TMPPRSS2-ERG Fusion Transcripts in Matched Urine and Needle Rinse Material after Biopsy for the Detection of Prostate Cancer: Really a Step Forward?

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Prostate cancer (PCA)3 is the most common malignancy in America, Western Europe, and Australia, and there are large discrepancies in incidence rates. In a few countries in South America and Africa and in Sweden, PCA is the leading cause of cancer deaths (1). Prostate-specific antigen (PSA) is the best available tumor marker. It has an irreplaceable role for PCA follow-up and prognosis but has severe limitations for diagnosing PCA (2). The low diagnostic specificity and positive predictive value of only approximately 25% for screening (3) encourages opponents of PSA to be overly critical and to neglect some of its contributions (e.g., dramatic reduction of metastatic disease and a mortality rate reduced by approximately 20% (4)). Other problems, such as a reduced diagnostic sensitivity and the overdetection with a 4-μg/L PSA cutoff and subsequent overtreatment (5), support the need for new biomarkers that overcome these obstacles. Although the vast majority of patients with PCA will not die from the disease, the goal is to detect aggressive and life-threatening PCA. Therefore, scientists are searching for more PCA-specific markers that can preferentially detect aggressive cancer. As recent examples, a subform of free PSA, [−2]proPSA (6), and the urinary PCA antigen 3 (PCA3) have already shown some promising results (7).

The discovery of fusion transcripts for the TMPPRSS2 (transmembrane protease, serine 2) and ERG [v-ets erythroblastosis virus E26 oncogene homolog (avian)] genes (i.e., TMPPRSS2-ERG) in PCA tissue was one of the most important developments in the field of PCA research in the last decade (8). Meanwhile, other gene fusions, such as SLC45A3-ERG (solute carrier family 45, member 3–ERG), TMPPRSS2-ETV1 (TMPPRSS2–ets variant 1), SLC45A3-ETV1, and NDRG1-ERG (N-myc downstream regulated 1–ERG) have been described (9). If there is a detectable TMPPRSS2-ERG gene fusion, it is almost certainly cancer associated (10); however, the prevalence of the TMPPRSS2-ERG gene fusion is only about 50% in PCA patients (9), and its occurrence in some premalignant prostate tissue lesions (10) suggests that such a test will hardly function as a screening tool. In contrast, the high diagnostic specificity indicates that the TMPPRSS2-ERG gene fusion could be used as a noninvasive adjunct marker in urine, in combination with other markers such as PSA and PCA3, to improve overall diagnostic accuracy (11). Therefore, a urinary assay for the TMPPRSS2-ERG fusion gene that requires stabilization of the urine sample after collection is currently in development (12). Thus, this approach prevents possible errors due to inappropriate sample collection or analyte preparation.

In a study reported in this issue of Clinical Chemistry, Bories et al. combined the data obtained from a biopsy rinse material and TMPPRSS2-ERG fusion data obtained from urine sediments after digital rectal examination to evaluate 57 patients undergoing prostate biopsy (13). After the sampling of 10–12 cores, the biopsy needle (without any tissue) was taken at the end of a biopsy procedure and rinsed repeatedly into a tube containing a reagent that prevents RNA degradation. The authors showed the feasibility of detecting TMPPRSS2-ERG in biopsy rinse material (13); however,
several questions regarding the procedure and the possible improvement in PCa diagnosis remain unanswered.

First, from a methodologic point of view, it is relatively unlikely to find enough cancer cells in the situation in which only 1 core of 12 is positive for PCa. For example, it is difficult to understand how it would be possible to detect TMPRSS2-ERG if only the first core had cancer, but not the remaining 11. It seems very unlikely that enough cancer cells would remain on the needle after the needle had been inserted several times through benign prostate tissue. This consideration may explain the low detection rate of the fusion gene in instances when biopsies show only a microfocal cancer [see Table 3 in (13)]. What would happen if the rinse procedure were performed after each biopsy core? That would interfere with the biopsy procedure itself, but the detection rate should be comparable or better, compared with the proposed method. It is important to emphasize that there is a clinical need to obtain at least 10 different cores in a typical biopsy session, because PCa is often multifocal (14) and because the information obtained with fewer cores would be insufficient to guide further treatment.

Second, in routine practice, the needle is relatively bloody after collection of a biopsy core and is usually wiped clean. To refrain from this routine procedure to allow for a slightly higher chance that cancer cells may adhere to the biopsy needle seems unrealistic.

Third, the diagnostic sensitivities of 69% obtained with the urinary TMPRSS2-ERG measurements and 62% obtained with the biopsy rinse material not only confirm the limited diagnostic sensitivity due to preanalytical variables but also demonstrate no advantage to examining the rinse material after a biopsy. A recent study suggested that including other fusion genes into a multiplex assay could improve the diagnostic sensitivity (9).

Fourth, the high PCa-detection rate of 55% obtained in such a feasibility study may be due to serum PSA values of up to 43 μg/L. The method should be evaluated in the future with a more typical cohort (e.g., 2–10 μg/L PSA).

In summary, the pilot study of Bories et al. has shown that in addition to the use of TMPRSS2-ERG gene fusion data obtained from tissue, data might also be derived from biopsy rinse material, but at a lower diagnostic sensitivity (13). Thus, it is necessary to confirm this observation in a larger study and to compare the findings with those from tissue data. We appreciate the authors’ efforts to search for the TMPRSS2-ERG gene fusion, an approach that in principle could also be applied to other potential markers with a new specimen, such as biopsy rinse material, but we believe it is too early to claim that this approach can improve PCa diagnosis or prognosis.

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References


