Re: Prostate-Specific Antigen: A Misused and Maligned Prostate Cancer Biomarker

We thank Drs Thompson, Tangen, and Kristal for their thoughtful editorial (1) pertaining to our publication entitled “The influence of statin medications on prostate-specific antigen levels” (2). They have insightfully identified potential limitations to the clinical implications of our findings. However, we feel there are some key points in the study that they did not take into account in their discussion.

First, the editorial suggests that our finding of a lower prostate-specific antigen (PSA) after starting statins in our observational study was artifactual and can be explained by “regression to the mean,” whereby excluding men with prostate cancer, PSA values higher than the mean, would tend to return closer to the mean on a second PSA test regardless of whether the man was taking a statin. We believe that there are four reasons that argue that our findings are not explained by regression to the mean: 1) the PSA change between two tests before starting statins was 0%, compared with a 4.1% decline after starting statins; 2) the change in PSA was statistically significantly related to the dose of statin; 3) the change in PSA was statistically significantly related to the decline in low-density lipoprotein (LDL) after starting statins; 4) in men with the highest pre-statin PSA values (ie, those most susceptible to regression to the mean), we still observed a clear dose- and LDL-proportional response. If regression to the mean were the sole or even chief explanation for the PSA decline, how could the PSA decline be related to both the statin dose and the statin-induced LDL decline?

Second, the editorial suggests that a change in PSA from 4.5 to 3.9 ng/mL does not meaningfully change the risk of being diagnosed with prostate cancer at biopsy. However, one of the biggest risk factors for prostate cancer is meeting an urologist with a biopsy gun. Our concern was such a statin-associated decline in PSA would be enough for a family doctor (or urologist) to defer referral for biopsy. Furthermore, the Prostate Cancer Prevention Trial (PCPT) prostate cancer risk calculator (3) computes the risk for one man at one point in time. Thus, the editorial argument compares two separate men: one with a PSA of 4.5 and another with a PSA of 3.9. We fully agree that the risk difference between these two men, all else being equal, is minimal. However, the PCPT calculator does not compute the risk of one man who has a 0.6 ng/mL decline in PSA immediately before biopsy. The risk of having cancer in such a man is likely much lower, should that man even go to biopsy (see previous point). Although we also agree that PSA should be used in a continuous fashion ideally in a risk calculator, as the editorial points out, many physicians still use PSA dichotomously based on a cut point. Thus, for the 39% of men in our study whose PSA was greater than 4.0 ng/mL and then dropped below 4.0 ng/mL after starting statins, this endpoint could be clinically meaningful.

Finally, the editorial concludes that the urological and epidemiological community should not use PSA as a biomarker for prevention studies and should not launch a primary prevention randomized trial of statins’ influence on prostate cancer risk but offers no alternatives for how to move the field forward. The statin literature as it pertains to prostate cancer may be conflicting at times but should not be ignored. We recently highlighted the many possible avenues of study that could move the field forward in the absence of a clear rationale for conducting a large primary prevention trial for statins and prostate cancer (4). The prospect of reducing the burden of the most prevalent male cancer with a drug that already reduces cardiovascular disease, warrants further exploration.

ROBERT J. HAMILTON
ELIZABETH A. PLATZ
STEPHEN J. FREEDLAND

References

Notes
Affiliations of authors: Division of Urologic Surgery, Department of Surgery, and the Duke Prostate Center, Duke University Medical Center, Durham, NC (RJH); Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada (RJH); Department of Epidemiology, Johns
Hopkins Bloomberg School of Public Health, Baltimore, MD (EAP); James Buchanan Brady Urological Institute and the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD (EAP); Section of Urology, Veterans Affairs Medical Center, Durham, NC (RJH, SJF); Division of Urologic Surgery, Departments of Surgery and Pathology, and the Duke Prostate Center, Duke University School of Medicine, Durham, NC (SJF).

Correspondence to: Stephen J. Freedland, MD, Division of Urologic Surgery, Box 2626 DUMC, Duke University School of Medicine, Durham, NC 27710 (e-mail: steve.freedland@duke.edu).

DOI: 10.1093/jnci/djp043

© The Author 2009. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.