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RESEARCH HIGHLIGHT

Prostate-specific antigen (PSA) velocity: a test of controversial benefit in the era of increased prostate cancer screening

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Determining the need for prostate biopsy remains one of the most controversial questions in urology. Over the past 10 years, practice guidelines have changed dramatically, especially among asymptomatic men with low prostate-specific antigen (PSA) and negative digital rectal exam. Thompson *et al.* found that nearly 15% of men with PSA <4.0 had evidence of prostate cancer on biopsy;[1] however, the clinical significance of these tumors is unclear. PSA velocity (PSAV) has been suggested as a measurement to discriminate between aggressive and indolent cancers. Both the NCCN[2] and AUA[3] guidelines recommend considering prostate biopsy for men with PSA <4.0 and high PSAV (0.35 and 0.4 ng/ml/year, respectively); however, a recent article by Vickers *et al.*[4] has called these recommendations into question, suggesting that PSAV adds little predictive accuracy to the standard risk factor assessment for prostate cancer.

PSAV gained recognition as a prognostic marker in 2004 after D'Amico *et al.*[5] demonstrated worse pathologic features and increased prostate cancer-specific mortality among men undergoing radical prostatectomy with PSAV >2.0 ng/ml/year in the year prior to surgery. A lower threshold for PSAV was later recommended after a 2006 article by Carter *et al.*[6] demonstrated higher mortality among men with a PSAV greater than 0.35 ng/ml/year 10–15 years prior to diagnosis of prostate cancer.

In their current article, the authors investigate whether the inclusion of PSAV with traditional risk-stratification models results in improved disease prediction.[4] Their cohort was comprised of 5519 men from the placebo arm of the prostate cancer prevention trial (PCPT). These men, all aged 50 years or older with an initial PSA <4.0, were followed for 7 years with yearly PSA tests, digital rectal exam and an end of study biopsy. The authors created a logistic regression model based on accepted predictors for prostate cancer including age, family history, previous biopsy and PSA at time of biopsy. Using the area under the receiver–operator characteristic curves, they subsequently compared the predictive accuracy of this model with a model including all those factors and PSAV to determine the incremental benefit in predictive accuracy when PSAV is added.

The results of the study suggest that the inclusion of PSAV does add an incremental, albeit small, improvement in predicting disease. Compared to the baseline model, the addition of PSAV led to increased area under curves of 0.007, 0.005 and 0.001 for the detection of all prostate cancers, clinically significant cancers (as defined by the Epstein criteria) and Gleason score 7–10 cancers, respectively. Compared to PSA alone, the addition of PSAV led to increased area under curves of 0.01, 0.012 and 0.004. After describing their careful analysis, the authors then advocate for the removal of PSAV as a trigger for prostate biopsy from current guidelines with little explicit discussion of the tradeoffs involved, arguing that use of PSAV will lead to an excess number of unnecessary biopsies.

There are several limitations to the authors' arguments. The first are inherent to the study's limitations. While the authors argue that men from the PCPT are the 'perfect test case for PSAV', this is not necessarily true. The PCPT is indeed a useful cohort because men received regular PSA, digital rectal exam and end of study biopsy regardless of cause. However, men in the PCPT had to be at least 55 years old at enrollment; thus, by the time biopsy was performed, they were at least 62 years old, limiting the ability to generalize the results to younger men with elevated PSAV. This is further problematic when considering that young men (<50 years old) may be the group where PSAV may be most informative.[7] It is therefore conceivable that while the PSAV did not greatly improve predictive accuracy among these older men, it may still have great value in a younger cohort. Furthermore, Carter *et al.*[6] demonstrated the association between PSAV and disease outcome 10–15 years prior to diagnosis. Since the PCPT followed patients for only 7 years, it is unclear whether the current study is affected by a verification bias; PSAV's predictive accuracy may be better demonstrated over a longer time period.

Another limitation to the study is the difficulty and confusion inherent in calculating PSAV. The predictive accuracy of PSAV has been shown to differ depending on the specific method by which it is calculated.[8] The authors attempt to account for this confusion by defining PSAV in a number of different ways; yet, questions about the validity of the PSA values themselves remain. D'Amico *et al.* point to limitations in 'quality assurance' of the PSA values in the PCPT in that they may have been influenced by pretest behavior and could have been reported differently based on the different assays used.[9]

The authors' conclusion that PSA velocity did not importantly add predictive accuracy is a value judgment. Despite their recommendations against using PSAV to help guide clinical decision making, they do demonstrate a benefit in predictive accuracy with

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the inclusion of PSAV. While inclusion of the criterion would undoubtedly lead to an increase in number of unnecessary biopsies (one out of seven without a conventional indication), it would also undoubtedly lead to increased detection of significant cancers, regardless of how infrequently this may occur. This raises the bigger question of the ideal number needed to treat for prostate biopsy. Each time an additional variable enters the clinical decision algorithm for prostate cancer, it increases an individual's likelihood to have an indication for prostate biopsy. Twenty years ago a man with a low PSA and negative family history would likely have been advised not to have a prostate biopsy. However, since the advent of new screening strategies such as PSAV, PCA3 and percent free PSA, the likelihood of such a man having an additional risk factor and thus undergoing a biopsy is higher.

The tradeoff between increased detection of significant and insignificant cancers should be considered from a number of different viewpoints. For the patient, biopsies come with the cost of time away from work, discomfort and risk for complications such as bleeding and infection. In fact, hospital admissions after biopsy are becoming increasingly common.[10] Furthermore, increasing the number of biopsies would result in a further increased cost to health care systems already struggling with the escalating cost of health care. Most importantly for the individual, lowering the threshold for biopsy or increasing the possible criteria indicating biopsy increases the risk that a cancer diagnosed may be one which would never have been detected and never would have caused morbidity during the patient's lifetime. The very diagnosis of cancer exposes the patient to the risk of the negative consequences of treatment, especially true considering that 90% of men with low-risk cases choose to undergo some form of curative therapy.[11]

The benefits of increased screening and diagnosis are also frequently debated. There is compelling evidence that prostate cancer screening can lead to decreased mortality.[12,13] Additionally, catching cancer in an early stage has the potential to reduce symptoms of advanced disease. On the other hand, since the introduction of PSA testing, prostate cancer has undergone a stage migration with an increasing incidence of low-risk disease. Many argue that the mortality benefit seen from screening is thus misleading and is more likely a result of overdiagnosis.[14]

The current study suggests that PSAV is not as beneficial a screening test as previously believed; however, that does not mean that PSAV should be disregarded altogether. By their own estimates, using PSAV would help diagnose more cancer and more aggressive cancer. The true question that remains unanswered is how many negative biopsies are worth the benefit of diagnosing an additional malignancy. Answering this question has the potential to drastically change practice patterns and is an area where further research is necessary and should be encouraged.

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