Mounting Evidence for Prediagnostic Use of Statins in Reducing Risk of Lethal Prostate Cancer

Lorelei A. Mucci, Harvard School of Public Health, Boston, MA
Meir J. Stampfer, Harvard School of Public Health; and Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

See accompanying article on page 5

The initial studies of statins and risk of cancer, including prostate cancer, were spurred by concerns of possible increases in incidence among statin users. Such concerns were rapidly dispelled, and indeed reports of an inverse association between prediagnostic statin use and prostate cancer began to appear, although findings were inconsistent and mostly null for overall risk. Platz et al were the first to focus on the prostate cancer began to appear, although findings were inconsistent reports of an inverse association between prediagnostic statin use and prostate cancer. A meta-analysis of 27 observational studies published in 2012 reported a pooled relative risk of 0.93 (95% CI, 0.87 to 0.99) on the basis of seven studies. One challenge in inverse association for advanced disease, with a relative risk of 0.80 from overall incidence. A meta-analysis of 27 observational studies and prostate cancer disappears when one distinguishes associations otherwise come to clinical attention.

Much of the apparent inconsistency among studies on statins and prostate cancer disappears when one distinguishes associations with risk of advanced-stage—or preferably lethal—prostate cancer from overall incidence. A meta-analysis of 27 observational studies published in 2012 reported a pooled relative risk of 0.93 (95% CI, 0.87 to 0.99) for total incident prostate cancer and a more pronounced inverse association for advanced disease, with a relative risk of 0.80 (95% CI, 0.70 to 0.90) on the basis of seven studies. One challenge in the interpretation of the findings is a lack of consistency in the definition of advanced prostate cancer, with investigators using various definitions and often classifying T3a or T2 as advanced. From the perspective of etiology and prevention, we propose that lethal prostate cancer is the optimal disease end point for epidemiologic investigations. Given the long natural history of prostate cancer, such studies require long-term and complete follow-up of large cohorts of men.

Since the publication of the 2012 meta-analysis, five additional epidemiologic studies have reported on associations between statin use and lethal prostate cancer, all suggesting inverse associations. Using SEER data in Washington state, Geybels et al reported a relative risk of 0.19 (95% CI, 0.06 to 0.56) on the basis of 39 lethal cases in a population registry-based study, statin users had significantly lower rates of prostate cancer mortality, with a relative risk of 0.81 (95% CI, 0.75 to 0.88). However, these results were adjusted only for age and not other risk factors for lethal prostate cancer. In a study showing that postdiagnostic use of metformin was associated with substantially reduced prostate cancer mortality in diabetics, Margel et al also noted that prediagnostic statin use was linked to significantly lower prostate cancer–specific death, although no quantitative data were provided in that publication. Similarly, Grytli et al reported an inverse association between statin use and lethal disease among 3,561 men with high-risk prostate cancer in Norway in a study that was designed to examine beta blockers.

In the article that accompanies this editorial, Yu et al add important new findings that further support a link between statin use and a lower risk of lethal prostate cancer. Their study is notable in several key respects. One is the use of prostate cancer–specific mortality as the primary outcome, with 1,791 patients with lethal disease during 4.4 years of follow-up, which allows for calculation of precise measures of effect. Another key feature is the appropriate focus on the timing of statin use. The authors’ initial hypothesis was that postdiagnostic statin use would be associated with lower risk of lethal prostate cancer, but they found that most of the apparent benefit was from earlier use of statins before diagnosis. These findings are consistent with those of previous studies and nicely illustrate the need to identify the specific window of timing for the effect of a chemopreventive agent. For example, Margel et al found that metformin use after diagnosis was associated with better prostate cancer–specific survival, but prediagnostic use had little or no apparent effect. Attention to timing of an exposure may help resolve apparent discrepancies across epidemiologic studies and are essential in guiding the design of randomized trials.

A lingering concern for observational studies of statins and lethal prostate cancer is the potential for residual confounding, including that from more intense PSA screening. One may argue that statin users may tend to be more health conscious and in greater contact with the health care system, and may therefore have greater frequency of PSA screening, which would reduce their risk for lethal prostate cancer. Several studies have adjusted closely for intensity of PSA screening and other risk factors, with little impact on the inverse association. Also,
one would expect confounding by PSA screening to lead to a concomitant increase in risk of total prostate cancer, but this has not been observed in epidemiologic studies. Finally, it seems unlikely that the residual effect of differences in diagnostic intensity on prostate cancer mortality would be sufficient to explain the large inverse associations observed for statins, such as in the study by Yu et al.10

So where does one go from here to provide strong evidence for the potential of statins in chemoprevention of lethal prostate cancer? Prostate cancer outcomes nested in randomized trials of statin use for cardiovascular disease might shed light on these issues, although most trials have a relatively short duration of statin use and follow-up for lethal prostate cancer that limits the interpretation of study results. A meta-analysis of 22 trials of statins versus placebo reported 65 deaths as a result of prostate cancer among statin users compared with 76 deaths in the control groups (P = .38), but this includes only patients who were diagnosed and died within the average trial duration of approximately 4 years.11 This time frame of follow-up is too short and the etiologic window too imprecise to obtain the necessary level of evidence needed.

A randomized primary prevention trial for lethal prostate cancer seems unlikely because of the need to test the use of statins before diagnosis. This would require a trial of such large size and long duration that it may not be feasible. A preprostatectomy, neoadjuvant study among men undergoing surgery could be useful in elucidating molecular mechanisms of statins on the local tumor environment. Administrative medical databases with linkage to long-term cancer outcomes will also be useful to help refine decisions on statin use as a primary preventive agent as more data on lethal prostate cancer emerge. Meanwhile, as we wait, the current data may be sufficient to sway some clinical decisions toward statin use for men who are on the borderline for cardiovascular disease prevention.

REFERENCES


DOI: 10.1200/JCO.2013.53.2770; published online ahead of print at www.jco.org on November 25, 2013
Acknowledgment

Supported by National Institutes of Health/National Cancer Institute Grant No. CA141298, Dana-Farber/Harvard Cancer Center Specialized Program of Research Excellence in Prostate Cancer (M.J.S. and L.A.M.), and a Prostate Cancer Foundation Young Investigator Award (L.A.M.).