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Statin Use and Fatal Prostate Cancer: A Matched Case-Control Study

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Abstract

Background—Statins are one of the most commonly prescribed medications in medical practice and prostate cancer is the most common male malignancy. While there has been no consistent evidence that statins affect cancer incidence, including prostate cancer, several reports suggest they may decrease the rate of advanced prostate cancer. However, no study has examined statin use and prostate cancer mortality specifically. We report here a population-based case-control investigation that examines this association.

Methods—We conducted a matched case-control study. Cases were residents of New Jersey ages 55 – 79 who died from prostate cancer between 1997–2000. We individually matched population-based controls by five-year age-group and race. Medication data were obtained identically for cases and controls from blinded medical chart review. We used conditional logistic regression to adjust for confounders.

Results—We identified 718 cases and obtained cooperation from 77% of their spouses (N=553). After review of medical records, 387 were eligible and 380 were matched to a control. The unadjusted odds ratio was 0.49 (95% CI, 0.34–0.70) which decreased to 0.37 ($p<0.0001$) after adjustment for education, waist size, BMI, comorbidities, and anti-hypertensive medication. There was little difference between lipophilic and hydrophilic statins but more risk reduction was noted for hi-potency statins (73%, $p<0.0001$) as compared to low-potency statins (31%, $p=0.32$).

Conclusion—Statin use is associated with substantial protection against prostate cancer death, adding to the epidemiologic evidence for an inhibitory effect on prostate cancer.

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Keywords

prostate cancer neoplasms; statins; mortality; cholesterol

INTRODUCTION

Statins have been sold in the United States since 1987 and have become the dominant drugs used to treat hyperlipidemia. By 1999–2002 nearly 25% of adults over 60 were using statins (1). Because of early interest in a possible association of low serum cholesterol levels with cancer (2), and the pleiotropic effects of these drugs, several meta-analyses have been carried out to look for evidence that statin use might affect cancer incidence or overall cancer mortality (3–6). Overall, these meta-analyses have not found an association between statin use, either positively or negatively, and cancer incidence.

The data on prostate cancer are similar to those for overall cancer (7). However, several studies that have used advanced or aggressive prostate cancer as an endpoint have shown a protective effect of statin use (7–11). A recent report found that statin medication is associated with a dose-dependent reduction in the risk of biochemical recurrence (12). These studies have been summarized in two reviews (13, 14). Because these investigations have included relatively few prostate cancer deaths, we examined this issue using data from a previously reported case-control study that we carried out to evaluate prostate cancer screening in New Jersey (15). The value of this database is supported by an earlier analysis (15) that correctly predicted the finding of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial that PSA screening provides no benefit from mortality in U.S. patients (16).

METHODS

Study Subjects

We identified potential cases from New Jersey Vital Records. Only white and black men who died from prostate cancer as defined by the underlying cause of death on the death certificate between 1997 and 2000 at age 55 – 79 years were eligible. In order to prevent possible misclassification of non-prostate cancer deaths, we excluded 10% of potential cases in whom medical records did not document metastatic prostate cancer. We required cases to have been married at the time of death to increase the probability that there would be a knowledgeable, surviving informant to assist in identifying medical care providers. To prevent a selection bias and possible confounding, controls also had to have been married. The overall response rate for cases was 77% (N=553) with 387 (70%) eligible after the interview and medical record review, based on confirmation of age, diagnosis, and residence, and on successful acquisition of usable exposure information. The control response rate was 57% (N= 610) with 442 eligible after review. The chief reasons for ineligibility for both cases and controls were age outside our criteria, not being married, and inability to obtain medical records. There were no systematic differences in reasons for ineligibility between cases and controls. We were able to match 380 cases with controls.

For each case, we matched one control subject by age (same five-year age group), race as designated by the interviewee, and for the amount of available time for exposure as indexed by the date of death of the case going back to 1989. Potential controls aged 55–64 years living in New Jersey were identified by Northeast Research, Inc. or The Watsroom, Inc. using random digit dialing methods (17). Potential controls aged 65–79 were identified by Westat, Inc. from New Jersey Medicare tapes. Controls with prostate cancer (10.5%) were eligible as long as there was no evidence of advanced disease at the time of death of the matched case and the diagnosis came after the date of suspicion of cancer in the case. The study was approved by Institutional Review Boards from the UMDNJ-Robert Wood Johnson Medical School and the New Jersey Department of Health and Senior Services. Informed consent was obtained from control subjects and from spouses of deceased cases.

Data Measurements

Information on demographics, education, occupation, and personal measurements were obtained from spousal report for cases and from controls directly. Medical records were reviewed from all health care providers known to have cared for the subject from 1989 onwards. This review was performed to obtain information on comorbidity and clinical stage, Gleason score, pathology, and all PSAs performed prior to diagnosis. All chronic medications were abstracted and recorded identically for both cases and controls from blinded medical chart review. Due to the difficulty in obtaining accurate dates for chronic medication use, we recorded the use of a medication as “ever used”. All listings of medications by study data abstracters were further reviewed by a research nurse knowledgeable about the major classes of prescription medications. Information on the cancer was supplemented when necessary from the New Jersey Cancer Registry. This registry is part of the SEER Program and was established in 1979. New Jersey State Law mandates that hospitals, physicians, dentists, and clinical laboratories must report all new cancer cases within six months to the New Jersey Cancer Registry (18). Residents of New Jersey diagnosed with cancer outside the state are identified through information provided by agreements with neighboring states. Existing data in the registry are periodically verified using information from hospitals and physicians, death certificates, motor vehicle and income tax records, as well as federal databases such as the National Death Index.

Analysis

Statin use was the principal exposure analyzed. We also examined other medications such as hypertensive medications, nonsteroidal anti-inflammatory drugs (NSAIDS), medications used for coronary heart disease (other than those classified as antihypertensive), lipid lowering agents other than statins, diabetic medications, and medications used for erectile dysfunction. We did not capture specific dates or cumulative doses of medications. We further classified statins as high- or low-potency and as hydrophilic or lipophilic (19). We explored possible effect modification of hypertensive medication on statins with an interaction term in the logistic model. Education was categorized into less than high school graduate, high school graduate with or without some college, college graduate, and graduate or professional degree. The number of comorbidities was tabulated as: none, 1 – 2, 3 – 5, 6 – 10, and > 10. A comorbidity was counted if present prior to the year of prostate cancer diagnosis. We calculated body mass index (BMI) as weight/height^2 and ordered into <25, 25

– 29.9, 30 – 34.9, and =>35 categories that represent normal weight, overweight, mild obesity, and morbid obesity, respectively. Waist size in inches was divided into <=32, 32.1 – 36, 36.1 – 40, and > 40 categories. These measurements were obtained for a period before the decedent was clinically ill and a similar time period for the matched control.

Descriptive analysis was performed with contingency tables and chi square tests for categorical variables. Means were obtained and compared for continuous variables using Student's *t*-test. We considered a p-value of .05 or less as statistically significant and used 95% confidence intervals.

In the matched analysis we employed conditional logistic regression (SAS, Carey, North Carolina) with 1:1 matching for race, age, and amount of observation time (the amount of time prior to the diagnosis or suspicion of diagnosis in the case and an equivalent amount of time for the matched control). We first obtained univariate odds ratios for statin use and then adjusted for education level, BMI, waist size, and the number of comorbidities. Our final model also adjusted for antihypertensive use (ever, never). Obesity is thought to be associated with more aggressive prostate cancer (20, 21) and could confound the relationship of statin use and prostate cancer mortality. Similarly, use of an antihypertensive is an indirect marker of the metabolic syndrome that has been linked to prostate cancer mortality (21). In another report on the same subjects (15), we found no relationship between PSA screening and prostate cancer mortality, so screening status was not considered as a confounder.

RESULTS

Table 1 shows that prostate cancer decedents and controls were well-matched for age and race. The slight discrepancy in race between cases and control was due to one mismatched pair that was excluded from further analysis. Controls were more educated than cases: more controls had achieved a college or graduate degree and more cases had not graduated from high school. The median number of comorbidities was three and two for cases and controls, respectively. Controls who agreed to participate were 13.8% black and had a median age of approximately 72 years as compared to those refusing to participate who were 16.4% black with a median age of 73 years. Table 2 displays the Gleason score and stage at diagnosis for the cases. Forty percent of these fatal cases presented with distant disease at diagnosis. The median length of survival from suspicion of cancer until date of death was 2.9 years for cases with distant disease as compared to 6.2 years for cases with non-distant disease. Forty (10.5%) controls had a history of prostate cancer that was identified subsequent to the date of suspicion of prostate cancer in the matched case.

In unadjusted analysis (Table 3), the odds that a man dying from prostate cancer was exposed to a statin was half that of a control (OR 0.49, 95% CI 0.34–0.70). Although a lower education level, greater number of comorbidities, and larger waist size all predicted an increased risk of prostate cancer death, their inclusion in the model did not significantly change the risk associated with statin use. After adjusting for exposure to any antihypertensive medication, the odds of dying from prostate cancer death associated with statin use decreased to 0.37; 95% CI, 0.23–0.60. Antihypertensive agents, which were used

by two-thirds of the cases, were associated with an increased odds ratio of 2.9; (95% CI, 1.87–4.49) for prostate cancer death. We explored a possible interaction of antihypertensive medication with that of statins. The interaction term was of borderline statistical significance and suggested that most of the protection offered by statins was in men who were also exposed to an antihypertensive medication (data not shown).

Analysis of statin type suggests that there is little difference between lipophilic and hydrophilic statin medications (Table 4). However, there is a trend based on potency: high potency statins were associated with a risk reduction of 73% ($p<0.0001$) while it was only 31% for low potency statins ($p=0.32$).

We also checked if calendar year had any effect on statins as the more potent statins were more often prescribed later in the time period under study. We categorized calendar years into three categories: 1989–1992, 1993–1995, and 1996–1999 with roughly similar number of subjects. After adding interactions of these time periods with any statin use, the inverse association of exposure to statins with prostate cancer mortality was weakest in the earliest years (OR= 0.887, p-value = .75), strongest in the latest years (OR =0.11, p-value for interaction = 0.0009), and intermediate in the middle years(OR=0.32, p-value for interaction = .07). When we analyzed exposure only to high-potency statins, this smoothed out the trend considerably and these interactions were no longer significant.

PSA testing may be a measurement of compliance and possibly adherence, so we added an interaction term for statin use with PSA screening (ever vs. never) in the model, but this was not significant (p-value for interaction = 0.68).

DISCUSSION

Statin use in this population of New Jersey men is inversely associated with prostate cancer death. This association is equivalent to a 50 percent reduction in prostate cancer deaths. To our knowledge, this is the first population-based study to show statin protection specifically from prostate cancer death, and it adds to a growing body of literature suggesting that statins protect against advanced prostate cancer. The protective association in this study persisted regardless of adjustment for possible confounders such as markers of obesity, educational level, and the number of chronic comorbidities. Adjustment for the use of any antihypertensive medication further increased the apparent protective effect of statins.

We found seven previous observational studies that examined statin use and advanced prostate cancer (including some admixture of fatal cases in two studies). Of these, four were cohorts reporting hazard ratios ranging from 0.26 to 0.93, two of which were statistically significant, for the use of a statin for five or more years (7, 8, 10, 22). The other studies were case-control designs and report odds ratios for ‘ever use’ of statins of 0.75 to 0.9, one being statistically significant, but all three having lower confidence limits that are consistent with a substantial clinical effect of 0.6 or less (9, 23,24).

Statins are most commonly given for hyperlipidemic conditions, especially in patients who have other cardiovascular risk factors such as hypertension, obesity, and diabetes that are components of the metabolic syndrome (25). There is evidence that obesity is associated

with advanced and fatal prostate cancer, although probably not with prostate cancer incidence (26). For these reasons, if statins have no biological activity against the development of advanced or fatal prostate cancer, then one might expect them to be associated *positively* with prostate cancer mortality based on their being prescribed for conditions associated with this outcome. Thus, it is not surprising that the estimate for statin protection becomes stronger after adjusting for antihypertensive use, an indirect marker for the metabolic syndrome. These results are also consistent with the recent study by Farwell et al. showing that statin users were60 percent less likely to be diagnosed with high-grade prostate cancer as compared to antihypertensive users (27).

Our analysis suggests a possible mechanism that might be responsible for this risk reduction. We did not see a significant difference between lipophilic and hydrophilic statins, but there is a significant difference based on potency. High-potency statins were associated with a 73 percent risk reduction compared to no statins and nearly 2.5 times the protection seen by low-potency statins. This points to cholesterol-lowering as a possible mechanism. Decreasing cholesterol changes the lipid composition in cell membranes that has been linked to changes in intracellular signaling including that of the Akt pathway (28, 29). The Akt-mTOR signal transduction pathway has been implicated in increasing the response in prostate cancer cells to hypoxia-inducible factor-1 (HIF-1) that is central to cancer cell survival in a hypoxic environment (28).

Another possible mechanism reflective of cholesterol-lowering potency is that of decreasing mevalonate, an important precursor for isoprenoids. Just as for cholesterol, high-potency statins cause large decreases in mevalonate and, in turn, isoprenoids. Isoprenoids facilitate intracellular signaling by Ras and Rho that promote both cell survival and proliferation (29, 30). Statins may also reduce the risk of cancer through their anti-inflammatory (31), pro-apoptotic (32), and anti-angiogenic effects (31).

There are some limitations to this investigation. While medical records usually capture medications that are used regularly and require a prescription, they do not systematically capture all comorbidities. For example, we found it difficult to find documentation of “hyperlipidemia” or “dyslipidemia” even when a person was on a statin. For this reason, our estimate of the number of comorbidities is probably a lower boundary of the actual total. However, the number of comorbidities did not change the association of statin use with prostate cancer mortality.

We could not obtain accurate measurements of the cumulative dose or starting dates of medications so we used “any exposure” as a positive history for medication use. This prevents us from examining a dose effect other than what we could characterize by the potency of the statin. Similarly, we could not pinpoint the timing of the initial prescription so we are limited in determining if the potential biological effect is on the development of the cancer, or on its progression. We do note that most previous studies have not shown a relationship with prostate cancer incidence. Also, the greatest opportunity for exposure to statins in our subjects was before the diagnosis in the case (and an equivalent amount of time for the matched control).

Case-control studies are more prone to selection bias, so we carefully compared our controls with the population of New Jersey males with respect to PSA screening. Controls had a PSA screening rate that was nearly identical to the 2001 Behavioral Risk Factor Surveillance Survey (BRFSS) for New Jersey that supports representativeness of the population (33). Controls were chosen to be representative of the source population that gave rise to the cases: New Jersey male residents who were capable of developing lethal prostate cancer. It is expected that controls would be a mix of subjects without prostate cancer and those with non-lethal prostate cancer (at the time of death of the matched case). Controls were allowed then to have non-advanced prostate cancer, but we limited eligibility so that a control with prostate cancer had to have the diagnosis after his matching case was diagnosed. This was necessary to prevent a bias towards protection from PSA testing in the PSA screening study. However, we do not feel this possible source of selection bias is significant for statin exposure because our controls were very similar to the New Jersey male population with respect to prostate cancer prevalence and PSA screening for this calendar time period. Exposure to medications for hypertension, a comorbidity closely related to that of hyperlipidemia for which statins are indicated, had a strong and opposite relationship to the protective association seen for statins. If our findings are a result of selection bias, then it is unlikely that these two groups of medicines would have opposite associations with prostate cancer mortality. This design, though, does limit our ability to determine if the observed protective association is from prevention of more aggressive prostate cancer, or prevention of progression of existing prostate cancer.

There is also the possibility of a selection bias from competing risk due to cardiovascular death. If men on statins are more likely to die from cardiovascular death than those not on statins, then it is possible that this could result in an apparent lower of prostate cancer death for those men on statins, apart from any biological action. We believe that if present, this bias is not significant because adjusting for comorbidity did not change the estimates, and as noted above, persons with cardiovascular risk factors are more likely to have high grade and fatal prostate cancers. Moreover, one would expect to see the same trend with antihypertensive medications which is not the case.

Information bias is another concern for observational studies. We matched on the opportunity for exposure for each case and control dyad: 1989 through the time of death of the case, but we cannot state with certainty how comparable the documentation of statin use is between cases and controls. Cases were more likely to have contact with health care providers in their last few years, so this could result in more thorough documentation of medication use (conservative bias). Alternatively, cases may not have had statins prescribed, even if indicated, in their last few years because of competing concerns with their cancer (bias toward protective association). However, the largest interval of time for potential exposure for both case and control was before the diagnosis of prostate cancer in the case serving to decrease this source of bias. There is certainly some nondifferential misclassification based on incomplete information from medical records, and the level of adherence or true exposure but this would bias the results to the null.

Our response rate for controls was only 57 percent, but they were generally comparable to the source population. Cases had a good response rate but we limited their eligibility to

those who had a surviving spouse who could provide enough information for us to identify the decedent's source of health care and whose medical records provided proof of metastatic, symptomatic prostate cancer. This may have limited eligibility but ensured that cases had prostate cancer as the principal cause of death. By using only married cases, and for comparability, married controls, we may have decreased our generalizability; married men may be more adherent to medications than non-married.men so our result could be less in this population. Finally, although we adjusted for several potential confounders as well as matched for race, age, and potential time for exposure, we are aware that, similar to any observational study, this does not ensure the absence of unquantified biases and unknown confounding.

The strengths of this study are that it is population-based and that all cases were verified from chart review to have died from prostate cancer. An advantage of using disease – specific mortality as an endpoint is that it is not confounded by screening, which may be a problem in studies of cancer incidence. The key predictor variable, statin use, although not quantitative, was nevertheless, documented similarly for both cases and controls from review of medical records. The greater protection afforded by the more potent statins suggests a specific drug effect.

CONCLUSIONS

In summary, we describe an inverse association of prostate cancer death and the use of statin medications. This association is consistent with the protective effect cited in previous reports that have focused on advanced prostate cancer. This relationship is more striking with high-potency statins. In view of the good safety record of this class of drugs and the shared risk factors for cardiovascular disease and aggressive prostate cancer, we believe that it is now time to directly test the value of statins for inhibiting progression of prostate cancer in a randomized clinical trial.

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Table 1

Characteristics of cases and controls

	Cases		Controls	
	N	**(%)**	**N**	**(%)**
Race				
Black	39	(10)	40	(11)*
White	341	(90)	340	(89)
Education n (%)				
< high school	82	(22)	50	(13)
High school grad	195	(51)	193	(51)
College grad	57	(15)	65	(17)
Grad or pro school	41	(11)	70	(18)
Not available	5	(1)	2	(1)
Comorbidity number				
0	52	(14)	105	(28)
1 – 2	95	(25)	101	(27)
3 – 5	114	(30)	89	(23)
6 – 10	81	(21)	60	(16)
> 10	38	(10)	25	(7)
Age at time of diagnosis [mean, (SD)]	67.2	(5.7)	66.5	(5.9)

* One case-control pair was mismatched for race

Table 2

Gleason scores and clinical stage of cases

Gleason Score	N	(%)
5 or less	46	(12.1)
6	48	(12.6)
7	91	(23.9)
8	83	(21.8)
9	75	(19.7)
10	12	(3.2)
Not specified	25	(6.6)
Clinical Stage		
Localized (T1/2, node −)	144	(37.9)
Regional (T3/4 or node +)	61	(16.1)
Distant	153	(40.3)
Not assessed	22	(5.8)

Table 3

Effect of statin and antihypertensive use on prostate cancer mortality

	Odds Ratio	95% Confidence Interval	P Value
Unadjusted			
Statin use	0.49	0.34, 0.70	< 0.0001
Adjusted*			
Statin use	0.45	0.29, 0.71	0.0006
Adjusted†			
Statin use	0.37	0.23, 0.60	< 0.0001
Antihypertensive use	2.90	1.87, 4.49	< 0.0001

*Adjusted for education level, BMI, waist size, and comorbidity and matched for race and age

†Adjusted for all of above plus use of antihypertensive medication

Table 4

Effect of statin type on prostate cancer mortality

Statin Type	Odds Ratio*	95% Confidence Interval	P Value
Hydrophilic statin†	0.41	0.19, 0.86	0.02
Lipophilic statin‡	0.35	0.20, 0.61	0.0002
Hi potency statin//	0.27	0.15, 0.48	< 0.0001
Lo potency statin	0.69	0.33, 1.45	0.32

*Adjusted for education, BMI, waist size, comorbidity number, and matched for race and age. Reference category is “no statin” use for both comparisons.

†Hydrophilic statins include pravastatin, atorvastatin, and fluvastatin. Lipophilic statins include lovastatin, simvastatin, and cerivastatin.

‡May also have been exposed to a hydrophilic statin.

//May also have been exposed to a weak statin. Hi potency statins include cerivastatin, atorvastatin, and simvastatin. Lo-potency statins include pravastatin, lovastatin, and fluvastatin.