Assessing Risk: Does This Patient Have Prostate Cancer?

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Prostate-specific antigen (PSA) is used routinely in the United States to screen for prostate cancer, a disease that accounts for a similar number of yearly male cancer deaths as colon and rectal cancers combined. PSA screening followed by prostate biopsy leads to the detection of early-stage prostate cancers for which a cure is more likely (1). However, the extent to which PSA screening has influenced declining prostate cancer mortality rates in the United States and whether routine PSA screening improves overall health outcomes remain matters of debate.

Physicians (especially urologists) are aware that PSA test results, digital rectal examination (DRE) findings, family history of prostate cancer, and other risk factors (such as race) can influence the chance that prostate cancer will be found on a biopsy. Furthermore, because of the frequency of serial PSA testing, physicians now have a heightened suspicion of prostate cancer in men whose PSA level increases over time (referred to as PSA velocity). However, since 1989, when an assay manufacturer reported that a serum PSA level in the range of 0–3.99 ng/mL was “normal” (2), PSA level has been used primarily as a dichotomous biomarker, with a threshold value of 4.0 ng/mL, as a prompt for recommending a prostate biopsy; urologists commonly recommend prostate biopsies (at least initially) when a man’s PSA level exceeds this “normal” range, regardless of other risk factors. This approach has remained commonplace even though Gann et al. (3) in 1995 clearly showed that, during the 10 years following a baseline PSA measurement, the risk of being diagnosed with a life-threatening prostate cancer increased incrementally with increasing PSA levels that remained well below 4.0 ng/mL and cautioned that information would be lost by dichotomizing PSA test results.

In this issue of the Journal, Thompson et al. (4), who have previously reported that prostate cancer is common in men who have PSA levels below 4.0 ng/mL (5) and that virtually no PSA threshold can be used to exclude the presence of a prostate cancer (6), have explored the value of PSA level in combination with other factors (i.e., family history of prostate cancer, race, DRE results, previous biopsy results, and PSA velocity) for estimating the risk that prostate cancer is present. The factors that were predictive of prostate cancer were a higher PSA level, a positive family history, and an abnormal DRE; a prior negative biopsy reduced the risk. Factors that were predictive of high-grade prostate cancer were a higher PSA level, an abnormal DRE, older age at biopsy, and African American race; a prior negative biopsy reduced this risk. PSA velocity was not an independent risk predictor of either prostate cancer or high-grade disease, and age at prostate biopsy was not a predictor of prostate cancer. The data indicate that PSA level is such a strong predictor of prostate cancer that neither age nor the rate at which the PSA level rises is important. How might we explain these findings?

We know that a baseline PSA level is a strong predictor of the development of life-threatening disease over the subsequent decade: a PSA level of 4.0–10.0 ng/mL is associated with a relative risk of prostate cancer diagnosis three to 10 times higher than that associated with a PSA level of 1.0–4.0 ng/mL (3). Yet Thompson et al. found that the sharpest increase in the risk of prostate cancer was when PSA levels were below 4.0 ng/mL [Fig. 1 in (4)]. Also, men who have life-threatening prostate cancers have a higher PSA velocity than men who do not have prostate cancer (7), and PSA velocity is associated with death from prostate cancer both before and after treatment (8,9). Yet Thompson et al. (4) found that PSA velocity was not associated with the development of prostate cancer or the development of high-grade cancer. One explanation for the findings reported by Thompson et al. is that the cancers detected (or a substantial proportion of them) were not life threatening. Almost half of the cancers detected were in men who had PSA values of 2.0 ng/mL or less [table 3 in Thompson et al. (4)]. The probability of finding a small-volume, potentially harmless prostate cancer increases as PSA level decreases (10). Thus, the risk assessment tool described in the current study may not be relevant for the detection of life-threatening prostate cancers. However, other factors not found to be important in the current study may turn out to be important predictors of life-threatening cancer.

What are the implications of this study? According to the risk assessment tool described by Thompson et al., to avoid a 20% risk of harboring prostate cancer would require the biopsy of all men (regardless of family history and DRE findings) at or before they reached a PSA level of 2.0 ng/mL [fig. 3 in (4)], a level well below the “standard” dichotomous value of 4.0 ng/mL. Although the authors do not endorse a specific threshold probability of prostate cancer risk at which a biopsy should be performed, most physicians (and, probably, patients) would not be comfortable with a 20% likelihood of cancer. The authors previously reported (5) a positive biopsy rate of 15% for men with PSA levels below 4.0 ng/mL who underwent a six-core biopsy (most urologists today perform 12 or more cores). Approximately 80% of men in the U.S. population have PSA levels below 4.0 ng/mL (11). Thus, among all men with PSA levels below 4.0 ng/mL, the proportion of prostate cancers that could be detected with a biopsy would be 12%. By contrast, approximately 10% of the male population has a PSA level of 4.0–10.0 ng/mL (11) and the positive biopsy rate in these men is approximately 30%. Thus, among all men with PSA levels between 4.0 ng/mL and 10.0 ng/mL, the proportion of cancers that could be detected with a biopsy would be 3%. The current estimated prevalence of prostate cancer in the United States is 1.8 million (12). If we were to diagnose only a fraction of those cancers in men who have a PSA level below 4.0 ng/mL, we would easily double the current prevalence of prostate cancer, at which point the prevalence of prostate cancer would be greater than that of all other cancers combined among men (12). In light of current estimated prostate cancer overdiagnosis rates of 30%–50% (13,14), further increases in overdiagnosis would have a huge impact on the unnecessary treatment of prostate cancer.

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Finally, the cohort chosen by Thompson et al. to create a risk assessment tool was likely to be enriched in small-volume, low-grade cancers. Thus, the use of this cohort is more likely to lead to the diagnosis of prostate cancer that is not life threatening. In the absence of accurate markers of life-threatening disease, I do not believe that physicians should endorse any approach to predicting the risk of prostate cancer that is likely to increase the diagnosis of biologically unimportant cancers. Once we have the ability to assess multiple risk factors (e.g., PSA or other new markers) in populations for which the long-term outcomes are known, approaches like the one described by Thompson et al. will help identify those men who will benefit from active treatment.

REFERENCES