Editorial

Epidemiologic Musing on Statin Drugs in the Prevention of Advanced Prostate Cancer

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Introduction

In this issue of *Cancer Epidemiology, Biomarkers, and Prevention*, the journal has published three large prospective studies: Cancer Prevention Study II Nutrition Cohort (1), California Men's Health Cohort Study (CMHCS; ref. 2), and a case-control study nested in the Finnish population (3), each investigating the association between use of statin drugs and prostate cancer. Along with work in the Health Professionals Follow-up Study reported last year by my colleagues and me (4), four prospectively conducted studies now support an inverse association between statin use and, specifically, advanced prostate cancer. This, thus far, quite consistent finding is biologically plausible and has already been discussed (5-7), as has the possible role of statins in the etiology of cancer in general (8, 9). This editorial, in contrast, provides epidemiologic arguments about whether statin drugs prevent prostate cancers that have a poorer prognosis and points to the epidemiologic and translational work that remains to be conducted to establish whether statin drugs should be prescribed for the prevention or treatment of advanced prostate cancer, irrespective of cardiovascular disease indication.

In prostate cancer epidemiology, consistent results across studies are rare. The variability in findings may be due to differences in the person, place, and time characteristics of the study populations. To appreciate why the consistency in findings for these four studies is remarkable, I first briefly summarize the very distinct settings in which the studies were conducted. One characteristic that is similar among the studies, though, is the prevalence of statin use by calendar year.

- Participants in the Health Professionals Follow-up Study live throughout the United States, are mostly White, have graduate degrees, and were recruited through professional organizations. In 1990, 4.4% used cholesterol-lowering drugs, which increased to 9.3% in 1994 and 23.8% in 2000 (4).
- Participants in the Cancer Prevention Study II Nutrition Cohort live throughout the United States, are mostly White, mostly have more than a high school education, and were recruited by American Cancer Society volunteers. In 1997, 20.7% were current statin users, of which 8.8% had been using it for 5 years or more (1).
- Participants in the CMHCS live in two regions of California, are multiethnic, and are members of a health maintenance organization. In 2002, 33% had ever been dispensed >100 days of a statin, and 19% of the men were considered to have used statins for 5+ years (2).
- In the Finnish study, all prostate cancer cases diagnosed in the country during 1995 to 2002 were included, and matched controls were sampled from the Population Register Center, apparently via incidence density sampling. During 1995 to 2002, 10.6% of cases and 9.9% of controls had used statins (3).

Despite the notably different characteristics of the four study settings, in each study, an inverse association was observed between longer-term use of statins and prostate cancer, with point estimates of 0.26 (4), 0.60 (1), 0.57 (2), and 0.75 (3). In Health Professionals Follow-up Study, the inverse association with advanced disease (n = 316 cases) was present for current and ever-use of statins, and the risk of advanced prostate cancer decreased with increasing duration of use. In Cancer Prevention Study II Nutrition Cohort, the inverse association with advanced disease (n = 317) was present only for longer-term users. In the CMHCS, the inverse association for advanced disease was not statistically significant, and although the relative risk for shorter term users was intermediate between the nonusers and the long-term users, the trend was not statistically significant. The CMHCS had the shortest follow-up time and consequently the smallest number of advanced cases (n = 131). In the Finnish study, the lower risk of advanced prostate cancer (~27% of 13,616 total cases with known stage) was seen for ever-use and risk decreased with increasing number of dose-days. In contrast to advanced disease, the findings for statins and prostate cancer overall were not compatible with an inverse association in the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, or the Finnish study, but an inverse association

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was suggested for total prostate cancer for 5 years or more use in the CMHCS (relative risk, 0.72; 95% confidence interval, 0.53-0.99), which might have been driven, in part, by the inverse association for advanced disease.

Prior work supports the lack of an association between statin use and prostate cancer overall. Most of that work can be categorized as randomized trials that evaluated statin drugs in the primary and secondary prevention of cardiovascular end points and in which cancer was recorded as a safety outcome or observational studies, including population-based record linkage studies, studies embedded in existing medical and prescription databases, and case-control studies. The relevant trials were recently summarized in three metaanalyses (10-12). Unfortunately, these metaanalyses, for the most part, have been highlighted as indicating that statins do not influence prostate cancer — end of story. This is probably because the trials are perceived as being the optimal source of data for evaluating the overall association: misclassification of statin use is reduced via drug assignment and monitoring of change in serum cholesterol concentration, and selection bias and confounding are minimized via randomization. However, for the purpose of considering the consistency of the literature on statins and advanced prostate cancer, the main limitations of the trials are (*a*) short duration of statin use in the trials — the four prospective studies each indicate that the association is stronger or limited only to long-term use of statins, (*b*) relatively small sample sizes given the age and duration of trials for evaluating prostate cancer, and (*c*) lack of evaluation of the association by stage or grade at diagnosis (4, 13, 14). The main limitations of the observational studies (which were published through 2005) included in the Browning et al. metaanalysis (12) include (*a*) lack of presentation of the results by stage and grade and (*b*) lack of collection or availability of data on potentially confounding factors beyond simple demographics or on PSA screening history, although many had high quality information on the prescription of statins and other drugs. There is one notable exception, a clinic-based case-control study (15), the study that spurred the recent interest in whether statins specifically influence risk of prostate cancer. The study included detailed information on prescription of statins, potentially confounding factors, and diagnosis of prostate cancer and reported inverse associations with statins for prostate cancer overall, especially with high-grade disease, and decreasing risk with increasing duration of use. The study included 100 cases, 92% of which were clinically organ-confined and, thus, did not assess the association with advanced disease.

The only contradictory findings to date come from a large hospital-based case-control study (n = 1226 prostate cancer cases) that was included (16) in the observational studies metaanalysis (12) but was updated subsequently (17). No association was observed between statin use and advanced prostate cancer or prostate cancer overall.

Currently, the epidemiologic literature supports an inverse association between longer-term use of statin drugs and advanced prostate but no consistent association for total prostate cancer. Is this association causal? To justify the dedication of resources to the conduct of translational studies to support use of statins in preventing and intervening on advanced prostate cancer, agreement that the observed association is unlikely to be due to bias is essential. First, we should consider alternative explanations.

The most concerning alternative explanation for statins and advanced prostate cancer finding is detection bias-a different accuracy of prostate cancer detection in statin users compared with nonusers. This detection bias is not due to flawed study design, but it can result in some populations because of patterns of medical care uptake: men who seek preventive care are more likely to be screened for both elevated cholesterol and PSA than men who do not. Doctors typically prescribe a statin to men who have high cholesterol and refer men with elevated PSA to urologists for prostate biopsy; the converse applies for men who do not seek preventive care. Among the latter, a cancer may go undetected until it is advanced. If statins do not influence prostate cancer at all, these patterns of medical care utilization would produce a positive association between use of statin drugs and prostate cancer overall, but an inverse association for advanced disease. Detection bias is particularly plausible in countries like the United States: statin drugs were approved by the Food and Drug Administration and were offered on the market around the same time that PSA screening became available; the prescription of statins (18, 19) and the uptake of PSA testing (20) subsequently rose very rapidly.

Of the four prospective studies, Health Professionals Follow-up Study and Cancer Prevention Study II Nutrition Cohort were the most susceptible to detection bias. There was a high prevalence of reported PSA testing overall, but it was ~10% higher in statin users than nonusers. The inverse association with advanced disease persisted when PSA testing was taken into account, although detection bias cannot be ruled out entirely because of imperfect information on PSA screening history.

The two other studies, in theory, should have been less susceptible to detection bias because the opportunity to undergo PSA screening should have been more equal between statin users and nonusers. Because participants in the CMHCS were members of a managed care plan, uptake of screening was through to be less likely to differ between those prescribed with a statin and those who are not. Those who used statins for 5 years or more and <5 years were 11.1% and 8.7%, respectively, more likely to have had a PSA test than nonusers after age adjustment. The Finnish study encompassed the entire population, health care costs are subsidized, and PSA testing is not a routine component of services, reducing the likelihood of differences in PSA screening between users and nonusers.

None of the three U.S. prospective studies observed the positive association between statin use and total prostate cancer predicted if this detection bias applied. Accordingly, either detection bias is not important, or the association between statin use and total prostate cancer is also inverse but obscured by detection bias. If the latter, then an inverse association with total prostate cancer should have been observed in the Finnish study with the low prevalence of PSA testing (7% in 1996 and 14% in 1999; ref. 21) versus >70% in the three U.S. cohorts. To the contrary, a very weak positive association was noted for statins and total prostate cancer (odds ratio, 1.07; 95% confidence interval, 1.00-1.13), the confidence interval for

which was not compatible with an inverse association. Taking all this evidence together, I contend that the likelihood of detection bias as the sole explanation for this finding is not high. Critics of these studies, nevertheless, may argue that the small differences in the extent of uptake of PSA screening between statin users and nonusers could still explain the inverse association with advanced disease.

Although raised by the reviewers of several of these studies, selection bias seems a less likely explanation for the inverse finding. To explain such an association, cases with advanced disease would have had to be preferentially excluded from the users but not from the nonusers. The Finnish study (3) virtually excludes the possibility of selection bias because the whole male population of Finland, over a defined period, was captured using their national cancer registry (mandatory reporting), population registry, and national insurance registry pharmacy database.

Confounding is also unlikely. Each study accounted for the most obvious potential confounders, including the use of other medications, notably NSAIDs (22, 23) and diabetes treatment (24, 25), and risk factors for cardiovascular disease that are also associated with prostate cancer (e.g., age, race, body mass index, which has a complex association with prostate cancer; ref. 26).

It is unlikely that, by chance alone, an inverse association would be observed in each of four unrelated studies.

Thus, detection bias cannot be excluded altogether, but other alternative explanations are unlikely. As a second step in thinking further about the likelihood that this association is causal, I discuss the findings using Hill's 1965 framework (27).

Temporality. The design of each of the four studies was prospective; that is, the use of statins predated the diagnosis of prostate cancer (note that one or more foci of yet undetected prostate cancer could have been present at the time that statins were prescribed). The key is that the presence or absence of occult prostate cancer was unlikely to have influenced whether a man was prescribed a statin.

Consistency. As already mentioned, we rarely observe perfect consistency in findings among epidemiologic studies on prostate cancer, but in the context of statins and advanced prostate cancer, all of the cohort studies that specifically evaluated advanced disease observed inverse associations for longer-term use of statins. These studies were conducted in very different settings, used very different methods for exposure assessment with variable accuracy in the classification of use and duration, and used very different methods for outcome ascertainment yet the direction of the association was the same. However, the details of the inverse association are not perfectly in agreement.

Strength of the Association. The size of the relative risks ranged from modest to moderate across the four studies and had varying degrees of precision. The association is not so large as to preclude the possibility of confounding or residual confounding, though.

Dose-response. Statistically significant trends across measures of duration of use were observed in two of the studies (3, 4). In the other two, the inverse association was essentially restricted to the longer-term users.

Biological Plausibility and Coherence. As noted, there is biological plausibility for the inverse association, and it is compatible with experimental research (e.g., ref. 28).

Analogy. Other exposures are differently associated with total prostate cancer versus advanced prostate cancer (29), so it is not implausible that statins also would show different associations by stage.

Specificity. I do not expect that statins would protect against only prostate cancer; their actions are quite diverse. On the other hand, the same consistency of findings between statins and the incidence of cancer overall (12, 17, 30) or lung (30), breast (31), colorectal (32), and hematologic (33) cancers has not been observed.

I cannot comment on *Experiment* (if we remove the exposure, does risk of the outcome change?) because statins are usually prescribed for a long term.

Based on thinking using Hill's casual framework, the data are not adequately robust at present to deem a causal link between longer-term statin use and advanced prostate cancer, however, I am encouraged by these findings and look forward to additional epidemiologic studies investigating this association. Outlined below are some of the research questions that remain to be addressed.

The most urgent question is, does the differential uptake of PSA testing between users and nonusers of statins explain all or part of the inverse association between statin drugs and advanced prostate cancer? Identifying a feasible approach that will allow us to rule out this source of detection bias will be a challenge. In most settings in which prostate cancer can be adequately studied (e.g., good research infrastructure and financial resources), PSA testing is used to some extent; thus, studying populations that are completely without PSA screening is not an option. We must be more thorough in collecting updated PSA screening (versus testing for suspicion of prostate cancer). In data analysis, statin-exposed person-time at risk should be compared with unexposed person-time at risk within strata of updated PSA screening history. Most individual studies are not large enough to generate precise estimates from this type of analysis; collaborative pooling will be necessary.

Do statin drugs influence the accuracy of the PSA test, and if so, what is the nature of the detection bias that would occur? One small preliminary study (34) and one large longitudinal study reported in abstract form (35) have suggested that men have lower serum PSA concentrations after starting a statin compared with baseline. This source of detection bias could not explain the inverse association between statins and advanced prostate cancer observed now, ~20 years after both statins and PSA testing were first introduced. However, if statins do lower PSA, then, in the future with very long-term use and in a setting wherein nearly all men are screened for elevated PSA, the likelihood of detecting a prostate cancer that has the inherent capacity to be invasive or metastatic may be delayed, and thus, statins may seem to be associated with an increased risk of advanced prostate cancer.

If we are able to exclude detection bias as an explanation for the inverse association, then the following question arises: what is optimal timing of administration of statin drugs for the prevention of advanced prostate cancer in men who do not currently have a diagnosis of prostate cancer? If the statins/advanced

prostate cancer association is causal, then we need to distinguish between two scenarios to determine when to administer statins to apparently health men: chemoprevention (statins prevent the development of prostate cancers that have the greatest potential to invade, metastasize, and cause death) and intervention (statins inhibit the further growth and metastatic potential of extant, but occult, prostate cancers; in other words, treatment of yet undetected early prostate cancer or preneoplastic lesions). Statins might need to be given at an earlier age and, thus, for a longer period for chemoprevention than for intervention. Distinguishing between these two scenarios will require large sample sizes and some cleverness in the statistical analysis; for example, we might evaluate whether the risk of advanced prostate cancer in statin users compared with nonusers differs by age at first use while taking into account duration of use.

If statins do prevent the development of advanced prostate cancer, we will also want to know the therapeutic utility of this class of drugs: do statins decrease the risk of progression to biochemical recurrence, metastases, or prostate cancer death after the treatment of clinically organ-confined prostate cancer? We began to investigate this question in a cohort of men treated by radical prostatectomy for clinically organ-confined prostate cancer at Johns Hopkins. We reported in 2007, in abstract form, that users at the time of surgery were less likely to have extraprostatic disease than nonusers; however, based on small numbers, baseline use was not associated with likelihood of progression (36). Moyad et al. has reported that men with early-stage prostate cancer treated with brachytherapy had a nonstatistically significant lower risk of recurrence if they used a statin (37). Certainly, much more work is needed on this area, including analyses that incorporate updated use after surgery or radiation therapy and that take into account pathologic stage and grade as confounders. Statins may have broad applicability as therapeutic agents, for example as adjuvant therapy or as a treatment for early disease; findings from an observational study suggest that statins might reduce the risk of early-stage breast cancer recurrence (38). The National Cancer Institute has already funded work on statins as a treatment for aberrant crypt foci in patients at high risk for colorectal cancer and dysplastic nevus, a melanoma precursor.[1]

Some of the observational studies conducted within medical settings or that used pharmacy databases have already begun to explore which types of statin drugs, dose, and duration of use are optimal for reducing the risk of advanced prostate cancer? Statins have varying solubilities; some are more fat soluble (lovastatin, simvastatin, atorvastatin and fluvastatin) and some are more water soluble (rosuvastatin and pravastatin; ref. 39). The hydrophilic statins are absorbed preferentially by the liver, where they inhibit production of cholesterol. More lipophilic statins are readily distributed to sites beyond the liver (39), where they inhibit intracellular synthesis of cholesterol. Given that the mechanism by which statins may influence advanced prostate cancer is elusive, the importance of the pharmacokinetic properties of statins is unclear. For cardiovascular indications, the dose required for lowering cholesterol depends on structural and pharmacokinetic properties of statins. Whether these same doses are optimal for the prevention of advanced prostate cancer will need to be checked. There are no adequate data on other aspects of the timing of the administration for optimal effectiveness against advanced prostate cancer. Using colon cancer as an analogy, data that regular, long-duration use of aspirin is required to observe a reduced risk are emerging (40). The four prospective studies on statins and prostate cancer presented different time metrics, making comparisons of timing patterns problematic. In future studies, epidemiologists must collect more detailed data on the type of statin, starting and stopping dates, dose, and frequency of use for each statin taken.

Concurrent with addressing all of these observational questions, we need input on, what is/are the mechanism(s) of action underlying the observed inverse association between statins and advanced prostate cancer? Knowing the most likely candidate pathways will allow the refining of our research questions. By inhibiting hydroxymethylglutaryl-CoA reductase, statins may influence the risk of advanced prostate cancer via numerous downstream pathways. Cholesterol lowering itself may play a role via influencing cell membrane receptor signaling (13, 41) and/or the activation of sonic hedgehog (9). Although the Finnish study did not observe an association between nonstatin cholesterol-lowering medications and advanced prostate cancer (3), this observation does not rule out a role for prostate-specific intracellular reductions in cholesterol synthesis. A recent paper suggested that cholesterol lowering by statins does not influence circulating concentrations of testosterone (42), the precursor for which is cholesterol. This observation possibly rules out one mechanism by which statins might influence advanced prostate cancer. Unfortunately, the study's findings were misportrayed in the media as ''no evidence that widely prescribed statins protect against prostate cancer''[2] and ''statins may have no effect on prostate cancer risk.''[3] Other possible effects of statins may include reducing the availability of isoprenoid groups for posttranslational modification of proteins known to be involved in carcinogenesis (8) and reducing inflammation (5). One group has begun to address whether statins influence intraprostatic inflammation and reported, in abstract, that no difference was found in the prevalence of inflammatory infiltrates on prostate biopsy by statin use (43). Because inflammation may influence PSA and thus the likelihood of biopsy and because inflammatory infiltrates are common in the prostate, more work is needed on the extent and biological nature of inflammatory infiltrates in prostate tissue from men who did not have an elevated PSA as an indication for biopsy.

With answers to the above questions (and others), trialists may be prepared to launch phases I and II (e.g., dose finding and safety) and, possibly, efficacy trials addressing these following therapeutic questions. Do

[1] http://www.cancer.gov/cancertopics/factsheet/statins

[2] http://www.sciencedaily.com/releases/2007/08/070809114127.htm

[3] http://www.medscape.com/viewarticle/561480

statins used as adjuvant therapy to radical prostatectomy, radiation therapy, or other treatments for organ-confined prostate cancer reduce the risk of progression to biochemical recurrence, metastasis, or death from prostate cancer? Do statins used as adjuvant or salvage therapy to hormonal therapy reduce the risk of death from prostate cancer in men diagnosed with metastatic prostate cancer or who progress to metastatic prostate cancer posttreatment for clinically organ-confined prostate cancer? Whether we will ever be able to conduct randomized trials on statins in the prevention of prostate cancer with a poor prognosis (cf. the Prostate Cancer Prevention Trial or SELECT; refs. 44, 45), is questionable. The cost of such a trial would be enormous, given the number of men who would need to be randomized to be able to detect a reduction in the rare outcome of advanced prostate cancer. Perhaps, the more important feasibility consideration would be the lack of middle-aged men who would be eligible for such a trial — never users who do not already have cardiovascular indication. If trials are conducted in the general population, close monitoring of known (e.g., myopathy and changes in liver enzymes; ref. 46) and unexpected effects of such therapy will be necessary. Concern was raised recently about the possibly increased risk of cancer with low-achieved LDL-cholesterol resulting from statins treatment in 23 randomized trials (47); absolute or percentage reduction was not associated with cancer. A prior metaanalysis by the Cholesterol Treatment Trialists' Collaborators reported no association between reduction in LDL-cholesterol resulting from statins treatment and cancer in 14 randomized trials (10).

In summary, promising findings are emerging from well-conducted prospective studies on an inverse association between longer-term use of statin drugs and advanced prostate cancer. Despite the consistency of the findings of the three studies published today and the one published elsewhere last year, it is still premature to recommend the use of statins for the chemoprevention of advanced prostate cancer. Further work is needed to address the role of PSA screening as possible explanation for the inverse findings and to identify the possible biological mechanisms that may underlie the inverse association, if this association is indeed causal.

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