Re: An Empirical Evaluation of Guidelines on Prostate-Specific Antigen Velocity in Prostate Cancer Detection

As authors of a recent article on prostate-specific antigen (PSA) velocity (1), we find ourselves in the unusual position of needing to respond to a critique made directly to the media (2,3), including a news piece published in this Journal (4). The main conclusion of our article—that there is no justification to perform a biopsy on men with a high PSA velocity in the absence of any other biopsy indication—was described (2,3) as being based on “flawed data”. Specifically, it was claimed that “sexual activity, riding on a bicycle or on horseback, a recent colonoscopy, a bladder or prostate infection, even variations in the ways laboratories perform the test can radically affect (PSA) readings,” something that would lead to an inaccurate estimate of PSA velocity (2).

We would first like to examine the evidence on alleged modifiers of PSA level. The effects of assay variation on PSA are well known to be influenced by assay design, choice of assay manufacturer, or whether the World Health Organization (WHO)—96/760 standard was used to standardize the assay (5,6). However, the PSA values in the Prostate Cancer Prevention Trial (PCPT) were based on a uniformly standardized assay provided by a single assay manufacturer. Data on bicycle riding are also quite clear, with several studies concluding that bicycle riding has no statistically significant effect on PSA levels (7–10). As for sexual activity, several studies have also failed to find an important effect on PSA (11–14). We accept that some studies have reported an impact of sexual activity on PSA, but these have generally found only short-term elevations, reporting, for example, “Ninety-two percent of subjects returned to baseline (PSA) by 24 hours” (15). We were unable to find any data on horseback riding or colonoscopy; however, these are not particularly common activities.

The effects of prostate infection on PSA cannot reasonably be doubted. Nonetheless, it is easy to demonstrate that infection, or indeed any other cause of PSA fluctuation, would not have an important impact on our results. We will assume that a sophisticated clinician is able to determine from a careful history that, for a proportion of men with high PSA velocity, the change in PSA was evidently caused by something other than prostate cancer. Accordingly, the cancer risk in these men will be the same as for men with low PSA velocity. It is straightforward to calculate how this would affect our findings that if a clinician were to conclude that the PSA threshold of +ng/mL was insufficiently sensitive, it would be better to lower the PSA threshold than to use PSA velocity. For example, let us assume that in 25% of cases with high PSA velocity, the cause of the PSA change is clearly attributable to a cause such as infection. We report in our article that there were 548 men with low PSA and negative digital rectal exam who had a PSA velocity greater than 0.35 ng/mL per year, and who would therefore be biopsied according to National Comprehensive Cancer Network guidelines; 115 of these men had prostate cancer. If a clinician were able to verify that the PSA rise was not due to cancer in 25% of these men, then the result would be 137 fewer men being biopsied. We reported a 15% cancer rate in men with PSA velocity less than 0.35 ng/mL per year, meaning that there would be 20 cancers in these 137 men. In total then, using PSA velocity would lead to 548 – 137 = 411 biopsies and 115 – 20 = 95 cancers. This means that 23% of biopsies would be positive. This remains a poorer positive predictive value than a PSA cut point of 2.5 ng/mL (24%).

Moreover, some of the men meeting the PSA threshold would presumably also be advised against biopsy (“your PSA is only above 2.5 ng/mL because of an infection”) and so the positive predictive value of PSA would also rise. Indeed, a quick analysis of our data shows that approximately 50% of the men with PSA velocity greater than 0.35 ng/mL per year also had PSA greater than 2.5 ng/mL.

We repeatedly contacted Dr D’Amico, our main critic, asking for an approximate estimate of the number of patients for whom PSA rises could be ascribed to a cause other than cancer. He consistently refused to provide such an estimate. Accordingly, we investigated a wide number of different scenarios. In brief, we were only able to find a higher positive predictive value for PSA velocity if 1) at least half of high PSA velocities could be accurately identified as artifacts and 2) fewer than half of these inflated PSA velocities lead to PSAs above the threshold, that is, although there was a rapid increase in PSA, PSA remained below 2 or 2.5 ng/mL. For the endpoint of high-grade cancer, the scenario would have to be even more extreme: For the positive predictive value for PSA velocity to be higher than for PSA, two-thirds of PSA velocities would have to be related to noncancer causes. This strikes us as a highly implausible scenario, especially as it assumes that clinicians can infallibly identify which PSA rises are artifactual. We have developed a simple Excel spreadsheet to apply these calculations and would be happy to share this on request.

In sum, our article was criticized on the grounds that factors other than cancer can increase PSA. For most of these factors, there are either no data or data suggesting no important effect. But even assuming that a sophisticated clinician could identify men for whom a rise in PSA was not cancer related, this would make little difference to our conclusions. We stand by our assertion that there is no justification to recommend a prostate biopsy for a man purely on the basis of PSA velocity, in the absence of any other indication.

References

Andrew J. Vickers On behalf of the study team Memorial Sloan-Kettering Cancer Center


Notes

Affiliation of author: Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY (AJV).

Correspondence to: Andrew J. Vickers, PhD, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 E, 63rd St, New York, NY 10021 (e-mail: vickersa@mskcc.org).

DOI: 10.1093/jnci/djr353

© The Author 2011. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

Advance Access publication on September 16, 2011.