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

Ian M. Thompson, Catherine M. Tangen, Alan R. Kristal

Prostate cancer is a conundrum. It is ubiquitous in aging men and, although the lifetime risk of death is only about 3%, it causes almost 30000 deaths per year. The cancer is asymptomatic until metastatic and at that stage, median survival is about 3 years. The advent of prostate-specific antigen (PSA) testing in combination with ultrasound-guided biopsy has dramatically increased cancer detection; a PSA test result is currently the “prompt” for the majority of prostate biopsies, and although only about half of the population receives regular PSA testing, it has effectively doubled the lifetime risk of receiving a prostate cancer diagnosis. It is currently unclear to what extent PSA screening has decreased prostate cancer mortality, but overdiagnosis leading to treatment of cancer that would never metastasize is certain.

The science supporting PSA as a screening biomarker is strong. For overall prostate cancer detection, the area under the receiver operating characteristic curve (AUC) is 0.68; for Gleason 8–10 tumors (the high-grade cancers that pose the highest risk of mortality) the AUC is 0.83 (1). PSA performs even better in men receiving finasteride, for whom the AUC for high-grade cancer is 0.89 (2). For a simple blood-based screening test, PSA is about as good as it gets.

It is unclear whether PSA has other uses beyond screening and monitoring recurrence following treatment. In particular, when studying prevention or treatment of prostate cancer, can we use PSA as a surrogate for effectiveness? Said another way, if the intervention reduces PSA, is cancer risk reduced? Certainly, this is not the case for reducing the risk of prostate cancer mortality following diagnosis. Finasteride profoundly lowers PSA, but it is not an effective prostate cancer treatment. Also consider that weight loss will increase PSA (3) yet obesity is a well-established risk factor for high-grade disease (4). Even for well-established biomarkers of disease risk, such as CD4 levels in persons infected with human immunodeficiency virus or serum cholesterol in middle-aged men, a treatment that lowers the level of the biomarker may not affect disease risk (5,6). Using PSA as a surrogate marker of prostate cancer risk may ultimately be correct for some interventions, but currently there is little or no support for doing so.

In this context, consider the report of Hamilton and associates in this issue of Journal, in which the authors examine change in PSA in 1214 men who had a PSA measure both before and after beginning a statin medication. Why statins? Because there is preclinical and epidemiologic evidence that these agents may affect prostate carcinogenesis. The authors find an overall 4.1% average PSA decline, from a mean of 0.9 to 0.86 ng/mL. They also note that the higher the PSA pre-statins, the larger the decline post-statins. They then reflect on the central question: cause or effect? Did statins simply affect PSA levels alone (if so, one would anticipate lower detection of prostate cancer simply due to fewer prostate biopsies) or did statins prevent (or treat, a hypothesis that the authors did not entertain and one that is far more likely if there is truly an effect on the prostate given the generally indolent nature of the disease in most men) prostate tumors and, through this effect, cause a fall in PSA? The answer to these questions cannot be known from this study.

Observational studies based on samples of convenience may yield intriguing results but have challenges. The first is related to spectrum and bias (7). The authors appropriately exclude men with a diagnosis of prostate cancer. As a result, if a man otherwise eligible for this analysis began a statin and his subsequent PSA increased beyond some threshold level (eg, 2.5 or 4.0 ng/mL), it would often prompt a prostate biopsy. If the biopsy found prostate cancer, he was then excluded from the analysis. Thus, the study sample excluded some men whose PSA was rising. A second problem is the interpretation of the higher PSA declines among men with the highest PSA. This observation is a well-understood statistical phenomenon termed “regression to the mean.” Simply stated, in any sample with repeated measures, those with the highest values will on average go down and those with the lowest values will on average go up. Although in this case regression to the mean is obvious, it can be subtle. In a series of men who elected active surveillance for the management of localized prostate cancer and who had a positive repeat biopsy, 55% experienced a fall in PSA after a cancer diagnosis (8). Presumably, the initial prostate cancer diagnosis was related to a transiently higher PSA.

A major issue is whether the magnitude of PSA decline observed in this report is clinically meaningful. The change with the higher PSA values may be associated with the movement of the PSA from above a biopsy threshold to below the threshold when the test is used dichotomously (as “elevated” or “normal”). We recognize that PSA values are often reduced to a dichotomous measure, a practice we strongly discourage based on the overwhelming evidence that it is a continuous marker of risk.

Affiliations of authors: Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, TX; Fred Hutchinson Cancer Research Center, Seattle, Washington, DC.

Correspondence to: Ian M. Thompson, MD, Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (e-mail: thompsoni@uthscsa.edu).

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A more reliable method to determine the risk that biopsy will detect prostate cancer uses multiple measures of risk including PSA: the Prostate Cancer Prevention Trial (PCPT) Prostate Cancer Risk Calculator (9). Taking a PSA level from the highest risk range (>4.0 ng/mL), let us assume a man with a PSA of 4.5 achieves the median absolute decline in PSA after beginning a statin (0.6 ng/mL) to 3.9 ng/mL. If he is age 60 and has no other risk factors, his calculated risk of prostate cancer would drop from 37% to 34% and his risk of high-grade prostate cancer from 8% to 7%. These changes are clinically insignificant.

The most important question is whether statins might be preventive, therapeutic, or simply affect PSA level itself. To test prevention is an enormous undertaking with tens of thousands of subjects and as much as a decade of follow-up. As we learned in the PCPT, determining efficacy for a prevention strategy that may have an interaction with PSA requires an end-of-study biopsy; without biopsy, detection bias cannot be eliminated. Testing therapeutic interventions in the majority of prostate cancer patients, who have screen detected, localized disease, is no less difficult, as few of these men die of prostate cancer and, even if they do, it is only after a decade of follow-up. Testing whether statins affect PSA requires a randomized trial. If statins do lower PSA, only a randomized trial with histological endpoints can determine whether statins affect a man’s risk of prostate cancer.

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References