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Longer-term lipid-lowering drug use and risk of incident and fatal prostate cancer in black and white men in the ARIC Study

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Abstract

Lipid-lowering medications, particularly statins, may protect against aggressive prostate cancer. Fatal prostate cancer, the most clinically relevant outcome, remains understudied for this association. We prospectively studied lipid-lowering medication use and both incident and fatal prostate cancer in black and white men in the Atherosclerosis Risk in Communities (ARIC) Study.

6,518 men without cancer at visit 2 (1990–1992), the start of the statin era, were followed for prostate cancer incidence and death through 2012. Medication use was collected during study visits and telephone calls at up to 9 time points during follow-up. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of total (white N=541, black N=259) and fatal (white N=56, black N=34) prostate cancer overall and by race. Lipid-lowering medication use was modeled as time-dependent current use or duration (never, <10, ≥10 years).

By visit 4 (1996–1998), 21% of white and 11% of black men had used a lipid-lowering medication, mostly statins. There was a suggestion that current users were less likely to die from

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prostate cancer than non-users (HR=0.67, 95% CI=0.42–1.07) after multivariable adjustment. We observed no statistically significant differences between black and white men. Current use was not associated with incident prostate cancer, although long-term use was statistically significantly inversely associated with incidence (HR=0.68, 95% CI=0.50–0.92).

Long-term lipid-lowering medication use was associated with lower risk of prostate cancer. Current use was possibly associated with fatal prostate cancer.

Keywords

statin; prostate cancer; men; cohort; risk

Introduction

Accumulating evidence supports that lipid-lowering medications, particularly statin drugs, the most widely prescribed class since the 1990s, may preferentially protect against aggressive prostate cancer [1]. For example, a recent meta-analysis reported a modest inverse association between statin drug use and incident prostate cancer (relative risk [RR]=0.93, 95% confidence interval [CI]=0.87–0.99) based on 27 studies, but a more pronounced inverse association for advanced disease (RR=0.80, 95%CI=0.70–0.90) based on 7 studies [2]. Some studies have observed that advanced/aggressive disease risk decreases with increasing duration of use [2], but these studies were able to only investigate shorter-term use. While these results are intriguing as we seek new prevention strategies, the definition of advanced (stage-based) or aggressive (grade, or stage plus grade) disease is not consistent among these studies, making it difficult to determine whether such drugs might be useful in preventing disease that is the most likely to progress to being fatal. Further, fatal prostate cancer, the most clinically relevant outcome for this cancer with a heterogeneous prognosis, remains understudied for statin drugs including for long-term duration of use; its study requires long follow-up of large cohorts of men in the statin era. The two studies that have examined statin drugs and fatal prostate cancer among men without the diagnosis at the start of follow-up report their use to be inversely associated with fatal prostate cancer [3, 4], but questions remain about the needed duration of use for maximal benefit and which subpopulations, including black men, will benefit.

Thus, to address these gaps, we undertook an analysis of current and long-term use of lipid-lowering medications and risk of incident, lethal (i.e. first primary prostate cancer case that either had distant metastasis at diagnosis or that led to death with prostate cancer as the underlying cause), and fatal prostate cancer (i.e. death due to prostate cancer as the underlying cause, regardless of whether prostate cancer was the first primary cancer diagnosis) in the Atherosclerosis Risk in Communities (ARIC) Study overall and separately in white and black men.

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Methods

Study population

We conducted this analysis in the ARIC Study, a community-based, multicenter, prospective cohort study of 15,792 men (45%) and women aged 45–64 years who were recruited from four US communities – Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi. 27% of participants are black. Study enrollment began in 1987 and continued through 1989. Participants returned every 3 years for follow-up study visits in 1990–1992, 1993–1995, and 1996–1998, and for a fifth study visit in 2011–2013. At each visit, participants received an extensive examination, which included measurement of anthropometric variables by trained study personnel and interviews asking detailed questions about their medical history, healthcare access and utilization, as well as demographic and lifestyle factors including medication use. In addition, blood and urine were collected and stored or shipped to central laboratories for analyses. Follow-up telephone calls have been conducted annually between study visits and semi-annually since 2012. Local institutional review boards approved the ARIC protocol and informed consent was obtained from participants. The majority (99.7%) of participants gave approval for follow-up for the occurrence of non-cardiovascular diseases including cancer.

For this analysis, we excluded women (N=8,710), men with a history of cancer at visit 1 or were not otherwise eligible for studies on incident cancer (N=374), men who were not white or black (N=23), and men who did not consent to follow-up for non-cardiovascular diseases (N=1). Given that the first approved statin drug reached the market in 1987 and use did not become common until the early 1990s, we used visit 2 (1990–1992) as the start of follow-up and thus, also excluded men who had a cancer diagnosis or died before visit 2, or who attended visit 1 but not visits 2, 3, or 4 (N=166). These exclusions left 5,007 white and 1,511 black men in the analytic cohort.

Lipid-lowering drug use and duration

At each study visit, participants were asked to bring all medications they had taken during the previous 2 weeks to the visit. Trained study personnel recorded the name and dose of each medication taken. Beginning in 2006, during each follow-up telephone call participants were asked to retrieve any prescription medications they had taken in the previous 2 weeks and read the labels to the telephone interviewer. Thus, use of lipid-lowering drugs was ascertained from information collected at each study visit through visit 4 (1996–1998) and from information collected during the follow-up telephone calls beginning in 2006 through the end of follow-up. The validity of self-reported lipid medication use in ARIC has been found to be highly accurate [5]. We classified the following medications as lipid-lowering: statins, fibrates, bile acid sequestrants, and niacin. By visit 4 (1996–1998), 76% of lipid-lowering medication use was of a statin, and by 2011, 85% was a statin [5]. Men were categorized as non-users of a lipid-lowering medication until the first report of lipid-lowering medication use at a visit or on a follow-up call. If information on lipid-lowering medication use was missing at any assessment, medication use from the prior assessment was carried forward into the next time period. Once a participant became a lipid-lowering medication user, use status was assumed to be unchanged until the date of censor. We made

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this conservative assumption to minimize the bias that might occur if men who discontinued medications near the end of life were classified as not current users; such a bias would make lipid-lowering medication use appear protective against fatal prostate cancer. With the conservative assumption we made, if men discontinued use for other reasons, and given that we have prospectively collected data, any misclassification should be non-differential by disease status and the bias in the association should be toward the null. Duration of use was calculated as time of first reported use beginning at Visit 1. As described in detail below in the statistical analysis section duration was modeled as a time-dependent variable.

Covariate assessment

We used data collected at the study visits, including age (years, visit 1), race (visit 1), field center (visit 1), attained education (visit 1), height (cm, visit 1), body mass index (BMI in kg/m^2; each visit), cigarette smoking status (each visit), aspirin use (self-reported use in the past 2 weeks, each visit), regularity of routine physical examinations self-reported, (visit 1), and health insurance status (self-reported, visit 1) and type of health insurance (self-reported, visit 3). We also categorized men (at each visit) as having diagnosed diabetes if they self-reported a physician diagnosis or used pharmacologic treatment for diabetes. Men without a diagnosis of diabetes were categorized as 1) having undiagnosed diabetes if they had a fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL, 2) being at risk for diabetes if they had a fasting glucose of 100 to <126 mg/dL or non-fasting glucose of 140 to <200 mg/dL, or 3) as not diabetic and not at risk for diabetes. We used total cholesterol concentration that was previously measured in blood collected during study visits (each visit) and categorized participants as having borderline high or high cholesterol (≥5.2 nmol/L) or normal (<5.2 nmol/L).

Ascertainment of prostate cancer cases and deaths

We identified incident prostate cancers diagnosed from 1987 through 2012 by linkage with state cancer registries (MD, MN, MS, and NC) supplemented by active surveillance of the cohort, including for cases diagnosed before the registries were established and for cases among participants who moved out of an ARIC state [6, 7]. Cases diagnosed before the registries were established were ascertained from routinely collected hospital discharge summaries and confirmed with medical record abstraction. Beginning in 2014, we contacted participants who ever reported at a visit or on an annual or semi-annual follow-up telephone call that they had a cancer diagnosis for more information on their diagnosis, and collected and reviewed pertinent medical records. For prostate cancer that was self-reported, identified by a prostate cancer code on a hospital discharge summary or as the underlying cause of death assigned to a death certificate, all available sources of data, including from the registry and medical records, were reviewed to confirm or refute the diagnosis. Date of diagnosis, pathologic and clinical TNM stage, and Gleason sum were abstracted from the combination of registry linkages and medical record abstractions. All of these sources of data were adjudicated using standardized protocols described in detail previously [8]. We defined incident prostate cancer as a first primary diagnosis of prostate cancer through 2012. We defined fatal prostate cancer as a death due to prostate cancer as the underlying cause through 2012, irrespective of whether the diagnosis of prostate cancer was a first or subsequent primary. For fatal prostate cancer cases, men were censored at their date of

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death. We defined lethal prostate cancer as a first primary prostate cancer case that either had distant metastasis to any organ at diagnosis (pathologic TNM stage 4 or SEER summary stage 3, 4, or 7) or that led to death with prostate cancer as the underlying cause. For lethal prostate cancer cases, men were censored at their date of diagnosis. Among the analytic cohort, we ascertained 750 incident cases, 91 lethal cases, and 90 fatal cases from visit 2 through 2012. Median follow-up for fatal prostate cancer was 20.6 years (maximum 22.9 years).

Statistical analysis

We calculated means and proportions of demographic, lifestyle and health-related characteristics by lipid-lowering drug use, overall and stratified by race, for men attending visit 4, after statins had been available on the market for several years. We used Cox proportional hazards regression to estimate the hazard ratio (HR) and 95% confidence interval (CI) of incident, lethal, and fatal prostate cancer for current lipid-lowering medication use (yes/no) or for duration of use (never, <10, ≥10 years). For the incident and lethal prostate cancer analyses, men contributed person-time at risk from visit 2 (when most participants with an indication would have had the opportunity to be prescribed a statin) until prostate cancer diagnosis, diagnosis of another cancer, death, or end of follow-up in 2012, whichever came first. For the fatal prostate cancer analyses, men contributed person-time at risk from visit 2 until prostate cancer death, death due to other causes, or end of follow-up in 2012, whichever came first. To test for trend across duration of use, we included a single continuous variable with values equal to the cumulative duration of use, the coefficient for which we evaluated using the Wald test. All models were adjusted for age (continuous) and joint terms for race and field center (Minneapolis White; Jackson Black; Forsyth County and Washington County White; Minneapolis, Forsyth County, and Washington County Black). Multivariable models were further adjusted for risk and protective factors for fatal prostate cancer in this cohort and others – height (continuous), BMI (time dependent, continuous), cigarette smoking status (time dependent; current/quit <10 years ago, quit ≥10 years ago, never smoker), diabetes status (time dependent), aspirin use (time dependent; yes, no) – and education level (baseline; less than high school, high school graduate/vocational school/some college, college graduate or graduate school, missing). We conducted a sensitivity analysis examining current use of statin drugs separately from current use of other lipid-lowering medications. We also conducted these analyses separately in white and black men, and evaluated statistical interaction using the Wald test.

Because statin drugs are sometimes prescribed to patients for indications other than an elevated serum cholesterol level and one mechanism by which statin drugs may influence prostate cancer is via cholesterol lowering [9], we stratified by measured circulating total cholesterol concentration (< vs. ≥5.2 nmol/L) prior to the report on use of a lipid-lowering drug. To address the possibility of biases related to uptake of screening for elevated cholesterol and screening for prostate cancer, we a) stratified by frequency of routine physical examinations (at least every 5 years vs. less frequently), b) restricted to participants who had health insurance at visit 1 (91% of the study population), and c) further restricted to

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participants who had private health insurance and/or Medicare at visit 3 (74% of the study population; excluded men without health insurance or on Medicaid only).

Because statin drugs are prescribed to reduce risk of death from cardiovascular diseases in persons with indication, we accounted for competing risks of death from other causes [10] in a sensitivity analysis for fatal prostate cancer.

Statistical analyses were conducted using SAS 9.4 (Cary, NC). All statistical tests were two sided and p-value <0.05 was considered to be statistically significant.

Results

At visit 4, when statins had been available on the market for several years, 20% of men were current users of a lipid-lowering medication (76% of which were statins), which differed between black (11%) and white (21%) men. Compared to men not taking lipid-lowering medications, men taking a lipid-lowering medication were less likely to be current smokers (black men), and more likely to have diabetes, ever to have hypertension, or ever to have had elevated cholesterol (Table 1).

Prostate Cancer Incidence

Current lipid-lowering medication use was not associated with incident prostate cancer after adjusting for age and jointly for race and field center, or after further multivariable adjustment (Table 2). Throughout our analysis, the multivariable adjusted results were similar to those adjusted only for age and jointly for race and field center; thus, we present multivariable adjusted results in text throughout the Results section. Compared with never use, shorter-term use (<10 years) was not associated with risk of incident prostate cancer, whereas long-term use (≥10 years) was associated with a statistically significantly reduced risk of incident prostate cancer (HR=0.68, 95% CI=0.50–0.92, Table 2). We observed similar patterns of association when we considered specifically statins. Current use of a statin was not associated with incident prostate cancer (HR=1.03, 95%CI=0.86–1.22). Compared with never use, shorter-term use (<10 years) was not associated with risk of incident prostate cancer (HR=1.07, 95% CI=0.90–1.28). The inverse association observed for use of long-term (≥10 years) lipid-lowering medications was inverse, but attenuated and not statistically significant when examining statins specifically (HR=0.78, 95% CI=0.56–1.10).

Current lipid-lowering medication use was not associated with incident prostate cancer in either white or black men (p-interaction=0.14, Table 3). There was no association with incident prostate cancer when stratifying by circulating total cholesterol concentration prior to starting a lipid-lowering medication (p-interaction=0.44; Table 3).

In a sensitivity analysis to minimize the potential for detection bias, the null association between lipid-lowering medications use and incident prostate cancer did not differ by frequency of routine physical examination (Supplemental Table 1, p-interaction=0.76). In addition, this null association persisted among the 91% of men who had health insurance

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and among the 74% of men who had private health insurance and/or Medicare (Supplemental Table 1).

Fatal and Lethal Prostate Cancer

Current lipid-lowering medication users were borderline statistically significantly less likely to die from prostate cancer than nonusers after adjusting for age and jointly for race and field center (HR=0.64, 95% CI=0.41–1.02; Table 4). This finding was similar after further multivariable adjustment (HR=0.67, 95% CI=0.42–1.07; Table 4). Current use of a statin (rather than any lipid-lowering medication) also was inversely associated with fatal prostate cancer (HR=0.65, 95% CI=0.40–1.05). Risk of fatal prostate cancer was similar for both shorter- and longer-term use of lipid-lowering medication (Table 4), and similar results were found with increasing duration of use of a statin (vs. never use: <10 years - HR=0.64, 95% CI=0.38–1.08; ≥10 years - HR=0.74, 95% CI=0.39–1.40). We observed no association for lethal prostate cancer (i.e., incident metastatic prostate cancer or death from a first primary prostate cancer) (current use vs. no: HR=1.11, 95% CI=0.65–1.89; duration of use vs. never use: <10 years - HR=1.17, 95% CI=0.68–2.01, ≥10 years - HR=0.83, 95% CI=0.28–2.51; p-trend=0.92).

Current lipid-lowering medication use appeared to be inversely associated with fatal prostate cancer in both black (HR=0.76, 95% CI=0.34–1.70) and white (HR=0.60, 95% CI=0.35–1.06; p-interaction=0.62; Table 5) men after adjusting for age and field center; results were similar for white men after multivariable adjustment, but somewhat attenuated for black men (Table 5). We observed no differences in the association with fatal prostate cancer when stratifying by circulating total cholesterol concentration prior to starting a lipid-lowering medication (Table 5).

We performed a number of sensitivity analyses. To minimize the potential for detection bias, we took into account access to and uptake of medical care (Supplemental Table 2). We observed no statistical interaction in the inverse association between lipid-lowering medications use and fatal prostate cancer by frequency of having a routine physical examination (p-interaction=0.34), although there was a suggestion that the inverse association was stronger among men who reported having a physical examination less frequently than once every 5 years (HR=0.48, 95% CI=0.22–1.03) compared to those who had a routine physical at least once every 5 years (HR=0.85, 95% CI=0.46–1.57; Supplemental Table 2). In addition, the inverse association between current lipid-lowering medications use and fatal prostate cancer was similar to overall among the 91% of men who had health insurance (HR=0.63, 95% CI=0.39–1.02) and among the 74% of men who had private health insurance and/or Medicare (HR=0.62, 95% CI=0.35–1.07). To minimize the potential for bias due to competing risks, taking into account all other causes of death (current vs. never use: HR=0.78, 95% CI=0.49–1.26) or other non-cardiovascular causes of death (HR=0.76, 95% CI=0.47–1.23) the inverse association was similar.

Discussion

In this prospective study of black and white men with long follow up in the statin drug era, we found that long-term use of lipid-lowering medications was associated with a lower risk

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of developing prostate cancer, and that current use, appeared to be associated with a lower risk of fatal prostate cancer among men without the diagnosis at the start of follow up. These findings were not explained by differences in access to and uptake of health care or by competing risks of death from other causes. Longer-term use of a statin, which was the most commonly used lipid-lowering drug in this cohort by 2011 [5] also appeared to be inversely associated with incident prostate cancer.

The suggested inverse association between lipid-lowering medications use and fatal prostate cancer in men without the diagnosis at the start of follow-up that we observed is consistent with the two published studies that have addressed this outcome [3, 4]. Both of these studies reported an inverse association for fatal prostate cancer [3] [4]. While studying a different point in the natural history of prostate cancer, studies among men with the diagnosis of prostate cancer who were followed to recurrence, metastasis, and prostate cancer death [1, 4, 11–14], have found that pre- and/or post-diagnostic statin drug use may be inversely associated with these poor outcomes. The fact that studies using both populations – men without and with prostate cancer at the start of follow up – have observed inverse associations suggest that statin drugs may have relevance for both primary and tertiary prevention, but teasing apart causal effects is complex and will require large cohorts or clinical trials of men with well documented lipid-lowering medication use, and follow-up for prostate cancer diagnosis, recurrence/progression, and prostate cancer death.

That we did not observe an association with lethal prostate cancer appears to not be consistent with these previous findings. However, it should be noted that the definition of lethal disease is conceptually different from that of fatal prostate cancer. Although there is considerable overlap in lethal and fatal cases, the person-time denominators differ for these two case definitions with person-time being truncated at the time of diagnosis for lethal cases, and accumulating until the date of death for fatal cases. Thus, with respect to exposure status, if some men began taking a lipid-lowering medication after diagnosis, they would be classified as a never user for lethal analyses, but as a current user from the time of diagnosis forward for fatal analyses. The differences in the findings for lethal and fatal disease may provide additional insight into the timing of the actions of these medications relative to the nature history of prostate cancer from development to progression to death.

Previous reports have highlighted the importance of distinguishing between overall prostate cancer and prostate cancer that has the potential to be fatal when studying the association with lipid-lowering medications [1, 2]. While a recent meta-analysis reported a summary relative risk <1.0 for statin use and incident prostate cancer, associations have ranged from weakly positive to null to weakly inverse [2]. Positive associations with incident prostate cancer could be due to detection bias [15]. Similar to some previous studies [2], we found no overall association between current use of lipid-lowering medications and risk of incident prostate cancer. However, we did observe a lower risk of prostate cancer among long-term users (≥10 years) compared with never users. Although the meta-analysis concluded that longer-term use was not associated with incident prostate cancer risk, most previous studies have only been able to address ≥5 years with a few studies being able to examine ≥10 or more years separately [2]. Given that long-term users of lipid-lowering medications may be systematically different from men who take these drugs for shorter periods of time and from

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never users, we 1) controlled for multiple potential confounding factors, 2) restricted to those with health insurance (likely able to access medical care for screenings), and 3) stratified by frequency of medical check-ups, and the results remained the same. Nevertheless, we cannot rule out residual confounding and/or detection bias as explanations for the inverse association for long-term users.

To our knowledge, this is the first study to examine the association between lipid-lowering medication use and risk of fatal prostate cancer in black men. We did not observe meaningful differences in the association between lipid-lowering medication use and either incident or fatal prostate cancer by race, although our sample size was small for fatal prostate cancer and, thus, our ability to detect differences for this outcome, in particular, was limited. One previous study found that statin drug use was associated with a reduced risk of prostate cancer, particularly high-grade disease, in both white and black men [16]. Interestingly, a recent analysis of nationally representative data in the US concluded that, among individuals with coronary heart disease, black men are approximately half as likely as white men to take a statin [17]. Meanwhile, the prostate cancer mortality rate is 2.6 times higher in black men than in white men in the US [18]. Increasing the prescription of clinically indicated lipid-lowing drug use in black men might have an impact on prostate cancer mortality in this high-risk group.

Plausible biologic mechanisms, both cholesterol and non-cholesterol related, by which lipid-lowering medications, in particular statin drugs may preferentially prevent prostate cancer with an aggressive phenotype have been extensively reviewed [9]. Prostate cancer cells tend to over-accumulate cholesterol in their cell membranes, forming large lipid rafts which, in the case of cancer cells, may facilitate pro-carcinogenic cell signaling [9]. Therefore, having lower cholesterol may inhibit cholesterol-sensitive pathways, such as sonic hedgehog and Akt, which are important in carcinogenesis. Further, high cholesterol, particularly high low-density lipoprotein cholesterol, is associated with increased inflammation, which may be associated with increased risk of prostate cancer [9]. Perhaps most relevant to prostate cancer mortality is the evidence suggesting that cholesterol is a substrate for intra-tumoral steroidogenesis, which could lead to castrate resistance and disease progression [9]. A role for cholesterol in prostate cancer is also supported by a recent review of epidemiologic studies which concludes that men with lower cholesterol have a lower risk of more aggressive prostate cancer [9]. Finally, a recent Mendelian randomization analysis examined genetic risk scores for lipid traits in relation to risk of prostate cancer. This study concluded that there was evidence that the genetic scores for higher low-density lipoprotein cholesterol and triglycerides were associated with an increased risk of aggressive prostate cancer, while a genetic variant in *HMGCR* that mimics the cholesterol-lowering effect of statin drugs, was associated with a lower risk of prostate cancer [19]. Taken together, this literature provides strong evidence for a protective biologic mechanism of lower cholesterol on prostate cancer mortality.

Our study has many important strengths including the prospective design, detailed, long follow-up time in the statin era, updated information on lipid-lowering medication use including duration of use, and estimation of the association specifically in black men. In addition, information was available on important covariates, allowing us to control for many

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potentially confounding factors of the association we studied here, including the fatal prostate cancer risk factors cigarette smoking [20] and obesity [21].

Several aspects of our study warrant discussion. First, based on analyses we performed and other evidence, we find little support for one possible non-causal explanation for our findings: detection bias. This bias could result from men with more contact with the healthcare system being more likely to receive a PSA-based prostate cancer screening, and if elevated, a follow-up biopsy, as well as screening for cholesterol and, if elevated, a prescription for a lipid-lowering medication. A simulation study performed previously by members of our team showed that such detection bias is unlikely to fully explain the inverse association with advanced disease, but could explain a modest positive association with incident prostate cancer [15]. Furthermore, the inverse association between lipid-lowering medication use and risk of more aggressive prostate cancer has been observed in European populations where use of PSA-based prostate cancer screening was low [22]. While we did not have information on prostate cancer screening or PSA concentration for ARIC participants, and therefore could not fully rule out this source of bias, we conducted analyses for incident prostate cancer among men who had health insurance and among men who had private insurance and/or Medicare as well as stratified by frequency of a routine physical examination, the usual time when cholesterol and prostate cancer screenings are done, and found no evidence that the association for current lipid-lowering drug use and incident prostate cancer differed notably by these factors. We had too few fatal cases to conduct these sensitivity analyses for fatal prostate cancer, although this type of bias would only be apparent in the short term for fatal disease.

Second, the overall small size of ARIC for the analysis of fatal prostate cancer especially in subgroups is a limitation of this study. Our small sample size limited our ability to detect differences by race and precluded analyzing the association between duration of use and fatal prostate cancer in black men. In addition, we did not have sufficient power to comprehensively examine associations by types of lipid-lowering medication, or the type of statin drug. All but one [3] of the previously-conducted studies discussed above [1, 4, 11–14] examined only statin medications rather than all lipid-lowering medications as was done in our study. Although, as mentioned above, the majority of lipid-lowering drug use in this cohort was statin use, and we did conduct sensitivity analyses restricted only to statins, which produced similar results to our overall findings. Additional studies in larger populations will be necessary to determine whether the observed associations differ by type of lipid-lowering medication or type of statin drug.

Third, we did not adjust for family history of prostate cancer because it was found not to be a confounder in sensitivity analyses.

Fourth, we did not perform an analysis to eliminate prevalent medication-use bias as described by Hernan et al. [23]. However, few men in the analytic cohort were using lipid-lowering medications at the start of follow-up for this analysis (3%) and thus, the majority of users were new users not prevalent users. In a previous analysis of data from another cohort on statin use and the incidence of lower urinary tract symptoms in which follow-up was also begun at the start of the statin drug era when the prevalence of use was low, results from the

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method of Hernan et al. [23] and the time-dependent Cox modeling of duration of use yielded virtually identical estimates [24]. Thus, we expect that the HRs we estimated using time-dependent Cox modeling of duration of use in this study in ARIC should approximate what would be observed in a trial on new use of lipid-lowering medication (barring other sources of bias and confounding).

Fifth, we previously documented that ARIC participants have similar prevalences of major cancer risk factors and cancer incidence and mortality rates to the US population within the same age, race and sex groups [8], and given the consistency of our findings and those of others for lipid-lowering medications, including statins, and with various definitions of advanced prostate cancer, we expect that our suggestive findings for lipid-lowering medications and fatal prostate cancer are likely generalizable to similar groups in the US as a whole.

In conclusion, longer-term use of lipid-lowering medications may decrease risk of incident prostate cancer, and current use may reduce risk of death from prostate cancer risk. Further work will need to be conducted to evaluate the full impact of the lower prevalence of statin use in black versus white men on prostate cancer incidence and mortality in the US population as whole. Further work is also needed to determine which lipid-lowering medications used for what duration may provide the most benefit against the development of prostate cancer and when in the natural history of prostate cancer interception should occur to prevent the fatal phenotype from manifesting. Although these questions must be addressed to support the testing of lipid-lowering medications for primary and tertiary prevention of prostate cancer, the US Preventive Services Task Force has issued a recommendation on the use of statin drugs for the primary prevention of cardiovascular disease [25], which if followed by clinicians may increase the number of older men taking a statin and as a consequence provide a possible ancillary benefit of preventing prostate cancer incidence and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mucci LA and Stampfer MJ, Mounting evidence for prediagnostic use of statins in reducing risk of lethal prostate cancer. J Clin Oncol, 2014 32(1): p. 1–2. [PubMed: 24276780]
2. Bansal D, et al., Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One, 2012 7(10): p. e46691. [PubMed: 23049713]
3. Platz EA, et al., Statin Drugs and Risk of Advanced Prostate Cancer. Journal of the National Cancer Institute, 2006 98(24): p. 1819–1825. [PubMed: 17179483]
4. Yu O, et al., Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol, 2014 32(1): p. 5–11. [PubMed: 24190110]
5. Bhaskara S, et al., Validity of self-report of lipid medication use: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis, 2015 242(2): p. 625–9. [PubMed: 26342332]
6. Mink PJ, et al., Serum insulin and glucose levels and breast cancer incidence the atherosclerosis risk in Communities Study. American Journal of Epidemiology, 2002 156(4): p. 349–352. [PubMed: 12181105]
7. Prizment AE, et al., Association of inflammatory markers with colorectal cancer incidence in the Atherosclerosis Risk in Communities (ARIC) study. Cancer Epidemiol Biomarkers Prev, 2011 20(2): p. 297–307. [PubMed: 21217085]
8. Joshu CE, et al., Enhancing the infrastructure of the Atherosclerosis Risk in Communities (ARIC) Study for cancer epidemiology research: ARIC Cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2017.
9. Pelton K, Freeman MR, and Solomon KR, Cholesterol and prostate cancer. Curr Opin Pharmacol, 2012 12(6): p. 751–9. [PubMed: 22824430]
10. Fine JP and Gray RJ, A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association, 1999 94(446): p. 469–509.
11. Geybels MS, et al., Statin use in relation to prostate cancer outcomes in a population-based patient cohort study. Prostate, 2013 73(11): p. 1214–22. [PubMed: 23633265]
12. Grytli HH, et al., Association between use of beta-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol, 2014 65(3): p. 635–41. [PubMed: 23351721]
13. Marcella SW, et al., Statin use and fatal prostate cancer: a matched case-control study. Cancer, 2012 118(16): p. 4046–52. [PubMed: 22180145]
14. Melvin JC, et al., An investigation into the relationship between statins and cancer using population-based data. BJU Int, 2015 116(5): p. 681–3. [PubMed: 25223474]
15. Mondul AM, Caffo B, and Platz EA, Minimal detection bias in the inverse association between statin drug use and advanced prostate cancer risk: a simulation study. Cancer Epidemiol, 2011 35(4): p. e6–11. [PubMed: 21167804]
16. Kantor ED, et al., Statin use and risk of prostate cancer: Results from the Southern Community Cohort Study. Prostate, 2015 75(13): p. 1384–93. [PubMed: 26012482]
17. Johansen ME, Hefner JL, and Foraker RE, Antiplatelet and Statin Use in US Patients With Coronary Artery Disease Categorized by Race/Ethnicity and Gender, 2003 to 2012. Am J Cardiol, 2015 115(11): p. 1507–12. [PubMed: 25840577]
18. DeSantis CE, et al., Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer J Clin, 2016 66(4): p. 290–308. [PubMed: 26910411]
19. Bull CJ, et al., Blood lipids and prostate cancer: a Mendelian randomization analysis. Cancer medicine, 2016 5(6): p. 1125–1136. [PubMed: 26992435]
20. Sebelius K and National Institutes of Health (U.S.), 50th anniversary of the Surgeon General's report on smoking and health. 2014, National Institutes of Health,: Bethesda, Md p. 1 online resource (1 streaming video file (59 min.
21. McTiernan A, The Wcrf/Aicr Continuous Update Project - Systematic Reviews on Nutrition, Weight, Physical Activity and Health Outcomes in Cancer Survivors. Annals of Nutrition and Metabolism, 2013 63: p. 63–63.

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22. Murtola TJ, et al., Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2007 16(11): p. 2226–2232.

23. Hernan MA, et al., Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology, 2008 19(6): p. 766–79. [PubMed: 18854702]

24. Mondul AM, Giovannucci E, and Platz EA, Re: “a prospective study of statin drug use and lower urinary tract symptoms in older men”. Author reply. Am J Epidemiol, 2014 179(7): p. 928. [PubMed: 24651168]

25. Force USPST, et al., Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. JAMA, 2016 316(19): p. 1997–2007. [PubMed: 27838723]

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Table 1:

Characteristics of current users and nonusers of lipid-lowering medications, men in ARIC at visit 4 (1996 – 1999)

	All men		Black men		White men	
	Current lipid-lowering drug use at visit 4 (1996–1999)					
	No	Yes	No	Yes	No	Yes
N	3,934	953	836	105	3,098	848
Age (years)	63	64	62	63	63	64
Black (%)	21.3	11.0	-	-	-	-
Education (%)						
Less than high school graduate	20.2	17.3	37.8	34.3	15.4	15.2
High school graduate, vocational school, some college	36.9	38.0	26.7	24.8	39.7	39.6
College graduate, some graduate school, graduate degree	42.7	44.5	35.2	40.0	44.8	45.1
Missing	0.2	0.2	0.3	0.9	0.1	0.1
Height (cm)	176	175	176	176	176	175
BMI (kg/m^2)	28.4	29	28.3	29.9	28.4	28.9
Waist-to-hip ratio	0.98	0.99	0.96	0.97	0.98	0.99
Cigarette smoking status (%)						
Never	31.9	25.5	30.7	33.3	32.2	24.5
Former/quit ≥10 years ago	39.0	48.6	29.2	38.1	41.6	49.9
Current/quit <10 years ago	29.1	25.9	40.1	28.6	26.2	25.6
Diabetes status (%)						
No	43.9	35.2	40.9	23.8	44.6	36.5
At risk for diabetes	39.4	39.3	36.1	40.0	40.3	39.3
Undiagnosed diabetes	5.1	4.9	6.7	1.9	4.7	5.3
Diabetes	11.6	20.6	16.3	34.3	10.4	18.9
Ever hypertensive (%)	49.8	66.0	69.0	85.7	44.6	63.6
Ever elevated cholesterol (%)	25.4	54.9	30.3	65.7	24.1	53.5
Baseline health insurance (%)	92.4	95.9	78.8	83.8	96.0	97.4

* - Values are means or percentages. All characteristics are assessed at visit 4, unless otherwise indicated. Visit 4 was chosen because by this point statins had been on the market for several years and 76% of the lipid-lowering medications used by ARIC participants were statins.

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Table 2:

Association of lipid-lowering medication use and duration of use with incident prostate cancer, 6,518 men in ARIC (1990–2012)

	# Incident prostate cancers	Person-years	HR*	(95% CI)	HR†	(95% CI)
Current use						
No	513	66,951	1	(Ref)	1	(Ref)
Yes	287	33,532	1.00	(0.86–1.18)	1.03	(0.87–1.21)
Duration of use						
Never	513	66,951	1	Ref	1	Ref
<10 years	233	23,562	1.11	(0.94–1.31)	1.13	(0.95–1.34)
≥10years	54	9,970	0.67	(0.50–0.91)	0.68	(0.50–0.92)

*Adjusted for age, and joint categories of race and field center.

†Adjusted for age, joint categories of race and field center, height, updated BMI, updated cigarette smoking status, updated diabetes status, updated aspirin use, and education level.

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Table 3:

Association between lipid-lowering medication use and incident prostate cancer stratified by race and plasma total cholesterol, men in ARIC (1990–2012)

	Current use	# Incident prostate cancer	Person- years	HR *	(95% CI)	HR †	(95% CI)
Race							
White Men	No	343	51,661	1.0	(Ref)	1.0	(Ref)
	Yes	198	27,602	0.93	(0.77–1.13)	0.94	(0.78–1.15)
Black Men	No	170	15,290	1.0	(Ref)	1.0	(Ref)
	Yes	89	5,930	1.21	(0.90–1.62)	1.27	(0.95–1.71)
			P-interaction		0.15		0.14
Total Cholesterol							
Normal range (<5.2 nmol/L)	No	326	39,354	1.0	(Ref)	1.0	(Ref)
	Yes	104	11,982	0.97	(0.76–1.24)	0.98	(0.76–1.26)
Borderline or elevated (≥5.2 nmol/L)	No	186	27,493	1.0	(Ref)	1.0	(Ref)
	Yes	183	21,521	1.07	(0.85–1.36)	1.11	(0.88–1.41)
			P-interaction		0.38		0.44

* Adjusted for age, and joint categories of race and field center.

† Adjusted for age, joint categories of race and field center, height, updated BMI, updated cigarette smoking status, updated diabetes status, updated aspirin use, and education level.

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Table 4:

Association of lipid-lowering medication use and duration of use with fatal prostate cancer, 6,518 men in ARIC (1990–2012)

	# Prostate cancer deaths	Person-years	HR *	(95% CI)	HR †	(95% CI)
Current use						
No	53	74,007	1	(Ref)	1	(Ref)
Yes	37	40,534	0.64	(0.41–1.02)	0.67	(0.42–1.07)
Duration of use						
Never	53	74,007	1	Ref	1	Ref
< 10 years	22	27,953	0.62	(0.37–1.04)	0.64	(0.38–1.08)
≥ 10 years	15	12,580	0.69	(0.37–1.30)	0.74	(0.39–1.40)

*Adjusted for age, and joint categories of race and field center.

†Adjusted for age, joint categories of race and field center, height, updated BMI, updated cigarette smoking status, updated diabetes status, updated aspirin use, and education level.

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Table 5:

Association between lipid-lowering medication use and fatal prostate cancer stratified by race and plasma total cholesterol, men in ARIC (1990–2012)

	Current use	# Prostate cancer deaths	Person- years	HR *	(95% CI)	HR †	(95% CI)
Race							
White Men	No	31	56,973	1.0	(Ref)	1.0	(Ref)
	Yes	25	33,029	0.60	(0.35–1.06)	0.58	(0.33–1.04)
Black Men	No	22	17,034	1.0	(Ref)	1.0	(Ref)
	Yes	12	7,505	0.76	(0.34–1.70)	0.95	(0.42–2.15)
			P-interaction		0.62		0.62
Total Cholesterol							
Normal range (<5.2 nmol/L)	No	32	44,134	1.0	(Ref)	1.0	(Ref)
	Yes	13	14,994	0.61	(0.31–1.21)	0.61	(0.30–1.24)
Borderline or elevated (≥5.2 nmol/L)	No	21	29,739	1.0	(Ref)	1.0	(Ref)
	Yes	24	25,511	0.64	(0.33–1.27)	0.67	(0.33–1.35)
			P-interaction		0.78		0.72

*Adjusted for age, and joint categories of race and field center.

†Adjusted for age, joint categories of race and field center, height, updated BMI, updated cigarette smoking status, updated diabetes status, updated aspirin use, and education level.