Cholesterol-Lowering Drugs and Advanced Prostate Cancer Incidence in a Large U.S. Cohort

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Abstract

Background: **3-Hydroxy-3-methylglutaryl CoA reductase inhibitors, commonly known as statins, account for the great majority of cholesterol-lowering drug use in the United States. Long-duration statin use was associated with substantially reduced risk of advanced prostate cancer in a recent large prospective study.**
Methods: **We examined the association between use of cholesterol-lowering drugs and prostate cancer incidence by disease stage and grade among 55,454 men in the Cancer Prevention Study II Nutrition Cohort. Proportional hazards modeling was used to calculate RRs.**
Results: **During follow-up from 1997 to 2003, we identified 3,413 cases of incident prostate cancer, including 317 cases of advanced prostate cancer. After adjustment for age, history of prostate-specific antigen testing, and other potential prostate cancer risk factors, current use of cholesterol-lowering drugs for 5 or more years was not associated with overall prostate cancer incidence (multivariate adjusted rate ratio, 1.06; 95% confidence interval, 0.93-1.20), but was associated with a marginally statistically significant reduction in risk of advanced prostate cancer (rate ratio, 0.60; 95% confidence interval, 0.36-1.00).**
Conclusion: **These results provide some support for the hypothesis that long-term statin use is associated with reduced risk of advanced prostate cancer.** (Cancer Epidemiol Biomarkers Prev 2007;16(11):2213–7)

Introduction

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors, commonly known as statins, were introduced in the United States in 1987 (1). By 1997, ~86% of people using cholesterol-lowering drugs were using statins (1). It is biologically plausible that statin use could reduce risk of prostate cancer incidence or progression because statins have anti-inflammatory effects (2), and considerable evidence indicates that chronic inflammation contributes to prostate carcinogenesis (3). Several statins inhibit proliferation of prostate cancer cells *in vitro* (4, 5), although lovastatin did not inhibit prostate cancer in a mouse model (4).

Randomized trials indicate that statin use is unlikely to have any important short-term effect on overall prostate cancer incidence. A meta-analysis of four randomized trials of various statins for cardiovascular disease prevention reported a combined rate ratio (RR) of 1.00 [95% confidence interval (95% CI), 0.85-1.17] for overall prostate cancer incidence (6). However, the meta-analysis did not examine either long-term statin use or risk of advanced prostate cancer.

The largest previous observational study of statins and prostate cancer was an analysis from the Health Professionals' Follow-up Study (HPFS) that included 2,579 total cases of prostate cancer, of which 316 were advanced (defined as stage III cancers with tumors classified as T_{3b} or above, or stage IV cancers; ref. 7). Statin use was not associated with overall prostate cancer incidence in the HPFS. However, statin use was associated with substantially reduced risk of advanced prostate cancer (RR, 0.51; 95% CI, 0.30-0.86), and the reduction in risk of advanced prostate cancer seemed even stronger for statin use of 5 or more years (RR, 0.26; 95% CI, 0.08-0.83). A hospital-based, case-control study found no association between statin use and either overall or advanced prostate cancer incidence (8). Five smaller observational studies have examined the association between statin use and overall prostate cancer (9-13), with one reporting significantly reduced risk (9), one reporting a substantial but statistically nonsignificant reduction in risk (13), and three reporting no association (10-12); however, none of these studies reported results for advanced prostate cancer.

We examined the association between use of cholesterol-lowering drugs and prostate cancer incidence by stage and grade at diagnosis in the Cancer Prevention Study-II Nutrition Cohort during the period from 1997 to 2003. We considered use of cholesterol-lowering drugs to be a reasonable surrogate measure for use of statins because, during this period, the great majority of users of cholesterol-lowering drugs took statins.

Materials and Methods

Study Cohort. Men in this analysis were drawn from the 86,406 male participants in the Cancer Prevention Study-II Nutrition Cohort, a prospective study of cancer

Received 5/16/07; revised 7/6/07; accepted 8/6/07.

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doi:10.1158/1055-9965.EPI-07-0448

incidence and mortality in the United States established in 1992, described in detail elsewhere (14). The Emory University Institutional Review Board approves all aspects of the Cancer Prevention Study-II Nutrition Cohort. At enrollment in 1992 or 1993, participants completed a mailed self-administered questionnaire, including information on demographic, medical, and lifestyle factors. Follow-up questionnaires to update exposure information and to ascertain newly diagnosed cancers were sent in 1997, 1999, 2001, and 2003. The response rate for each follow-up questionnaire was at least 88%.

Follow-up for this analysis began on the date of completion of the 1997 follow-up questionnaire, rather than at enrollment into the cohort in 1992 or 1993, because data from retail pharmacies in the United States indicate that ~86% of those on cholesterol-lowering drugs were using statins in 1997, compared with 62% in 1992 (1). A total of 65,045 men from the Nutrition Cohort completed the standard version of the 1997 questionnaire, which included information on use of cholesterol-lowering drugs. Of these, we excluded participants who had a history of prostate cancer (n = 5,798), who provided incomplete or uninterpretable information on use of cholesterol-lowering drugs (n = 1,443), who were lost to follow-up (n = 2,252), or who reported a prostate cancer diagnosis in 1999 that could not be confirmed (n = 98). A total of 55,454 participants remained for analysis.

Case Ascertainment. We documented 3,413 incident cases of prostate cancer between completion of the 1997 questionnaire and June 30, 2003. Of these, 3,362 were initially identified by self-report on the 1999, 2001, or 2003 follow-up questionnaires and were subsequently verified by obtaining medical records, or through linkage with state registries when complete medical records could not be obtained (14). An additional 51 cases of fatal prostate cancer among participants who did not report prostate cancer were identified through linkage with the National Death Index (15). A total of 297 participants self-reported a cancer diagnosis that could not be verified and, therefore, were not counted as cases. Fifteen men diagnosed with T_{1a} prostate cancers were censored at their diagnosis date rather than being counted as cases because these tumors are incidentally detected and tend to be relatively innocuous. We classified cases as advanced if they were stage III or IV at diagnosis (n = 298; ref. 16), or if prostate cancer was listed as the underlying cause of death on the death certificate and no information on stage at diagnosis was available from medical records or registry linkage (n = 19). Stage II (organ-confined) cancers were further categorized as high or low grade, with high grade defined as a Gleason score of 8 or more, or a histologic grade of 3 or more if a Gleason score was not available. Stage II cancers for which neither Gleason score nor histologic grade (n = 57) were available were censored from analyses requiring information on grade, but were included as cases in analyses of overall prostate cancer.

Ascertainment of Use of Cholesterol-Lowering Drugs. The 1997 questionnaire asked participants to report whether they had taken any ''cholesterol-lowering drugs'' regularly during the past year, and provided as examples the brand names for four statins commonly used at that time (lovastatin, pravastatin, simvastatin, and fluvastatin; ref. 1), as well as the brand names for the fibrate drug, gemfibrozil, and for the bile acid–binding resin, cholestyramine. The 1999 and 2001 follow-up questionnaires included a similar question about use of cholesterol-lowering drugs. Information on statin use before the start of follow-up for this analysis was available from the 1992 questionnaire, which also included a question similar to that on the 1997 questionnaire.

Statistical Analysis. We used Cox proportional hazards modeling (17) to calculate RRs for prostate cancer incidence. We categorized use of cholesterol-lowering drugs as never, former, or current, using a time-dependent variable initially defined by use reported in 1997 and updated by use reported in 1999 and again by use reported in 2001. Use of cholesterol-lowering drugs was relatively stable over time. Among men with complete data on use of cholesterol-lowering drugs in both 1997 and 2001, ~95% of current users in 1997 reported current use in 2001, and ~77% of never users in 1997 reported no use in 2001. Therefore, participants with missing data on use of cholesterol-lowering drugs on the 1999 (n = 10,229) or 2001 follow-up questionnaires (n = 10,818) retained the same status (never, former, or current use) reported on their most recent questionnaire on which this was specified. Current users were further categorized as having less than 5 years of use, or 5 or more years of use, based on use reported on previous questionnaires. Specifically, participants were categorized as current users of 5 or more years during the 1997 to 1999 follow-up interval if they reported current use in both 1992 and 1997; during the 1999 to 2001 follow-up interval if they reported current use in 1992, 1997, and 1999; and during the 2001 to 2003 follow-up interval if they reported current use in 1997, 1999, and 2001.

All models were adjusted for age, race, education, body mass index (BMI), use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAID) in 1992, use of NSAIDs in 1997, self-reported history of prostate-specific antigen (PSA) testing, history of elevated cholesterol, history of diabetes, history of heart attack, and family history of prostate cancer. Although history of heart attack is not an established risk factor for prostate cancer, we adjusted for it because reported history of heart attack was associated with slightly reduced risk of prostate cancer diagnosis in this cohort. We adjusted for age using the stratified Cox procedure with 1-year age strata (18). We adjusted for history of PSA testing using a time-dependent variable incorporating updated information from the 1999 and 2001 questionnaires. For each follow-up interval, history of PSA testing was categorized as never, not recently (more than 2 years ago), recently (in the last 2 years), or unknown. Information on indication for PSA testing (routine or for symptoms) was first asked on the 1999 questionnaire. For follow-up after 1999, we subcategorized the recent PSA test category into those reported as being for ''routine tests'' only, and those reported as being for symptoms. Unless otherwise noted above, all covariates were based on status in 1997 and were modeled using the categories shown in Table 1.

We examined whether the association between long-term use of cholesterol-lowering drugs and overall or

Table 1. Selected prostate cancer risk factors by use of cholesterol-lowering drugs, Cancer Prevention Study II Nutrition Cohort

	Never use (n = 41,872), %	Former use (n = 2,057), %	Current use, <5 y (n = 6,653), %	Current use, ≥5 y (n = 4,872), %
Age (y)				
50-59	4.3	3.1	3.4	2.4
60-69	51.6	44.6	56.3	51.4
70-79	40.4	48.9	38.6	43.6
≥80	3.7	3.5	1.7	2.5
Race				
White	97.8	96.8	98.1	97.9
Black	0.9	1.7	0.6	0.8
Other or unknown	1.2	1.5	1.4	1.3
Education				
<High school	7.2	8.6	6.8	6.1
High school graduate	18.2	18.7	17.9	17.7
Some college	25.1	27.5	26.2	25.2
College graduate	22.3	21.0	22.8	24.4
Graduate school	26.6	23.7	25.7	25.9
Unknown	0.6	0.4	0.6	0.7
BMI				
<25	34.5	33.9	30.6	30.4
25-<30	43.4	44.7	46.5	48.2
30-<35	11.6	11.3	12.3	12.0
≥35	2.5	2.1	2.4	2.5
Unknown	7.9	8.0	8.2	6.9
Family history of prostate cancer	17.0	14.5	16.0	15.2
NSAID use (pills/mo)				
None	34.3	25.3	17.8	17.8
1-14	23.8	22.9	22.5	22.6
15-29	8.5	8.6	6.7	7.8
30-59	14.6	18.3	24.6	24.8
≥60	7.5	8.1	8.0	7.9
User, unknown quantity	11.2	16.8	20.4	19.1
History of PSA testing				
Never	17.4	13.0	11.9	10.1
Yes, test in last 2 y	63.8	63.9	71.1	73.7
Yes, test >2 y ago	10.5	12.0	8.9	8.9
Unknown	8.3	11.1	8.0	7.3
Elevated cholesterol*	26.4	85.0	89.3	95.5
Heart attack history	12.5	34.8	49.1	49.5
Diabetes history	9.3	13.5	13.4	13.4

NOTE: Percentages were adjusted to the age distribution of the entire study population.
*Ever had elevated cholesterol, as self-reported by participants.

advanced prostate cancer varied by attained age, follow-up time, BMI, and use of aspirin and other NSAIDs. Specifically, we modeled multiplicative interaction terms between a dichotomous variable for use of cholesterol-lowering drugs for 5 or more years, and continuous variables for attained age, follow-up time, BMI, and NSAID pills per month.

We also conducted a subgroup analysis, focusing on advanced prostate cancer, among men with a recent history of PSA testing for ''routine'' reasons. We hypothesized that there would be less potential for residual confounding by history of PSA testing among this subgroup of men with a relatively uniform and well-characterized history of reported testing. This subgroup analysis included only person time after completion of the 1999 follow-up questionnaire, the first time that information on indication for PSA test was collected. Specifically, the subgroup analysis included person time from the 1999 to 2001 follow-up interval from men who reported on their 1999 questionnaire that they had received a PSA test for routine testing in the last 2 years, and person time from the 2001 to 2003 follow-up interval from men who reported on their 2001 questionnaire that they had received a PSA test for routine testing in the last 2 years. The subgroup analysis included ~46% of the person-time included in the overall analysis.

Results

Men who reported current use of cholesterol-lowering drugs in 1997 were generally similar to nonusers with respect to age, education, and family history of prostate cancer. Participants were predominantly White, regardless of use of cholesterol-lowering drugs (Table 1). As expected, most men who reported using cholesterol-lowering drugs also reported being told by a physician that they had elevated cholesterol, although a history of elevated cholesterol was not uncommon among nonusers. Men who used cholesterol-lowering drugs were more likely than nonusers to report a history of heart attack or diabetes, to use NSAIDs regularly, and to have had a PSA test.

Long-term use (5 or more years) of cholesterol-lowering drugs was not associated with overall prostate cancer incidence (RR, 1.06; 95% CI, 0.93-1.20) or with

incidence of either high-grade, or low-grade, stage II cancers (Table 2). In analyses by grade combining prostate cancers of all stages, long-term use of cholesterol-lowering drugs was not associated with either high-grade (RR, 0.91; 95% CI, 0.64-1.30) or low-grade (RR, 1.09; 95% CI, 0.95-1.25) prostate cancer (results not shown in tables). However, long-term use of cholesterol-lowering drugs was associated with reduced risk of advanced (stage III or stage IV) prostate cancer (RR, 0.60; 95% CI, 0.36-1.00), although this association was not formally statistically significant (P = 0.051). Only 19 cases of advanced prostate cancer were observed among men who had used statins for 5 or more years. Results were generally similar (RR, 0.68; 95% CI, 0.36-1.28) when we excluded stage III T_{3a} tumors from the analysis of advanced cancer, as was done in the HPFS analysis (7), or limited the analysis to prostate cancers that were stage IV at diagnosis or fatal prostate cancer of unknown stage at diagnosis (RR, 0.78; 95% CI, 0.36-1.69).

Any current use of cholesterol-lowering drugs (combining the <5 years and ≥5 years current use categories shown in Table 2) was not associated with risk of either overall prostate cancer (RR, 1.03; 95% CI, 0.94-1.13) or advanced prostate cancer (RR, 0.81; 95% CI, 0.58-1.12).

There were no statistically significant differences in the association between long-term use of cholesterol-lowering drugs and either overall or advanced prostate cancer by attained age, use of NSAIDs, or follow-up time. For advanced prostate cancer, but not overall prostate cancer, there was a statistically significant interaction between long-term use of cholesterol-lowering drugs and BMI (P = 0.02), driven by the fact that there were no advanced prostate cancer cases among long-term users of cholesterol-lowering drugs who were obese (BMI ≥ 30.0). The RR for long-term use of cholesterol-lowering drugs, compared with never use, was 0.57 (95% CI, 0.23-1.42) among men with a BMI of <25.0, and 0.91 (95% CI, 0.48-1.72) among men with a BMI between 25.0 and 29.9.

Self-reported history of PSA testing was not a strong confounder of the association between use of cholesterol-lowering drugs and advanced prostate cancer. Without adjustment for history of PSA, the multivariable-adjusted RR associated with long-term use of cholesterol-lowering drugs was 0.59 (95% CI, 0.36-0.99). Additional adjustment for history of PSA testing resulted in little change (RR, 0.60; 95% CI, 0.36-1.00). Potential confounding by history of PSA testing was a concern because it was associated with use of cholesterol-lowering drugs (Table 1). However, the negligible effect of adjustment for history of PSA testing may be explained by the fact that history of PSA testing (not including PSA testing for symptoms) was associated with only a small and non-statistically significant reduction in risk of advanced prostate cancer (RR, 0.89; 95% CI, 0.62-1.27), although it was associated with a substantial reduction in risk of stage IV or fatal prostate cancer (RR, 0.56; 95% CI, 0.33-0.93).

To assess the potential for residual confounding by PSA testing, we conducted a subgroup analysis, focusing on advanced cancer, limited to men who reported having received a PSA test in the last 2 years for routine reasons (see Materials and Methods). We hypothesized that there would be less potential for residual confounding by history of PSA testing among this subgroup of men with a relatively uniform and well-characterized self-reported history of PSA testing. The association between long-term use of cholesterol-lowering drugs and advanced cancer among this subgroup (RR, 0.56; 95% CI, 0.24-1.34) was similar to that seen in the overall analysis (RR, 0.60; 95% CI, 0.36-1.00), although statistical power for this subgroup analysis was limited.

To further assess concerns about residual confounding by PSA testing, we examined the association between risk of advanced prostate cancer and two factors related to routine preventative medical care, having received a colorectal endoscopy (colonoscopy or sigmoidoscopy) for routine screening, and having had a routine physical exam in the last 2 years (both factors as reported on the 1997 questionnaire). If these factors were associated with reduced risk of advanced prostate, it would have indicated strong potential for confounding in analyses of other preventative behaviors, including use of cholesterol-lowering drugs. However, there was no apparent association between advanced prostate cancer and either routine screening endoscopy (RR, 1.10; 95% CI, 0.83-1.45) or a recent routine physical exam (RR, 0.90; 95% CI, 0.72-1.12).

Table 2. Prostate cancer incidence by use of cholesterol-lowering drugs, Cancer Prevention Study II Nutrition Cohort, 1997 to 2003

	Never use	Former use	Current use, <5 y	Current use, ≥5 y
All prostate cancers				
RR (95% CI)	1.00 (Reference)	0.88 (0.72-1.07)	1.02 (0.92-1.13)	1.06 (0.93-1.20)
Cases/person-years	2,350/193,971	114/10,925	559/47,009	390/32,147
Stage II, low grade*				
RR (95% CI)	1.00 (Reference)	0.79 (0.62-0.99)	1.03 (0.92-1.16)	1.13 (0.98-1.30)
Cases/person-years	1,825/193,971	79/10,925	441/47,009	321/32,147
Stage II, high grade†				
RR (95% CI)	1.00 (Reference)	1.40 (0.85-2.31)	1.10 (0.81-1.5)	1.03 (0.70-1.51)
Cases/person-years	250/193,971	18/10,925	63/47,009	42/32,147
Advanced prostate cancer‡				
RR (95% CI)	1.00 (Reference)	1.05 (0.59-1.87)	0.92 (0.65-1.30)	0.60 (0.36-1.00)
Cases/person-years	239/193,971	13/10,925	46/47,009	19/32,147

NOTE: Data were adjusted for age, race, education, BMI, NSAID use, history of PSA testing, elevated cholesterol, history of diabetes, history of heart attack, and family history of prostate cancer.

* American Joint Committee on Cancer stage II (organ confined), and Gleason score of 7 or less.

† American Joint Committee on Cancer stage II (organ confined), and Gleason score of 8 or more.

‡ American Joint Committee on Cancer stage III or IV, or fatal prostate cancer of unknown stage at diagnosis.

Discussion

In our study, use of cholesterol-lowering drugs for 5 or more years was associated with reduced risk of advanced (stage III or IV) prostate cancer (RR, 0.60; 95% CI, 0.36-1.00). Although this association was not statistically significant at the $P < 0.05$ level, it is consistent with results from the HPFS (7), where use for 5 or more years was associated with a strong and statistically significant reduction in risk of advanced prostate cancer (RR, 0.26; 95% CI, 0.08-0.83). The only other study to report results for advanced prostate cancer was a hospital-based case control study (8), which reported no association with advanced prostate cancer but did not present separate analyses of the association between long-term use and advanced prostate cancer.

Overall prostate cancer incidence was not associated with even long-term use of cholesterol-lowering drugs in our study. These results are consistent with published analyses of long-term use from the HPFS (7) and a hospital-based case-control study (8), but differ from those of a small case-control study that found long-term statin use to be associated with substantially reduced risk of overall prostate cancer (9).

The main strengths of our study are its prospective design and relatively large size. The large size of the study enabled us to examine the association between long-term use of cholesterol-lowering drugs and advanced prostate cancer, an association which, to our knowledge, has been examined in only one previous study (7).

Several limitations of this study should be considered. First, use of cholesterol-lowering drugs was used as a surrogate measure for use of statins. By the start of follow-up for this analysis in 1997, ~86% of users of cholesterol-lowering drugs in the United States were using statins (1). However, for the first 4 of the 6 years of follow-up included in this analysis, our definition of long-term use relied on reported use of cholesterol-lowering drugs in 1992 or 1993, a time when only ~62% of users of cholesterol-lowering drugs were using statins (1). If use of other cholesterol-lowering drugs is not associated with risk of advanced prostate cancer, our results may underestimate any reduction in risk associated with long-term statin use. Second, we were also unable to examine if risk varied by statin type or dose. Third, statistical power was limited when examining interactions between use of cholesterol-lowering drugs and other factors, such as BMI or NSAID use, particularly in analyses of advanced prostate cancer. Finally, although we adjusted for self-reported history of PSA testing, history of PSA testing is reported with some error (19, 20), and we cannot rule out the possibility that residual confounding by history of PSA testing may have contributed to the observed reduction in risk of advanced prostate cancer.

Our results provide some support for the hypothesis that long-term statin use may be associated with reduced risk of advanced prostate cancer. If this association is causal, it would be of considerable importance, given that advanced prostate cancer remains an important cause of morbidity and mortality in older men. Long-term randomized trials would ultimately be required to definitively determine whether the reduced risk of advanced prostate cancer observed among long-term users of cholesterol-lowering drugs in this study and the HPFS cohort is causal. Additional observational studies with accurate and complete information on the PSA timing and indication, as well as on statin dose and duration, could provide useful evidence to determine if randomized trials are warranted.

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