and risk of recurrence (6) or death (1); and two reported inverse associations for “ever use” and prostate cancer death (7, 8). We examined postdiagnostic statin use among men diagnosed with localized disease and risk of lethal prostate cancer in the Health Professionals Follow-Up Study.

Materials and Methods

Our study population consisted of participants in the Health Professionals Follow-up Study, who were diagnosed with localized disease (stage T3a or lower) in 1992–2008. Our primary outcome was lethal prostate cancer (N = 242), defined as metastasis to any organ or prostate cancer–specific death, with follow-up through January 2010 (33,302 person-years). Secondarily, we examined all-cause mortality.

We focused on current statin use and overall duration of use assessed on biennial questionnaires. Between 1992 and 2000, we used the variable “cholesterol lowering drug” to indicate statin use (yes/no), under the assumption that the great majority of this was statins at the time. From 2002 to 2010, we categorized current statin use based on the specific statin use question. Duration of use was computed by counting total years of statin use starting in 1992. Exposure status was updated every2years. For example, the exposure used for the follow-up period of 1992 to 1994 was data from the 1992 questionnaire; for 1994 to 1996, we used the 1994 questionnaire data, and so forth.

We used Cox proportional hazards regression to estimate the HR of lethal prostate cancer and 95% confidence intervals (CI). To adjust for potential confounding, the main multivariate model included age at diagnosis (years), time period (2-year intervals), time from diagnosis to questionnaire (years; continuous), body mass index (BMI; <25, 25 to <30, ≥30 kg/m^2), hours engaged in vigorous physical activity per week (<1, 1 to <3, and ≥3 hours/wk), smoking status (never, former, current), aspirin use, clinical stage (T1, T2, T3), PSA at diagnosis (<4, 4–9.9, 10-20, >20 ng/mL), Gleason score (<7, 7, >7), primary

treatment (surgery, radiotherapy, hormones, other), and comorbidities (stroke, myocardial infarction, hypertension, and diabetes). We also considered additional adjustment for other factors, previously found to be associated with lethal prostate cancer in this cohort [i.e., walking pace, dietary factors (red meat, fish, tomato sauce, selenium supplements, eggs, whole milk, low fat dairy, coffee, vegetables)], but these did not change the estimates and were not retained in the final multivariate analyses. We conducted sensitivity analyses limited to men who had a prior history of PSA screening; and also adjusting for prediagnostic statin use. We examined the potential for interaction effects by aspirin use, high cholesterol, grade, stage, BMI, family history of prostate cancer, and treatment.

This work was approved by the relevant Institutional Review Boards. All analyses were conducted using SAS 9.3.

Results

Sociodemographic characteristics of the study population are shown in Table 1. Among 3,949 men initially diagnosed with localized prostate cancer, there was no statistically significant association between postdiagnostic current statin use and the outcome of lethal prostate cancer [*N* = 242 cases; multivariate HR = 0.97 (95% CI, 0.72–1.31) for current use yes/no; Table 2). Similarly, we observed no association for duration of use and lethal prostate [HR = 0.96 (95% CI, 0.66, 1.38) for 6+ years of use vs. none].

Results were unchanged when either limiting to 3,881 men with prior history of PSA screening or after adjusting for prediagnostic statin use (data not shown). There was no evidence of effect modification by investigated *a priori* factors, with the exception of stage. Among men diagnosed with T2+ prostate cancer, current use of statins was associated with an HR of 0.65 (95% CI, 0.43–0.97); whereas among those diagnosed with T1 disease, the HR was 1.26 (95% CI, 0.84–1.87; *P*-value interaction = 0.02).

As expected, statin use was inversely associated with all-cause mortality (HR = 0.84; 95% CI, 0.71–0.99).

Discussion

In conclusion, in contrast with our earlier findings of an inverse relation with prediagnostic statin use, (3) these data provide little support for the hypothesis that statin usage after diagnosis of localized prostate cancer offers benefit against progression to lethal disease. Further study may be warranted for the potential benefit among men diagnosed with stage T2+ versus T1 disease.

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Table 1

Age-standardized clinical and demographic characteristics of 3,949 men initially diagnosed with localized prostate cancer in the Health Professionals Follow-up Study (1992–2010), by statin use at the time of diagnosis (numbers are percentages unless otherwise indicated)

	No statin (*N* = 3,264)	Statin (*N* = 685)
Age (y, SD)	69.1 (7.4)	70.7 (6.8)
Tumor stage		
T1	64	69
T2	34	29
T3	2	2
Gleason sum[a]		
2–6	59	60
7	25	27
8–10	8	7
PSA at diagnosis (ng/mL, SD)	11.5 (73.6)	7.8 (8.8)
History PSA screening	63	68
Primary treatment (%)[a]		
Surgery	46	44
Radiation	36	40
Hormones	5	4
Other	14	12
History of diabetes	7	12
History of hypertension	41	60
History of myocardial infarction	7	18
History of stroke	2	2
Family history of prostate cancer	10	8
Aspirin use	69	79
BMI (kg/m^2, SD)	25.8 (3.3)	26.1 (3.2)
Smoking status		
Current	5	3
Past	44	50
Vigorous exercise (hrs/wk, SD)	1.7 (3.2)	1.9 (5.0)

[a] Values of categorical variables may not sum to 100% due to rounding (treatment) or missing data (Gleason sum).

Table 2

Statin use and duration and lethal prostate cancer and all-cause mortality among 3,949 men diagnosed with prostate cancer in the Health Professionals Follow-up Study, followed from 1992 to 2010

	Current use of statin drugs			
	N	**Non-user**	**Current user**	
Lethal prostate cancer[a]	242	168	74	
Age-adjusted HR (95% CI)[b]		1.00	0.86 (0.65–1.14)	
Multivariable HR (95% CI)[c]		1.00	0.96 (0.72–1.29)	
Multivariable + CM HR (95% CI)[d]		1.00	0.97 (0.72–1.31)	
All-cause mortality	746	510	236	
Age-adjusted HR (95% CI)[b]		1.00	0.80 (0.68–0.93)	
Multivariable HR (95% CI)[c]		1.00	0.93 (0.79–1.09)	
Multivariable + CM HR (95% CI)[d]		1.00	0.84 (0.71–0.99)	
	Duration of statin use			
	N	**1–5 y**	**6 y+**	
Lethal prostate cancer[a]	242	43	47	P_{trend}
Age-adjusted HR (95% CI)[b]		0.88 (0.63–1.25)	0.81 (0.58–1.15)	0.25
Multivariable HR (95% CI)[e]		0.84 (0.59–1.19)	0.95 (0.67–1.36)	0.81
Multivariable + CM HR (95% CI)[f]		0.85 (0.59–1.22)	0.96 (0.66–1.38)	0.85
All-cause mortality	746	171	170	
Age-adjusted HR (95% CI)[b]		1.20 (1.00–1.44)	0.85 (0.71–1.03)	0.07
Multivariable HR (95% CI)[e]		1.26 (1.05–1.52)	1.00 (0.83–1.21)	0.87
Multivariable + CM HR (95% CI)[f]		1.11 (0.92–1.34)	0.87 (0.71–1.06)	0.11

[a] Lethal disease includes metastasis to bone or other organs at diagnosis or over follow-up, or prostate cancer-specific death.

[b] Age-adjusted models adjusted for age at diagnosis, time period (2-year intervals), and time since diagnosis to questionnaire (years; continuous).

[c] Multivariable models adjusted for age at diagnosis (years), time period (2-year intervals), time since diagnosis to questionnaire (years; continuous), BMI (<25,25 to <30, ≥30), vigorous physical activity (<1,1 to <3, and ≥3 hours/wk), smoking status (never, former, current, missing), aspirin use (yes, no), clinical stage (T1, T2, T3), PSA at diagnosis (<4, 4-9.99,10-20, >20, missing), Gleason score (<7, 7, >7, missing), and treatment (surgery, radiation, hormone, other).

[d] Multivariable + CM (co-morbidity) models additionally adjusted for stroke, myocardial infarction, hypertension, and diabetes.

[e] Multivariable models adjusted for age at diagnosis (years), time period (2-year intervals), time since diagnosis to questionnaire (years; continuous), BMI (<25,25 to <30, ≥30), vigorous physical activity (<1,1 to <3, and ≥3 hours/wk), smoking status (never, former, current), aspirin use (yes, no), clinical stage (T1, T2, T3), PSA at diagnosis (<4, 4-9.99,10-20, >20, missing), Gleason score (<7, 7, >7, missing) and treatment (surgery, radiation, hormone, other).

[f] Multivariable + CM (co-morbidity) models additionally adjusted for stroke, myocardial infarction, and hypertension.