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Statin and NSAID Use and Prostate Cancer Risk

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Abstract

Purpose—Some studies have reported reduced risks of advanced, but not early, prostate cancer among statin users, and one study found a reduced risk only among statin users who had also used nonsteroidal anti-inflammatory drugs (NSAIDs). We have previously reported no association between statin use and prostate cancer in our hospital-based Case Control Surveillance Study. The purpose of the present analyses was to update the findings by cancer stage and to evaluate the joint use of statins and NSAIDs.

Methods—Cases were 1367 men with prostate cancer and controls were 2007 men with diagnoses unrelated to statin or NSAID use. We used multivariable logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for statin use compared with no use, and joint use of statin and NSAIDs compared with use of neither.

Results—The odds ratio among regular statin users was 1.1 (95% CI 0.9–1.5), and odds ratios were similar among early and late stage cancers. The odds ratio among joint statin and NSAID users was 1.1 (95% CI 0.7–1.6).

Conclusion—The present results do not support a protective effect of statin use, or statin and NSAID use, on the risk of advanced prostate cancer.

Introduction

Despite laboratory data suggesting that statins have chemopreventive properties against prostate cancer,¹ most epidemiologic data show no effect of statin use on overall prostate cancer risk.^{1,2} However several studies^{3–7} have reported risk reductions for advanced stage prostate cancer and another study found a reduced risk only among statin users who also used nonsteroidal anti-inflammatory drugs (NSAIDs).⁶ We have previously reported no association between statin use and overall or advanced prostate cancer in our hospital-based Case Control Surveillance Study.⁸ The purpose of the present analyses is to update the findings by cancer stage and evaluate the joint use of statins and NSAIDs.

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Note on conflict of interest. Patricia Coogan, Judith Kelly, and Lynn Rosenberg declare no conflicts of interest. Brian Strom has been a consultant to most major pharmaceutical companies. The only consulting he has done on statins is unrelated to the topic of this paper.

Methods

Data were collected from patients admitted to participating hospitals in New York, Philadelphia, and Baltimore from 1992 through 2008. The population base for the study comprised people living within 50 miles of a participating hospital. Eligible patients were aged 18 to 79, under the care of a physician participating in the study, able to complete the interview (e.g., not deaf), and did not have certain excluded diagnoses (e.g., psychiatric). The present analysis was confined to men aged 40 through 79. Nurse-interviewers administered questionnaires and elicited medication histories by asking about 43 indications including those for which statins and NSAIDs are used. For each episode of use, the drug name and the duration, timing, and frequency of use were recorded. From 1992 through 1997, an annual average of 95% of patients approached for an interview participated. The corresponding figure for 1998 through 2008 is 84%. The study was approved by the institutional review boards of all participating institutions.

The prostate cancer cases comprised 1367 men of median age 62 with no history of cancer with the exception of nonmelanoma cancer of the skin. Cases were assigned a cancer stage of 1 through 4 as defined by the American Joint Committee on Cancer (AJCC).⁹ Controls comprised 2007 men of median age 54 admitted to the hospital for diagnoses that were unrelated to statin or NSAID use: trauma (35%), acute infection (18%), gallbladder/hernia (22%), and others (25%) (e.g., kidney calculus, ureterolithiasis, diverticulitis, urethral stricture, bowel obstruction, gastritis). Controls had no history of cancer with the exception of nonmelanoma cancer of the skin.

Regular statin use was defined as use at least 4 times/week for at least 3 continuous months, beginning 12 or more months before hospital admission. Regular NSAID use was defined in the same way. Joint statin/NSAID use was defined as regular use of both a statin and NSAID that overlapped for at least 3 months.

Logistic regression models were used to estimate odds ratios for prostate cancer among statin users compared to never statin users, and joint statin and NSAID users compared to never users of either statins or NSAIDs. Estimates were adjusted for the design variables in our study (5-year age categories, study center, interview year) and for potential confounding factors (body mass index, alcohol use, pack-years of smoking, race, family history of prostate cancer, number of doctor visits made two years before hospital admission, and education). Estimates for statin use alone were also adjusted for NSAID use.

Results

The odds ratio among regular statin users was 1.1 (95% CI 0.9–1.5), and odds ratios did not differ by duration (Table 1). Odds ratios were compatible with 1.0 for early (stages 1 and 2) and late (stages 3 and 4) stage cancers. The OR was lowest for advanced (stages 3 and 4) cases with 5 or more years of use (OR=0.80, 95% CI 0.4–1.6). In analysis confined to stage 4 cancers only (5 case statin users) the OR was 1.0 (95% CI 0.3–3.3); 3 of the 5 case users had used statins for more than 5 years. The odds ratio among regular users of hydrophobic statins (simvastatin, atorvastatin, lovastatin, and fluvastatin) (208 case and 148 control users) was 1.1 (95% CI 0.9–1.5); among regular users of hydrophilic statins (pravastatin, rosuvastatin) (29 case and 23 control users) it was 1.1 (95% CI 0.6–2.2). The odds ratios for regular use of statins were similar among obese and nonobese subjects (p for interaction = 0.70) (Table 1).

The odds ratio among joint statin and NSAID users was 1.1 (95% CI 0.7–1.6), with no difference by duration or cancer stage (Table 1). The odds ratio among the 84% of joint statin/NSAID users who used a hydrophobic statin was 1.2 (95% CI 0.8–1.8).

Discussion

We found no association between statin use and overall or late stage prostate cancer, and no effect of joint statin and NSAID use.

Our findings are consistent with the lack of association between statin use and overall prostate cancer found in follow-up of randomized clinical trials of statins^{2,10–12} and in most observational studies.^{1,2} However several studies have reported reduced risks of advanced prostate cancer, especially among men who used statins for 5 or more years.^{3–7} For example, the relative risks for advanced cancer for statin use of 5 or more years were 0.60 (95% CI 0.36–1.00) in the Cancer Prevention Study II Nutrition cohort³ and 0.67 (95% CI 0.46–0.96) in the Kaiser Permanente Medical Care Program of Northern California,⁷ based on 19 and 30 case users, respectively. Both studies defined advanced cancer in a way similar to our definition. We found a nonsignificant 20% reduction in the analysis confined to stage 3 and 4 cancers based on 36 case users; there was no reduction in risk among stage 4 cancers alone.

We did not confirm the finding from the California Men's Health Study Cohort where a risk reduction was apparent only among regular NSAID users who had used statins for 5 or more years (RR = 0.64, 95% CI 0.44–0.93).⁶ The Cancer Prevention II Study also did not confirm that finding.³ Nor did we confirm the findings of a recent population-based case-control study wherein the risk of prostate cancer was significantly increased among obese men (OR for ≥ 5 years of statin use = 1.80, 95% CI 1.06–3.03); the corresponding OR for men with body mass index <30 kg/m² was 0.83 (95% CI 0.59–1.15).¹³

Strengths of our study include the large numbers of statin and NSAID users and long durations of drug use. Recall bias is a concern since our exposure assessment was based on self-report. However, drug use was elicited by a long list of indications and the hypothesis under consideration was unknown to interviewers and participants. Furthermore, statin drugs are used daily and for long periods of time, which is likely to improve recall. Nondifferential misclassification of exposure may have biased the odds ratio towards the null. To minimize the possibility of selection bias, we chose as controls patients with diagnoses that we judged to be unrelated to statin or NSAID use, and odds ratios calculated with subgroups of controls were similar. We were not able to control for PSA testing, but we did adjust for number of doctor visits previous to hospital admission. Residual confounding by the use of screening could lead to detection bias that might mask a protective effect of statins overall. In conclusion, our results did not support a protective effect of statin use, or statin and NSAID use, on the risk of advanced prostate cancer.

Key points

- Despite a dearth of evidence that statin use reduces prostate cancer risk overall, three studies have reported reduced risks of advanced prostate cancer among statin users.
- Results of an analysis based on 1367 prostate cancer cases and 2007 hospital controls did not support a protective effect of statin use, or joint statin and NSAID use, on the risk of advanced prostate cancer.

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Table 1

Statin and NSAID use among prostate cancer cases and controls, Case Control Surveillance Study, 1992–2008

	Cases	Controls	OR (95% CI) *
STATIN Use			
None	1058	1790	1.0
Recent [†]	34	24	1.1 (0.6–2.1)
Sporadic	25	15	1.8 (0.8–3.9)
Regular [‡]	250	178	1.1 (0.9–1.5)
<2 years	38	32	0.9 (0.5–1.7)
2–<5 years	86	82	1.0 (0.7–1.5)
5–<10 years	69	42	1.4 (0.9–2.1)
10+	57	22	1.4 (0.8–2.5)
Regular use by cancer stage [¶]			
Stages 1 and 2	200	178	1.2 (0.9–1.6)
<5 years	104	114	1.0 (0.6–2.0)
5+ years	96	64	1.0 (0.7–1.5)
Stages 3 and 4	36	178	1.1 (0.7–1.8)
<5 years	16	114	0.9 (0.3–2.9)
5+ years	20	64	0.8 (0.4–1.6)
Regular use by body mass index			
<30 kg/m ²	182	117	1.0 (0.8–1.4)
<5 years	88	78	0.8 (0.5–1.2)
5+ years	94	39	1.4 (0.9–2.3)
≥ 30 kg/m ²	68	61	1.5 (0.9–2.4)
<5 years	36	36	1.5 (0.8–2.7)
5+ years	32	25	1.4 (0.7–1.7)
JOINT STATIN AND NSAID USE			
No use of statins or NSAIDs	441	704	1.0
Joint use [§]	134	66	1.1 (0.7–1.6)
<2 years	24	14	0.9 (0.4–2.2)
2–<5 years	48	26	1.2 (0.7–2.2)
5–<10 years	41	19	0.9 (0.5–1.7)
10+ years	21	7	1.0 (0.4–2.8)
Joint use by Prostate Cancer stage			
Stages 1 and 2	107	66	1.1 (0.7–1.7)
Stages 3 and 4	19	66	1.2 (0.6–2.3)

* Adjusted for 5-year age categories, study center, interview year, body mass index, alcohol use, pack-years of smoking, race, family history of prostate cancer, number of doctor visits made two years before hospital admission, education, and NSAID use.

[†] Regular use that occurred only in the year prior to hospital admission, and assumed to not have etiologic relevance.

[‡]Use at least 4 times/week for at least 3 continuous months, beginning at least 1 year prior to hospital admission.

[¶]197 cases were missing information on stage, including 14 regular statin users and 8 joint users of statins and NSAIDs.

[§]Regular use of NSAIDs and statins that overlapped for at least 3 continuous months.