Statin Drugs and Risk of Advanced Prostate Cancer

Statin Drugs and Risk of Advanced Prostate Cancer

Elizabeth A. Platz, Michael F. Leitzmann, Kala Visvanathan, Eric B. Rimm, Meir J. Stampfer, Walter C. Willett, Edward Giovannucci

Background: **Statins are commonly used cholesterol-lowering drugs that have proapoptotic and antimetastatic activities that could affect cancer risk or progression. Results from previous epidemiologic studies of the association between statin use and cancer have been inconsistent. We investigated the association of statin use with total and advanced prostate cancer, the latter being the most important endpoint to prevent.** ***Methods:*** **We analyzed data from an ongoing prospective cohort study of 34 989 US male health professionals who were cancer free in 1990 and were followed to 2002. Participants reported their use of cholesterol-lowering drugs on biennial questionnaires. Prostate cancer diagnosis was confirmed by medical record review. Multivariable-adjusted relative risks (RRs) were estimated from Cox proportional hazards regression models. Statistical tests were two-sided.** ***Results:*** **During 376 939 person-years of follow-up, we ascertained 2579 prostate cancer cases, 316 of which were advanced (regionally invasive, metastatic, or fatal). The age-standardized incidence rates of advanced prostate cancer were 38 and 89 per 100 000 person-years in current statin users and in past or never users, respectively. The multivariable-adjusted relative risk of advanced disease was 0.51 (95% confidence interval [CI] = 0.30 to 0.86) and of metastatic or fatal disease was 0.39 (95% CI = 0.19 to 0.77) for current statin use compared with no current use. The associations remained after adjusting for prostate-specific antigen screening history (advanced disease: RR = 0.57, 95% CI = 0.30 to 1.11; metastatic or fatal disease: RR = 0.35, 95% CI = 0.14 to 0.92). Risk of advanced disease was lower with longer statin use (P_{trend} = .003); compared with never use, the relative risk for less than 5 years of use was 0.60 (95% CI = 0.35 to 1.03) and for 5 or more years of use was 0.26 (95% CI = 0.08 to 0.83). We found no association between statin use and risk of total prostate cancer (RR = 0.96, 95% CI = 0.85 to 1.09).** ***Conclusions:*** **In this cohort of male health professionals, use of statin drugs was not associated with risk of prostate cancer overall but was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer. [J Natl Cancer Inst 2006;98:1819–25]**

Statins are commonly used cholesterol-lowering medications with documented effectiveness in the primary and secondary prevention of heart attack and stroke *(1)*. Among other activities, statins have proapoptotic and antimetastatic effects, which may make them relevant to cancer prevention or treatment *(2,3)*. Recently, a small clinic-based case–control study *(4)*, a large case–control study within a medical records database *(5)*, and a case–control study within a pharmacy database *(6)* each reported a 50%–65% reduced risk of prostate cancer in statin users compared with nonusers. However, other observational studies *(7–11)* and clinical trials *(12)* have not confirmed the inverse association between statin use and risk of prostate cancer. Statin use has also been inversely associated with breast cancer *(13,14)*, colorectal cancer *(15)*, and all cancers combined *(6,8,11)* in some studies, but other epidemiologic studies *(7,9,10,16–19)* and clinical trials *(12,20)* have not provided evidence for an inverse association.

Given that statin drugs alter biologic pathways that may influence carcinogenesis and metastasis, and given the contradictory results in the literature, we examined their use in relation to both total prostate cancer and the more clinically important advanced prostate cancer in a large prospective cohort study of American men during the period when statin drugs have been widely prescribed in the United States. This cohort, the Health Professionals Follow-up Study, has served as the study population for investigations of risk factors for a number of different cancers, including prostate cancer. Prostate cancer is the first cancer for which we have investigated the association for statins.

Subjects and Methods

Study Population

Participants were members of the Health Professionals Follow-up Study, an ongoing prospective cohort study of diet and other risk factors for heart disease, cancer, and other conditions (http://www.hsph.harvard.edu/hpfs/). In 1986, 51 529 men aged 40–75 years enrolled by responding to a baseline questionnaire, which constituted consent. The men completed biennial mailed questionnaires on demographic factors, medical history, and lifestyle factors and every 4 years completed mailed semiquantitative food-frequency questionnaires. Deaths were reported by family members and the postal system or were identified through the National Death Index, with a sensitivity of more than 98% *(21)*. The overall response rate to the biennial mailed questionnaires was 94%.

To encompass the era of statin drug use, we began follow-up on February 1, 1990. We excluded men who returned an incomplete or invalid food-frequency questionnaire in 1990 (3.1%), men who had died (2.0%) or who had a cancer diagnosis (except

Affiliations of authors: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and The Sidney Kimmel Comprehensive Cancer Center (EAP, KV) and Department of Urology, James Buchanan Brady Urological Institute (EAP) Johns Hopkins Medical Institutions, Baltimore, MD; Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD (MFL); Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (EBR, MJS, WCW, EG); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (EBR, MJS, WCW, EG).

Correspondence to: Elizabeth A. Platz, ScD, MPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Rm. E6138, 615 N. Wolfe St., Baltimore, MD 21205 (e-mail: eplatz@jhsph.edu).

See "Notes" following "References."

DOI: 10.1093/jnci/djj499

for nonmelanoma skin cancer) (5.0%) before the start of follow-up, men who withdrew from the study (0.1%), and men who did not respond to the 1990 questionnaire or did not answer the section on medication use (22.0%), leaving 34 989 men. Men who did and did not provide information on medication use in 1990 were not systematically different with respect to mean age (58.0 years, standard deviation [SD] = 9.6 years, versus 57.1 years, SD = 9.5 years), the prevalence of having had routine screening for elevated prostate-specific antigen (PSA) by 2000 (92.0% and 88.8%, respectively, of those who responded to at least one questionnaire from 1994 and 2000), the prevalence of a history of elevated cholesterol at baseline in 1990 (31.8% and 27.7%, respectively), or the prevalence of use of statin drugs in 2000 (27.5% and 26.6%, respectively, of those who answered the 2000 questionnaire).

The Human Subjects Committee of the Harvard School of Public Health approved the specific study of risk factors for prostate cancer within the Health Professionals Follow-up Study.

Ascertainment and Classification of Prostate Cancer Cases

For each man who reported a prostate cancer diagnosis on a follow-up questionnaire or for whom prostate cancer was mentioned on the death certificate, we sought medical and pathology reports pertaining to the diagnosis. Medical records and/or pathology reports were obtained for 90% of the men with prostate cancer. Study investigators who were blinded to exposure information reviewed the records to confirm the diagnosis and to record tumor–node–metastasis (TNM) *(22)* stage and Gleason sum. Because the reporting of prostate cancer was found to be highly accurate, we included in the analysis the remaining 10% of cases that were based solely on self-report or on the death certificate. We excluded men who were diagnosed with stage T1a disease (n = 71) because such diagnoses are susceptible to detection bias due to differential rates of surgery for benign prostatic hyperplasia. From February 1, 1990, through January 31, 2002, 2579 cases of incident non–stage T1a prostate cancer were ascertained in 376 939 person-years of follow-up. From information in the medical records or pathology reports, we were able to determine TNM stage for 79.7% of the cases and Gleason sum for 82.1% of the cases. Cases with missing stage or grade information were included in the analysis for total prostate cancer but were excluded from the analyses for stage or grade. We categorized disease as organ confined (n = 1714; stage T1b to T2b and N0M0) or advanced (n = 316; regionally invasive, metastatic, or fatal [irrespective of stage at diagnosis]: stage T3b or worse, N1, M1, or death from prostate cancer) and further subdivided advanced disease into metastatic or fatal (n = 233; N1, M1, or death from prostate cancer) versus regionally invasive. Disease was considered to have been fatal if prostate cancer was recorded on the death certificate as the underlying cause. In the analysis by stage, we excluded men with T3a disease (i.e., minimal extraprostatic extension) to increase the specificity of the organ-confined and advanced disease categorizations. We also categorized disease as lower grade (n = 1265; Gleason sum < 7) or higher grade (n = 852; Gleason sum ≥7). Men without information on stage were slightly older than those with information on stage (66.9 years, SD = 7.5 years, versus 62.8 years, SD = 7.9 years); after age standardization both groups of men had a similar prevalence of ever having had a screening PSA test (97.3% and 97.5%, respectively), of a history of elevated cholesterol at baseline in 1990 (35.8% and 33.6%, respectively), and of current use of cholesterol-lowering drugs at baseline in 1990 (4.5% and 4.9%, respectively).

Assessment of Statin Drug Use

In 1990 and then every 2 years, participants were asked to report their use of listed medications, including cholesterol-lowering drugs, during the previous 2 years. On the 2000 questionnaire only, the men were asked to report separately on their use of statin drugs and other classes of cholesterol-lowering drugs. Statins probably constituted the majority of the cholesterol-lowering drugs used in this cohort because they were the most commonly used type of cholesterol-lowering drug in the United States during this period *(23,24)*. Indeed, responses to the 2000 questionnaire indicated that by that year, 91% of the cholesterol-lowering drug used in this cohort was statins. Thus, in the analysis the use of any cholesterol-lowering drug, including the other cholesterol-lowering drugs reported in 2000, was counted as statin use. Duration of use of statin drugs was estimated by summing use across the 2-year periods encompassed by the biennial questionnaires. No information was available on brand, type, or dose of medications taken.

Statistical Analysis

We computed the directly age-standardized means and proportions for demographic and other factors by current use of statin drugs in 1994, partway through follow-up. We used Cox proportional hazards regression analysis to calculate age-adjusted and multivariable-adjusted hazard ratios (as relative risks [RRs]) and 95% confidence intervals (CIs) of total prostate cancer and of prostate cancer that was organ confined, advanced, metastatic or fatal, lower grade, or higher grade. All models were stratified by age (years) and calendar time (2-year intervals). The proportional hazards assumption was tested by adding the interaction term for statin drug use and age (years) to the models; this term was not statistically significant by the likelihood ratio test, confirming the assumption.

In the main analysis we used simple updating of current use of statin drugs (i.e., we used a time-dependent variable by entering into the model whether or not a man at risk was currently using statin drugs at each failure time), where the reference group was not current users (i.e., never users or past users). Information from the prior questionnaire was carried forward when information on use was missing. We also evaluated associations with baseline (i.e., 1990) use of statins (reference group was those who did not use at baseline) and ever use of statins (reference group was never users). For updated duration of ever use, we entered into the model two indicator variables for less than 5 years and 5 or more years of use, both of which were compared with never use. To test for trend across duration of ever use, we entered into the model a continuous duration variable, the coefficient for which was evaluated by the Wald test.

We also carried out a multivariable analysis in which we adjusted not only for age but also for factors that have been associated with increased or decreased prostate cancer risk in previous studies of this cohort: body mass index (BMI; kg/m^2) at age 21 years; height (inches); updated cumulative cigarette smoking in the past decade (pack-years); cumulative first-degree family history of prostate cancer; major ancestry (Scandinavian, Southern European, other white, other race); updated diagnosis of type

2 diabetes mellitus; updated vasectomy status; updated extent of vigorous physical activity (metabolic equivalent [MET]-hours/week); baseline intakes of total energy (kcal/d), tomato sauce (servings/d), red meat (servings/d), fish (servings/d), and alcohol (g/d); baseline intakes of energy-adjusted calcium (mg/d), fructose (g/d), and α-linolenic acid (g/d); baseline intakes of supplemental zinc (mg/d) and of high vitamin E (≥15 mg/d) (mostly supplement users); and updated regular use of aspirin (defined as use at least twice per week). We did not adjust for specific racial ancestry because the proportion of African American men was only 0.7% and of Asian men was only 1.5%; among those men, only one and four men, respectively, were diagnosed with advanced prostate cancer.

In additional analyses, we further adjusted for factors that we hypothesized a priori might be associated with statin drug use, including updated current BMI and baseline use of medications used to treat conditions related to cardiovascular disease (e.g., beta-blockers, calcium channel blockers, diuretics, and antihypertensives, including angiotensin-converting enzyme inhibitors) and certain other ailments (e.g., oral steroids, antidepressants, and histamine type 2 receptor antagonists). In a separate set of analyses to investigate the influence of PSA screening on the main findings of the study, we began follow-up in 1994 (the first time we asked about PSA testing) and included in the model updated indicator terms for the cumulative number of 2-year periods in which a man reported having had a screening PSA test (we excluded PSA tests performed for symptoms). In another analysis, we restricted the 1994–2002 analysis to men who had ever had a screening PSA test; men entered that analysis during the first 2-year period in which they reported a screening PSA test. We ran stratified models to assess whether the association between use of statin drugs and prostate cancer differed by age, use of aspirin, family history of prostate cancer, or current BMI and tested for interactions using the Wald test on a cross-product term. All statistical tests were two-sided, with P value less than .05 considered to be statistically significant. All analyses were performed using SAS release 8.2 (SAS Institute, Cary, NC). Given the available number of cases and person-years of follow-up, this study had 80% power to detect as statistically significant for a two-sided test with $\alpha = 0.05$ a relative risk of total prostate cancer of 0.83 or lower and a relative risk of advanced disease of 0.52 or lower, comparing current statin use with nonuse.

Results

In 1990 and 1994, 4.4% and 9.3%, respectively, of the men in the cohort reported using cholesterol-lowering drugs. By 2000, 23.8% of the men used cholesterol-lowering drugs. Compared with nonusers, men who currently used statins in 1994 were older; more likely to have undergone routine physical examinations and cholesterol checks; more likely to have a history of diabetes, hypertension, and myocardial infarction; more likely to take aspirin and medications to treat cardiovascular disease risk factors; and more likely to have smoked in the past 10 years, although they ate less red meat and more fish (Table 1). Current users in 1994 were more likely than nonusers to report having been screened for an elevated serum PSA but were slightly less likely to report having had an elevated PSA test.

Current use of statin drugs was not associated with either total prostate cancer or organ-confined disease after age adjustment or after multivariable adjustment (Table 2). However, compared

Table 1. Selected characteristics of current users and nonusers of statin drugs midway through follow-up in 1994*

Characteristic	Current use of statin drugs in 1994	
	No	Yes†
Participants (n)	27 796	2847
Mean age in 1994 (y)	60.9 ± 9.3	63.2 ± 8.7
White race (%)	91.2	89.9
Mean height (inches)	70.2 ± 2.8	69.8 ± 2.9
Mean BMI in 1994 (kg/m^2)‡	25.9 ± 3.5	26.3 ± 3.5
Mean BMI at age 21 (kg/m^2)	23.0 ± 2.9	23.1 ± 2.9
Cumulative family history of prostate cancer by 1996 (%)	13.4	11.3
Routine physical examination by 2000 (%)§	85.2	93.6
Screening cholesterol test by 2000 (%)§	86.5	97.8
Routine screening for elevated PSA by 2000 (%)§	83.4	91.9
Elevated PSA on a screening test by 2000 (%)§	9.7	8.1
History of vasectomy by 1994 (%)	25.9	26.7
History of type 2 diabetes mellitus by 1994 (%)	4.6	9.1
History of hypertension by 1994 (%)	31.6	48.3
History of myocardial infarction by 1994 (%)	6.0	22.7
Aspirin use in 1994 (%)	40.3	61.8
Regular use of medications to treat cardiovascular disease risk factors in 1994 (%)		
Furosemide diuretics	2.2	3.5
Other diuretics	4.7	6.5
Beta-blockers	9.3	23.1
Calcium channel blockers	9.0	24.3
Other antihypertensive drugs, including angiotensin-converting enzyme inhibitors	7.8	12.4
Cigarette smoking in the 10 y before 1994 (%)	18.8	22.4
Pack-years smoked in the 10 y before 1994 among those who smoked at some point in the 10 y before 1994	5.0 ± 4.3	4.4 ± 4.3
Vigorous physical activity in 1994 (MET-hours/wk)‖	12.9 ± 23.0	12.3 ± 23.2
Mean intakes in 1994		
Energy (kcal/d)	2024 ± 625	1930 ± 630
Alcohol (g/d)	9.9 ± 14.5	10.1 ± 14.6
Calcium (mg/d)¶	915.2 ± 403.7	906.6 ± 406.9
Fructose (g/d)	49.5 ± 16.7	51.3 ± 16.8
α-Linolenic acid (g/d)¶	1.12 ± 0.35	1.11 ± 0.35
Tomato sauce (servings/wk)	1.5 ± 1.1	1.5 ± 1.1
Red meat (servings/wk)	7.4 ± 4.8	5.9 ± 4.8
Fish (servings/wk)	2.2 ± 1.7	2.8 ± 1.7
Use of zinc supplement in 1994 (%)	34.8	42.0
Use of vitamin E supplement in 1994 (%)	44.4	52.7

*All values (except age) were standardized to the age distribution of the study population in 1994. Age-adjusted standard deviations for the factors with a continuous distribution were estimated from linear regression models.

†Also includes users of nonstatin cholesterol-lowering drugs (see subjects and Methods: Assessment of Statin Drug Use).

‡BMI = body mass index (weight in kilograms divided by square of the height in meters).

§Among men who reported their answer to questions on physical examination, cholesterol test, or prostate-specific antigen (PSA) screening test on at least one questionnaire since the start of the cohort through 2000.

‖MET-hour = metabolic equivalent of sitting at rest for an hour. Vigorous activities include running, jogging, racquet sports, swimming, and biking.

¶Nutrient intake was adjusted for total energy intake.

Table 2. Relative risk of prostate cancer in relation to current use of statin drugs among 34 989 male health professionals, 1990–2002

Prostate cancer	Current use of statin drugs	
	No*	Yes†
Total		
No. of cases	2257	322
Person-years at risk	334 702	42 237
$RR_{age\text{-}adjusted}$ (95% CI)‡	1.00 (reference)	0.94 (0.84 to 1.06)
$RR_{multivariable}$§ (95% CI)	1.00 (reference)	0.96 (0.85 to 1.09)
Organ-confined		
No. of cases	1474	240
Person-years at risk	335 455	42 320
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	0.94 (0.82 to 1.09)
$RR_{multivariable}$§ (95% CI)	1.00 (reference)	0.96 (0.83 to 1.11)
Advanced		
No. of cases	300	16
Person-years at risk	336 476	42 518
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	0.48 (0.29 to 0.81)
$RR_{multivariable}$§ (95% CI)	1.00 (reference)	0.51 (0.30 to 0.86)
Metastatic or fatal		
No. of cases	224	9
Person-years at risk	336 546	42 524
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	0.36 (0.18 to 0.71)
$RR_{multivariable}$§ (95% CI)	1.00 (reference)	0.39 (0.19 to 0.77)

*The reference group is men who were not currently using statin drugs. This reference group differs from that in Table 3, in which never users are the reference group.

†Also includes users of nonstatin cholesterol-lowering drugs.

‡RR = relative risk; CI = confidence interval.

§Relative risk adjusted for age; body mass index at age 21; height; pack-years of cigarette smoking in the previous decade; first-degree family history of prostate cancer; major ancestry; diabetes mellitus; vasectomy; vigorous physical activity; use of aspirin; intakes of total energy, calcium, fructose, α-linolenic acid, tomato sauce, red meat, fish, and alcohol; intake of supplemental zinc; and high intake of vitamin E.

with nonuse, current use was inversely associated with risk of advanced disease after adjusting for age (RR = 0.48, 95% CI = 0.29 to 0.81) and after additionally adjusting for prostate cancer risk factors (RR = 0.51, 95% CI = 0.30 to 0.86) (Table 2). The age-standardized incidence rates of advanced prostate cancer were 38 and 89 per 100 000 person-years among current statin users and nonusers (i.e., never or past users), respectively. The inverse association for current use of statins was even stronger for risk of metastatic and fatal prostate cancer combined (RR = 0.39, 95% CI = 0.19 to 0.77) (Table 2) and for fatal prostate cancer alone (four cases among users and 157 cases among nonusers; RR = 0.31, 95% CI = 0.11 to 0.85).

We next investigated the associations for baseline use versus never use, ever use versus never use, and duration of statin use with prostate cancer. Both baseline use of statin drugs (RR = 0.41, 95% CI = 0.19 to 0.87) and ever use of statin drugs (RR = 0.54, 95% CI = 0.32 to 0.89) were inversely associated with advanced disease in comparison with never use. Risk of advanced disease decreased with increasing duration of ever use (P_{trend} = .003; Table 3). The relative risk of metastatic and fatal disease combined for fewer than 5 years of ever use compared with never use was 0.52 (95% CI = 0.27 to 1.00); no cases were observed for 5 or more years of ever use (P_{trend} = .002), although eight cases were expected based on the incidence rate of metastatic and fatal disease combined in the never users.

Current use of statin drugs was not associated with risk of either higher grade disease (Gleason sum ≥7: RR = 0.93, 95% CI = 0.75 to 1.14) or lower grade disease (Gleason sum <7: RR = 1.00, 95% CI = 0.85 to 1.19). However, among men who had ever used statin drugs for 5 or more years, the relative risk of higher grade disease (RR = 0.75, 95% CI = 0.55 to 1.03; P_{trend} for duration = .21) was lower than the relative risk of lower grade disease (RR = 0.92, 95% CI = 0.71 to 1.18; P_{trend} for duration = .81).

Because the decline over time in the incidence of advanced prostate cancer related to screening for elevated PSA may have paralleled the increase over time in the use of statins, we assessed whether PSA screening history may have confounded the associations we observed. To do so, we repeated the analyses but began follow-up in 1994, the first year in which we asked the men to report on PSA screening. Beginning follow-up in 1994, the relative risks of advanced prostate cancer (all comparisons are to men who did not have a screening PSA test) were 0.85 (95% CI = 0.56 to 1.30) for having a screening PSA test during one 2-year period, 0.43 (95% CI = 0.24 to 0.78) for having a screening test in two 2-year periods, 0.26 (95% CI = 0.10 to 0.66) for having a screening test in three 2-year periods, and 0.10 (95% CI = 0.01 to 0.85) for having a screening test in four or more 2-year periods. After adjusting for this PSA screening history, the inverse association persisted between current use of statin drugs and advanced prostate cancer (beginning follow-up in 1994, n = 131 cases; RR = 0.57, 95% CI = 0.30 to 1.11) and metastatic and fatal prostate cancer (n = 84 cases; RR = 0.35, 95% CI = 0.14 to 0.92). Restricting the analysis to only those men who reported ever having at least one PSA test and comparing current statin users with nonusers, the relative risk of total prostate cancer was 0.90 (95% CI = 0.78 to 1.08) and of advanced prostate cancer was 0.48 (95% CI = 0.24 to 0.98).

Finally, adjusting for current BMI (RR = 0.51, 95% CI = 0.30 to 0.86) or adjusting simultaneously for baseline use of other prescription medications (RR = 0.52, 95% CI = 0.30 to 0.87) did not attenuate the association between current use of statin drugs and risk of advanced disease. The association between the use of statin drugs and risk of advanced disease did not differ among strata of age, aspirin use, first-degree family history of prostate cancer, or BMI (all $P_{interaction}$>.25).

Discussion

In this large prospective study, statin drug use was not associated with the risk of prostate cancer overall. However, men who currently used statin drugs had about half the risk of advanced prostate cancer and less than half the risk of metastatic or fatal prostate cancer of men who did not currently use these drugs. The risk of advanced prostate cancer was lower among men with longer ever use of these drugs, compared with never use. Use of statin drugs was not associated with histologic grade. However, longer term ever users had a lower risk of high-grade disease, although the trend was not statistically significant.

The question of whether there is an association between statin use and prostate cancer risk has been addressed in two recent meta-analyses of clinical trials of statins. The first, which used the raw data from 14 eligible randomized clinical trials, reported a cumulative incidence of genitourinary cancers of 1.9% both in the statin and in the placebo arms; separate estimates for prostate cancer incidence were not given *(20)*. The other meta-analysis reported a summary odds ratio (OR) of 0.98 (95% CI = 0.83 to 1.15) for total prostate cancer incidence, based on the only three trials that provided data on prostate cancer out of 26 eligible

Table 3. Relative risk of prostate cancer by duration of use of statin drugs among 34 989 male health professionals, 1990–2002

Prostate cancer	Duration of use of statin drugs*			P_{trend}‡
	Never†	<5 y	≥5 y	
Total				
No. of cases	2212	241	126	
Person-years at risk	329 357	29 159	18 423	
$RR_{age\text{-}adjusted}$ (95% CI)§	1.00 (reference)	1.02 (0.89 to 1.17)	0.83 (0.69 to 1.00)	.30
$RR_{multivariable}$‖ (95% CI)	1.00 (reference)	1.04 (0.91 to 1.19)	0.85 (0.71 to 1.03)	.49
Organ-confined				
No. of cases	1439	174	101	
Person-years at risk	330 100	29 227	18 448	
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	1.04 (0.89 to 1.23)	0.85 (0.69 to 1.04)	.59
$RR_{multivariable}$‖ (95% CI)	1.00 (reference)	1.06 (0.90 to 1.25)	0.87 (0.70 to 1.07)	.82
Advanced				
No. of cases	298	15	3	
Person-years at risk	331 092	29 367	18 535	
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	0.57 (0.34 to 0.96)	0.25 (0.08 to 0.78)	.002
$RR_{multivariable}$‖ (95% CI)	1.00 (reference)	0.60 (0.35 to 1.03)	0.26 (0.08 to 0.83)	.003
Metastatic or fatal				
No. of cases	223	10	0¶	
Person-years at risk	331 161	29 372	18 537	
$RR_{age\text{-}adjusted}$ (95% CI)	1.00 (reference)	0.49 (0.26 to 0.93)	0.00 (–)	.001
$RR_{multivariable}$‖ (95% CI)	1.00 (reference)	0.52 (0.27 to 1.00)	0.00 (–)	.002

*Also includes users of nonstatin cholesterol-lowering drugs.

†The reference group is men who never used statin drugs. This reference group differs from that in Table 2, in which men who were not currently using statin drugs are the reference group.

‡From a Wald test of the β coefficient for duration of use.

§RR = relative risk; CI = confidence interval.

‖Relative risk adjusted for age; body mass index at age 21; height; pack-years of cigarette smoking in the previous decade; first-degree family history of prostate cancer; major ancestry; diabetes mellitus; vasectomy; vigorous physical activity; use of aspirin; intakes of total energy, calcium, fructose, α-linolenic acid, tomato sauce, red meat, fish, and alcohol; intake of supplemental zinc; and high intake of vitamin E.

¶The expected number of cases based on the age- and time period–specific incidence rates in the never users is 8.0.

trials that were reviewed as part of the meta-analysis *(12)*. Our findings for total prostate cancer are consistent with the latter meta-analysis; we cannot determine the consistency of our findings with the former meta-analysis because it did not report separate estimates for prostate cancer. However, trials included in both meta-analyses had several limitations. One was the relatively short follow-up times for cancer outcomes [mean of 5 years *(20)*, with only two studies performing extended follow-up of 2 years *(25)* and 5 years *(26)* after the end of the randomized part of the trial]; another was that none reported specifically on advanced prostate cancer, the endpoint for which we observed an inverse association.

Among the observational studies that reported on statin drug use and prostate cancer risk, two reported statistically significant inverse associations between statin use and risk of total prostate cancer: Shannon et al. *(4)* and Singal et al. *(5)* observed ORs of 0.35 (95% CI = 0.20 to 0.64) and 0.46 (95% CI = 0.45 to 0.48), respectively. Graaf et al. *(6)* observed an inverse association of the same magnitude, although it was not statistically significant (OR = 0.37; 95% CI = 0.11 to 1.25). Shannon et al. *(4)* also reported that the association was stronger for disease with a Gleason sum of 7 or more (OR = 0.24; 95% CI = 0.11 to 0.53) than for disease with a Gleason sum of less than 7 (OR = 0.56; 95% CI = 0.26 to 1.21). Another observational study *(10)* observed a modest increase in the risk of prostate cancer in statin users (OR = 1.3, 95% CI = 1.0 to 1.9). Shannon et al. *(4)* and Singal et al. *(5)* both observed inverse associations for total prostate cancer. Because these studies were conducted in the United States during the PSA era (i.e., 1990s and 2000s), most of these prostate cancer cases were likely to be early-stage cases. By contrast, we observed an inverse association between statin use and the risk of advanced, but not organ-confined, disease during the same general time period. The reasons for the differences in the findings are unknown.

We evaluated the association between use of statin drugs and both total prostate cancer and advanced disease because statins influence many pathways that could potentially be involved in cancer development, growth, and metastasis *(27)*. In particular, statins inhibit 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase, the enzyme that catalyzes the conversion of HMG coenzyme A to mevalonate, which is the rate-limiting step in cholesterol biosynthesis. The reduced availability of cholesterol for incorporation into the cell membrane could influence membrane-associated signaling that promotes cancer cell survival, such as Akt signaling in prostate cancer cells *(28–30)*. Moreover, the reduced availability of isoprenoids derived from mevalonate for posttranslational modification of proteins such as Ras and Rho could limit their localization to the cell membrane and thus their growth promotion and survival activities *(2,3)*. However, we have no data that allow us to address whether these or other biologic mechanisms account for the inverse association that we observed between statin use and the risk of advanced prostate cancer.

Several issues related to the design and analysis of this study may influence the inferences that may be drawn from it and thus warrant discussion. The first issue is how we classified statin use. Statins were first introduced to the US market in 1987, and soon afterward their use surpassed that of other cholesterol-lowering drugs *(23,24)*. Based on these national use patterns and on data from this cohort on types of cholesterol-lowering drug used as reported in the 2000 questionnaire, we considered any use of

cholesterol-lowering drugs to represent statin use in the analysis reported here. In any event, misclassification of other cholesterol-lowering drugs as statins or misclassification of use due to inaccurate self-reporting of the use of these drugs should not be differential with respect to diagnosis of prostate cancer because the analysis was prospective. The effect of this type of error would lead to a relative risk estimate closer to the no-association value of 1.0. Thus, misclassification of statin drugs is highly unlikely to account for the strong inverse association that we observed for advanced prostate cancer.

A second issue relates to the conduct of the study in the PSA era. Since the advent of widespread PSA screening, advanced prostate cancer is less often diagnosed, but when it is, it is more often diagnosed in men who have not undergone PSA screening or who have been screened infrequently. In this cohort, statin users were more likely than nonusers to have had one or more screening PSA tests and men with multiple screening PSA tests were more likely than men with fewer tests to be diagnosed with organ-confined prostate cancer but less likely to be diagnosed with advanced disease. Thus, we took steps to assess whether a different extent of use of PSA screening between statin users and nonusers might account for our findings by conducting subanalyses in which we began follow-up in 1994, which was fully in the PSA era. We used two approaches to consider PSA screening history in these subanalyses: adjusting for updated cumulative number of periods in which a man had a screening PSA test and restricting the analysis to person-time at risk during which a screening PSA test was performed. With both approaches, the inverse association between statin use and risk of advanced and metastatic and fatal prostate cancers remained. Nevertheless, although PSA screening did not appear to account for our findings, we cannot rule out bias due to subtle differences in patterns of PSA screening between statin users and nonusers.

A third issue is the nonresponse to the baseline questions on medications use; 22% of the otherwise eligible men were excluded from the analysis because they had not provided information on medication use at baseline. The analysis we conducted was prospective, and thus, the likelihood of selection bias as a result of differential nonresponse was small. Nevertheless, we explored this possibility. Men who did and did not provide information on medication use at the start of follow-up in 1990 did not differ substantially on age, PSA screening history, history of elevated cholesterol, or the prevalence of statin drug use in 2000. Further evidence that the findings of this study were not due to selection bias comes from the result of an additional analysis (not shown) in which we started follow-up in 1994 and counted as statin users men who indicated such use in either 1992 or 1994; 58% of the men excluded from the analysis for lack of information on medication use in 1990 did provide information on medication use subsequently on the 1992 or 1994 questionnaires. In that analysis, the multivariable relative risk of advanced disease was 0.39 (95% CI = 0.18 to 0.84), similar to what was observed in the main analysis.

The fourth issue is the possibility of confounding or differential detection of prostate cancer by use of medical care. However, because of the large study size and the extensive information collected on each cohort member, we were able to control for a number of known and suspected risk factors for prostate cancer that may co-occur with use of statins, such as dietary and lifestyle factors, including the use of aspirin. The inverse association between statins and advanced prostate cancer remained even after multivariable adjustment. We also adjusted for use of prescription medications, including antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, to assess confounding and differential detection. The inverse association between statin use and risk of advanced prostate cancer remained, indicating a lack of confounding by use of other medications. Furthermore, there was no consistent pattern of association between the use of prescription medications and risk of prostate cancer (data not shown). We would have expected that many prescription drugs would have been inversely associated with advanced prostate cancer if going to the doctor increased both the likelihood of receiving a prescription and the likelihood of having a screening PSA test.

The fifth issue is the small sample size in a few of the subgroup analyses. The overall study had a large sample size, which allowed us to investigate the association of current statin use, not only with total prostate cancer but also with advanced disease. The clinically important prostate cancer endpoint that should be the target for prevention is advanced disease, which is the most likely stage to lead to death. In the analysis of duration of ever use, the number of cases of total prostate cancer with longer term (≥5 years) ever use remained large, at 126. For advanced and metastatic plus fatal disease, the numbers of cases with longer term ever use were three and zero, respectively. However, the expected number of metastatic or fatal cases for 5 or more years of use was eight, which was calculated using the more than 18 500 person-years at risk in those with 5 or more years of use and the observed age- and period-specific incidence rates in the never users. Thus, the lack of men with metastatic or fatal prostate cancer among the longer term users was not due merely to a small number of person-years at risk contributed by those men but instead can be explained by a deficit of these cases (zero instead of an expected eight cases) during their time at risk when compared with the never users.

In summary, our prospective results do not support an association between the use of statin drugs and the risk of prostate cancer overall, but they do suggest that statin use is associated with a reduced risk of clinically important advanced prostate cancer in a population that reported a high prevalence of routine PSA screening. However, it is premature to recommend the use of statins for the prevention of advanced prostate cancer. Further work is needed to address the role of PSA screening as a possible explanation for these findings and to identify the biologic mechanisms that may underlie the inverse association, if this association is indeed causal.

References

(1) Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA 1997;278:313–21.

(2) Graaf MR, Richel DJ, van Noorden CJ, Guchelaar HJ. Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. Cancer Treat Rev 2004;30:609–41.

(3) Mo H, Elson CE. Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention. Exp Biol Med (Maywood) 2004;229:567–85.

(4) Shannon J, Tewoderos S, Garzotto M, Beer TM, Derenick R, Palma A, et al. Statins and prostate cancer risk: a case-control study. Am J Epidemiol 2005;162:318–25.

(5) Singal R, Khurana V, Caldito G, Fort C. Statins and prostate cancer risk: a large case-control study in veterans. J Clin Oncol, 2005 ASCO Annual Meeting Proceedings. Vol. 23, No. 16S, Part I of II (June 1 Supplement), 2005:1004.

(6) Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol 2004;22:2388–94.
(7) Olsen JH, Johansen C, Sorensen HT, McLaughlin JK, Mellemkjaer L, Steffensen FH, et al. Lipid-lowering medication and risk of cancer. J Clin Epidemiol 1999;52:167–9.
(8) Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Arch Intern Med 2000;160:2363–8.
(9) Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Shapiro S. Statin use and the risk of breast and prostate cancer. Epidemiology 2002; 13:262–7.
(10) Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. Br J Cancer 2004;90:635–7.
(11) Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, et al. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005;114:643–7.
(12) Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80.
(13) Cauley JA, Zmuda JM, Lui LY, Hillier TA, Ness RB, Stone KL, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt) 2003;12:749–56.
(14) Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl coenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case-control study. Cancer 2004;100:2308–16.
(15) Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352: 2184–92.
(16) Kaye JA, Meier CR, Walker AM, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. Br J Cancer 2002;86:1436–9.
(17) Beck P, Wysowski DK, Downey W, Butler-Jones D. Statin use and the risk of breast cancer. J Clin Epidemiol 2003;56:280–5.
(18) Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med 2005;165:2264–71.
(19) Jacobs EJ, Rodriguez C, Brady KA, Connell CJ, Thun MJ, Calle EE. Cholesterol-lowering drugs and colorectal cancer incidence in a large United States cohort. J Natl Cancer Inst 2006;98:69–72.
(20) Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
(21) Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. Am J Epidemiol 1984;119: 837–9.
(22) Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP, O'Sullivan B, Sobin LH, Yarbro JW, eds. AJCC Cancer Staging Manual. Philadelphia, PA: Lippincott-Raven, 1997.
(23) Lemaitre RN, Furberg CD, Newman AB, Hulley SB, Gordon DJ, Gottdiener JS, et al. Time trends in the use of cholesterol-lowering agents in older adults: the Cardiovascular Health Study. Arch Intern Med 1998;158: 1761–8.
(24) Siegel D, Lopez J, Meier J. Use of cholesterol-lowering medications in the United States from 1991 to 1997. Am J Med 2000;108: 496–9.
(25) LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet 2002;359:1379–87.
(26) Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004;364: 771–7.
(27) Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. Nat Rev Cancer 2005;5:930–42.
(28) Zhuang L, Lin J, Lu ML, Solomon KR, Freeman MR. Cholesterol-rich lipid rafts mediate akt-regulated survival in prostate cancer cells. Cancer Res 2002;62:2227–31.
(29) Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. J Clin Invest 2005;115:959–68.
(30) Freeman MR, Solomon KR. Cholesterol and prostate cancer. J Cell Biochem 2004;91:54–69.

NOTES

We thank the research staff of the Health Professionals Follow-up Study for their continued help in the conduct of this study. The Health Professionals Follow-up Study is supported by Public Health Service research grants CA55075 from the National Cancer Institute and HL35464 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (Harvard). This analysis was also supported by Public Health Service research grant P50 CA58236 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services (Hopkins). None of the sponsors played a role in the design, collection, analysis, and interpretation of this statin and prostate cancer study or in the decision to submit the manuscript for publication.

Manuscript received May 2, 2006; revised October 11, 2006; accepted October 27, 2006.