Prevalence of *TMPRSS2-ERG* Fusion Prostate Cancer among Men Undergoing Prostate Biopsy in the United States

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Abstract

Purpose: Fusion of the *TMPRSS2* prostate-specific gene with the *ERG* transcription factor is a putatively oncogenic gene rearrangement that is commonly found in prostate cancer tissue from men undergoing prostatectomy. However, the prevalence of the fusion was less common in samples of transurethral resection of the prostate from a Swedish cohort of patients with incidental prostate cancer followed by watchful waiting, raising the question as to whether the high prevalence in prostatectomy specimens reflects selection bias. We sought to determine the prevalence of *TMPRSS2-ERG* gene fusion among prostate-specific antigen–screened men undergoing prostate biopsy in the United States.

Experimental Design: We studied 140 prostate biopsies from the same number of patients for *TMPRSS2-ERG* fusion status with a fluorescent *in situ* hybridization assay. One hundred and thirty-four samples (100 cancer and 34 benign) were assessable.

Results: *ERG* gene rearrangement was detected in 46% of prostate biopsies that were found to have prostate cancer and in 0% of benign prostate biopsies ($P < 0.0001$). Evaluation of morphologic features showed that cribriform growth, blue-tinged mucin, macronucleoli, and collagenous micronodules were significantly more frequent in *TMPRSS2-ERG* fusion–positive prostate cancer biopsies than gene fusion–negative prostate cancer biopsies ($P \leq 0.04$). No significant association with Gleason score was detected. In addition, non-Caucasian patients were less likely to have positive fusion status ($P = 0.02$).

Conclusions: This is the first prospective North American multicenter study to characterize *TMPRSS2-ERG* prostate cancer prevalence in a cohort of patients undergoing needle biopsy irrespective of whether or not they subsequently undergo prostatectomy. Our results show that this gene rearrangement is common among North American men who have prostate cancer on biopsy, is absent in benign prostate biopsy, and is associated with specific morphologic features. These findings indicate a need for prospective studies to evaluate the relationship of *TMPRSS2-ERG* rearrangement with clinical course of screening-detected prostate cancer in North American men, and a need for the development of noninvasive screening tests to detect *TMPRSS2-ERG* rearrangement.

Translational Relevance

The high prevalence of *TMPRSS2-ERG* prostate cancer is clinically relevant because emerging data suggests a worse prognosis for tumors harboring the gene fusion (i.e., higher tumor stage and tumor-specific death or metastasis). The prevalence of the *TMPRSS2-ERG* gene rearrangement in the United States has previously been described only in single-institution studies of archival, retrospective tissue banks comprised of prostate cancer tissue from patients who underwent prostatectomy (‹35% of prostate cancers diagnosed in the United States are treated by prostatectomy). Thus, the actual prevalence of this fusion event among the entire spectrum of biopsy-confirmed prostate cancers in the U.S. population is lacking, and no American multicenter data regarding this gene alteration has been described. In the current study of a prostate-specific antigen – screened cohort from the United States, we show that *TMPRSS2-ERG* fusion prostate cancer has a prevalence of 46% in prostate needle biopsies and reveal morphologic features associated with gene fusion. Our findings (*a*) validate the feasibility of measuring *TMPRSS2-ERG* fusion in routine, clinical prostate biopsy samples; (*b*) show the histomorphologic consequences of gene rearrangement; and (*c*) provide a benchmark of the *TMPRSS2-ERG* rearrangement prevalence in a multicenter U.S. cohort that reflects the spectrum of prostate cancer diagnosed in the United States.

Since its initial discovery (1), the prevalence of *TMPRSS2-ERG* prostate cancer has been reported to vary. In a German cohort, in which prostatectomy specimens were studied, this approached 50%; whereas in an incidental watchful-waiting cohort from Sweden, the prevalence was close to 15% in samples from transurethral resection of prostate (2, 3). A subsequent study from Portugal confirmed the prevalence of *TMPRSS2-ERG* prostate cancer in 50% of patients who underwent radical prostatectomy for clinically localized disease (4). In more recent publications from Canada and the United States, the prevalence in prostatectomies ranged between 36% (including all Gleason scores) and 54%, respectively (5, 6). A question has been raised as to whether the high prevalence in prostatectomy specimens is due to selection bias or genetic differences between populations. Furthermore, systematic studies documenting the prevalence of *TMPRSS2-ERG* gene fusion in North American cohorts undergoing prostate biopsy are lacking.

In the United States, ∼1,300,000 prostate biopsies are done each year, and in 2006, 234,460 new cases of prostate cancer were diagnosed.[13] The American Cancer Society estimates that 186,320 men will be diagnosed with prostate cancer in 2008 and ∼28,660 will die from it, making it the most common noncutaneous cancer and the second most lethal cancer among men in the United States.[14] Emerging data suggests that

TMPRSS2-ERG prostate cancer has a worse prognosis. Specifically, higher tumor stage and tumor-specific death or metastases have been documented (2, 3, 6–8).

The purpose of this study was to assess the *TMPRSS2-ERG* gene fusion status among prostate-specific antigen (PSA) – screened men undergoing prostate biopsy in the United States. Given the most recent advances in the evolving story of *TMPRSS2-ERG* prostate cancer, our work may affect the clinical management of patients with fusion-positive prostate cancer detected on needle biopsies.

Materials and Methods

Cohort selection. The analysis involved 140 consecutive patients enrolled in the Institutional Review Board – approved Early Detection Research Network study from five separate urological practices in Massachusetts and Michigan. Eligible patients were men referred for consideration of prostate biopsy due to either abnormal rectal exam or elevated PSA levels, or clinical suspicion of prostate cancer. The biopsy paraffin blocks were available for analysis and all corresponding H&E-stained slides (three slides per paraffin block) were reviewed. A representative slide from each patient was selected for evaluation of *TMPRSS2-ERG* gene fusion by fluorescent *in situ* hybridization (FISH; see below). Of the 140 total evaluated biopsy subjects, available histology tissue from 6 samples was nonassessable by FISH. Of the remaining 134 subjects' biopsy samples, 100 had prostate cancer and 34 were benign biopsies randomly selected for comparison to the cancer cases. The latter included 25 benign biopsies from subjects without prostate cancer and 9 benign biopsies from subjects with prostate cancer. Table 1 summarizes the clinical characteristics of the cohort included in the study.

Pathologic analysis. The morphologic diagnosis was confirmed on H&E slides (12 biopsies per patient) by five pathologists (J.M. Mosquera, E.M. Genega, S. Perner, R. Mehra, and R.B. Shah) prior to evaluation of the *TMPRSS2-ERG* fusion status. All positive cases were acinar prostate cancer. The Gleason score for each case was assessed and the morphologic features below were evaluated blinded to the *TMPRSS2-ERG* fusion status. Evaluation of morphologic features was done by two independent groups composed of two observers each (J.M. Mosquera and S. Perner/R. Mehra and R.B. Shah). Common morphologic features of prostate cancer were assessed as previously described (9). These included intraluminal features (blue-tinged mucin), nuclear features (macronucleoli), architectural features (intraductal tumor spread and cribriform growth pattern), malignant-specific features (extraprostatic extension, perineural invasion, glomerulations, and collagenous micronodules), histologic variants (signet ring cell features and foamy gland morphology), and comedonecrosis.

Determination of TMPRSS2-ERG fusion status. We have previously described a dual-color interphase break-apart FISH assay to detect the fusion of *TMRSS2-ERG* (1, 3, 10). Briefly, the two probes used were differentially labeled and span the telomeric and centromeric neighboring regions of the *ERG* locus. Because the two genes are close together on chromosome 21, a break-apart probe system was shown to be accurate. The centromeric probe RP11-24A11 overlaps the 3' *ERG* coding region, and the telomeric probe RP11137J13 localizes to the intervening region between *ERG* and *TMPRSS2*. With this system, a nucleus without *ERG* rearrangement shows two pairs of juxtaposed red and green signals, forming yellow signals. A nucleus with *TMPRSS2-ERG* fusion through insertion shows a split of one juxtaposed red-green signal pair resulting in single red and green signals for the translocated *ERG* allele, and a still combined (yellow) signal for the nonrearranged *ERG* allele in each nucleus. If *TMPRSS2-ERG* fusion occurs through interstitial deletion of genetic material, only two signals are detected in each nucleus: a yellow signal (for the non-rearranged), and a single red signal for the rearranged allele.

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[13] American Cancer Society, Cancer facts & figures, 2006. http://www.cancer.org.
[14] American Cancer Society, Cancer facts & figures, 2008. http://www.cancer.org.

Table 1. Clinical variables of the cohort of 134 men undergoing prostate needle biopsy at two institutions in the United States

Variable	Institutions		All
	Institution 1, BIDMC	Institution 2, UM	
All patients	94 (70%)	40 (30%)	134 (100%)
Age (y)	65 (60-70)	61 (54-70)	64 (58-70)
Race*			
Caucasian	78 (83%)	35 (88%)	113 (84%)
Non-Caucasian	16 (17%)	5 (12%)	21 (16%)
PSA (ng/mL)	5.0 (4.0-7.0)	5.8 (4.7-10.0)	5.2 (4.0-8.0)
Prostate size by TRUS (cc)	43 (31-57)	43 (30-56)	43 (30-57)
PSA density (ng/mL/cc)	0.12 (0.08-0.19)	0.13 (0.09-0.24)	0.12 (0.08-0.19)
No. of cores taken	12 (12)	12 (12)	12 (12)
No. of cores involved	2 (1-4)	10 (1-12)	2 (1-6)
Cores involved (%)	17 (8-33)	77 (8-100)	17 (8-50)
Prostate cancer diagnosis			
No	17 (18)	8 (20)	25 (19)
Yes	77 (82)	32 (80)	109 (81)
Laterality			
Bilateral	23 (24)	23 (58)	46 (34)
Left	25 (27)	2 (5)	27 (20)
Right	28 (30)	1 (3)	29 (22)
Unknown	1 (1)	6 (16)	7 (5)
No cancer diagnosis	17 (18)	8 (20)	25 (19)
Gleason score			
Gleason ≤6	27 (29)	13 (33)	40 (30)
Gleason 7	39 (41)	11 (28)	50 (37)
Gleason ≥8	8 (8)	7 (18)	15 (11)
Not applicable or unknown	20 (21)	9 (23)	29 (22)

Abbreviations: BIDMC, Beth Israel Deaconess Medical Center; UM, University of Michigan; TRUS, transrectal ultrasound.
*See Supplementary Table S1 for results on ethnicity by *TMPRSS2-ERG* fusion status among 100 patient's prostate cancer–positive biopsy cores.

The samples were analyzed under a 60× oil immersion objective using an Olympus BX-51 fluorescence microscope equipped with the appropriate filters, a charge-coupled device camera (Olympus), and the CytoVision FISH imaging and capturing software (Applied Imaging). Evaluation of the tests was independently done by four pathologists (J.M. Mosquera, S. Perner, R. Mehra, and R.B. Shah). At one institution, two pathologists (J.M. Mosquera and S. Perner) evaluated 99 biopsies, and at the other institution, two pathologists (R. Mehra and R.B. Shah) evaluated 41 biopsies. For each biopsy, we attempted to score at least 50 nuclei.

Consistency between institutions. To ascertain consistency between institutions in the evaluation of pathology and *TMPRSS2-ERG* fusion status, a subset of 30 biopsies (16 from Institution 1 and 14 from Institution 2) was exchanged for validation of the results. For each case, one H&E slide and the corresponding FISH slide were sent for the evaluation of morphologic features, Gleason score, and *TMPRSS2-ERG*

fusion status. Twenty-six FISH slides were assessable. Of the 26 pairs of assessable slides exchanged for cross-evaluation among pathologists at the two institutions, there was complete agreement on the *TMPRSS2-ERG* fusion status by FISH in all cases. The fluorescent signals of the remaining four cases were faded. Signal enhancing was attempted but excessive background noise limited the interpretation. After re-cutting these four cases for repeat FISH, the initial small foci of cancer were not present for evaluation.

Statistical analysis. Exact binomial 95% confidence intervals were calculated for prevalence among cancer and benign biopsies, and compared using Fisher's exact test. Among cancer biopsies, associations of clinical, histologic, and morphologic features with *TMPRSS2-ERG* were assessed with Fisher's exact and Wilcoxon rank sum tests. A multivariable logistic regression analysis investigated which factors were most strongly associated with *TMPRSS2-ERG* fusion–positive status.

Table 2. *TMPRSS2-ERG* fusion status of 100 patients' cancer-positive biopsy cores at the two participating institutions

	Institutions, n (%)		Total, N (%)
	Institution 1, BIDMC	Institution 2, UM	
All cores	71 (100)	29 (100)	100 (100)
TMPRSS2-ERG	41 (58)	13 (45)	54 (54)
Negative			
Positive	30 (42)	16 (55)	46 (46)
All *TMPRSS2-ERG*–positive cores	30 (100)	16 (100)	46 (100)
Insertion	14 (47)	3 (19)	17 (37)
Deletion	16 (53)	13 (81)	29 (63)

Table 3. Morphologic features by *TMPRSS2-ERG* fusion status in 100 patients' prostate cancer–positive biopsy cores

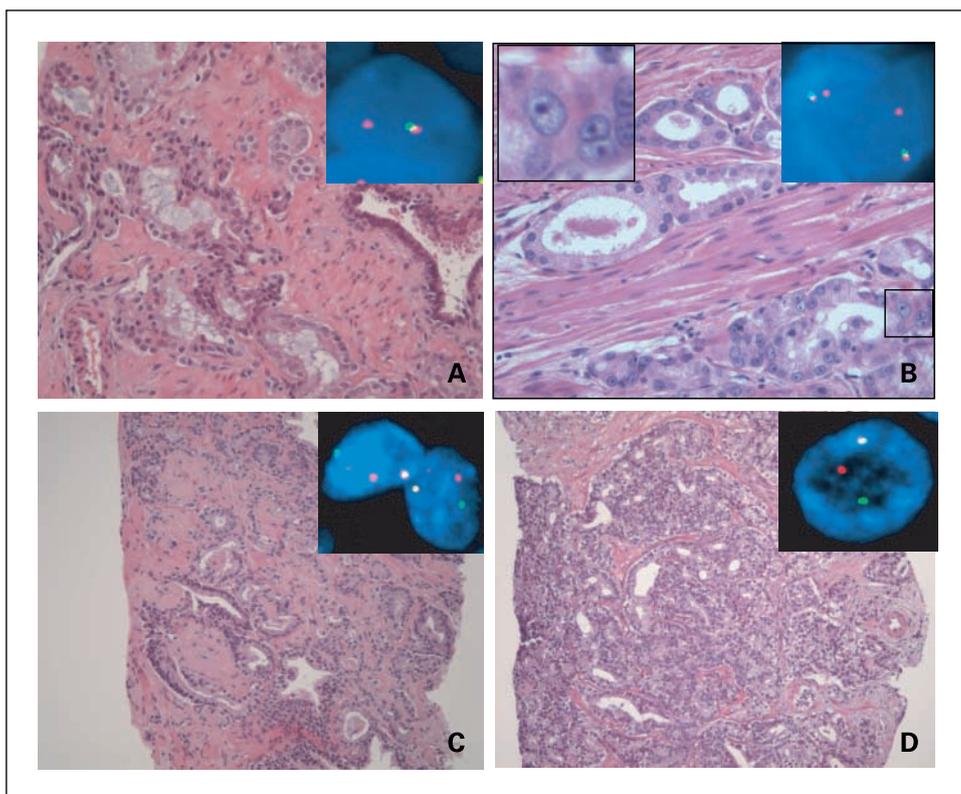| Morphologic features	*TMPRSS2-ERG* status			*P*
	Negative	Positive	All	
	n (%)	*n* (%)	*N* (%)	
All cores	54 (100)	46 (100)	100 (100)	–
Intraductal tumor spread	3 (6)	1 (2)	4 (4)	0.62
Cribriform growth pattern	4 (7)	11 (24)	15 (15)	0.03
Blue-tinged mucin	8 (15)	23 (50)	31 (31)	<0.01
Macronucleoli	16 (30)	25 (54)	41 (41)	0.02
Foamy gland morphology	4 (7)	0 (0)	4 (4)	0.12
Collagenous micronodules	0 (0)	4 (9)	4 (4)	0.04
Extraprostatic extension	1 (2)	0 (0)	1 (1)	–
Perineural invasion	6 (11)	9 (20)	15 (15)	0.27
Signet ring cell features	4 (7)	0 (0)	4 (4)	0.12
Comedonecrosis	1 (2)	0 (0)	1 (1)	–
Glomerulations	3 (6)	2 (4)	5 (5)	1.0

Results

From among the 100 prostate cancer biopsies evaluable by FISH, 46 (46%; 95% confidence interval, 36-56%) showed *TMPRSS2-ERG* gene fusion. In the fusion-positive prostate cancers, 63% of cases showed fusion through deletion and 37% showed fusion through insertion. All 34 benign biopsies, which included 9 benign biopsies from patients with prostate cancer, were fusion-negative (95% confidence interval, 0-10%; $P < 0.001$ versus cancer biopsies). In addition, normal prostatic glands adjacent to cancer areas in the same biopsy were negative for *TMPRSS2-ERG* gene fusion (Table 2). All histologic features were evaluated for their association with *TMPRSS2-ERG* fusion status. After univariate statistical analysis, the following morphologic features were determined to be associated with positive *TMPRSS2-ERG* fusion status: cribriform growth ($P = 0.03$), blue-tinged mucin ($P < 0.01$), macronucleoli ($P = 0.02$), and collagenous micronodules ($P = 0.04$). Table 3 summarizes the findings of evaluation of the morphologic features in all 100 cancer-positive cases, and Fig. 1 illustrates those with a significant association with *TMPRSS2-ERG* fusion–positive status. The presence of one or more of the abovementioned morphologic features was also associated with a positive *TMPRSS2-ERG* status, as fusion-positive cases had more morphologic features noted ($P < 0.01$ for the sum). No significant association was found between Gleason score and *TMPRSS2-ERG* fusion status (Table 4). When clinical characteristics were analyzed, non-Caucasian patients were less likely to have *TMPRSS2-ERG* fusion–positive prostate cancer (13% versus 52% fusion positive; $P = 0.02$; Supplementary Table S1).

Multivariable analysis showed that lower PSA density, cribriform growth pattern, blue-tinged mucin, and macronucleoli were most strongly associated with *TMPRSS2-ERG* fusion status (Table 5). None of the aforementioned significant associations with positive *TMPRSS2-ERG* fusion status correlated with the mechanism of gene rearrangement, either through deletion or through insertion. Although not systematically sought, FISH identified four cases of *TMPRSS2-ERG* gene fusion HGPIN that shared the same fusion pattern with prostate cancer in the same biopsy, and three cases of *TMPRSS2-ERG* gene fusion heterogeneity in prostate cancer, corresponding to separate areas of tumor within the same tissue core.

Fig. 1. Morphologic features associated with a positive *TMPRSS2-ERG* fusion status in prostate cancer. *A,* prostate cancer Gleason pattern 3 showing blue-tinged mucin. Inset, FISH image of representative nucleus. One yellow and one red signal are present, showing the presence of *TMPRSS2-ERG* fusion through deletion. *B,* prostate cancer Gleason pattern 3 showing macronucleoli. Insets, macronucleoli (*top left*) and FISH image of representative nuclei (*top right*). One yellow and one red signal are present in each nucleus, showing the presence of *TMPRSS2-ERG* fusion through deletion. *C,* prostate cancer Gleason pattern 4 with collagenous micronodules. Inset, FISH image of representative nuclei. One yellow and separate red and green signals are present in each nucleus, showing the presence of *TMPRSS2-ERG* fusion through insertion. *D,* prostate cancer Gleason pattern 4 with cribriform growth pattern. Inset, FISH image of representative nucleus. One yellow and separate red and green signals are present, showing the presence of *TMPRSS2-ERG* fusion through insertion. Original magnification of H&E images, ×20 (*A* and *B*) and ×10 (*C* and *D*). Original magnification of FISH images, ×60.

Table 4. Number of morphologic features and Gleason score by *TMPRSS2-ERG* fusion status of 100 patients' prostate cancer–positive biopsy cores

	TMP status, *n* (%)			*P*
	Negative	**Positive**	**All, *N* (%)**	
All cores	54 (100)	46 (100)	100 (100)	
No. of morphologic features				<0.001
0	26 (48)	6 (13)	32 (32)	
1	13 (24)	13 (28)	26 (26)	
2	9 (17)	20 (43)	29 (29)	
3	5 (9)	6 (13)	11 (11)	
4	1 (2)	1 (2)	2 (2)	
Gleason primary				0.53
3	41 (76)	33 (72)	74 (74)	
4	13 (24)	12 (26)	25 (25)	
5	—	1 (2)	1 (1)	
Gleason secondary				0.46
3	25 (46)	24 (52)	49 (49)	
4	27 (50)	22 (48)	49 (49)	
5	2 (4)	0 (0)	2 (2)	
Gleason sum				0.89
6	18 (33)	19 (41)	37 (37)	
7	30 (56)	19 (41)	49 (49)	
8	4 (7)	7 (15)	11 (11)	
9	2 (4)	1 (2)	3 (3)	

Discussion

The high prevalence of *TMPRSS2-ERG* prostate cancer is clinically relevant because emerging data suggests a worse prognosis of tumors harboring the gene fusion. Several studies have shown that *TMPRSS2-ERG* fusion prostate cancer is associated with higher tumor stage and tumor-specific death or metastasis (2, 3, 5, 6, 8, 11). One of the most relevant studies included men diagnosed with clinically localized prostate cancer in the pre-PSA era, and followed with expectant management. In that study, we observed that the presence of the *TMPRSS2-ERG* gene fusion was associated with either the development of prostate cancer metastases or prostate cancer–specific death after up to 22 years of clinical follow-up (2). More recently, Attard et al. have described extremely poor cause-specific survival in patients whose prostate cancers showed the duplication of *TMPRSS2-ERG* fusion and interstitial deletion of 5′ sequences to *ERG* during an 8-year follow-up (7).

Table 5. Multivariable logistic regression of positive *TMPRSS2-ERG* fusion status among 100 patients' prostate cancer–positive biopsy cores

Parameter	Odds ratio (95% CI)	*P*
PSA density (ng/mL/cc)		0.050
Quartile 1, <0.09	8.01 (1.8-36.8)	
Quartile 2, 0.09 to <0.15	5.7 (1.3-26.0)	
Quartile 3, 0.15 to <0.2	5.3 (1.1-26.1)	
Quartile 4, ≥0.20	1 (reference)	
Cribriform growth pattern	9.4 (2.3-38.6)	0.002
Blue-tinged mucin	11.6 (3.4-39.4)	<0.0001
Macronucleoli	5.3 (1.3-22.1)	0.022

Abbreviation: CI, confidence interval.

In the current study of a PSA-screened cohort from the United States, we show that *TMPRSS2-ERG* fusion prostate cancer has a prevalence of 46% in prostate needle biopsies, similar to that observed in radical prostatectomy specimens (3–6). Therefore, the higher prevalence of *TMPRSS2-ERG* prostate cancer observed in prostatectomy specimens from Portugal, Germany, and the United States (3–6) compared with transurethral prostate tissue from Sweden and United Kingdom (2, 7) is probably due to the high frequency of clinically insignificant tumors in the latter, and not due to genetic differences in these populations. In fact, 71 prostate biopsies (from Sweden) with cancer as assessed by FISH showed a 45% prevalence of *TMPRSS2-ERG* prostate cancer with the same distribution of mechanism of gene rearrangement seen in our study; that is, 62.5% of cases through deletion and 37.5% of cases through insertion (12).

We have previously described five morphologic features associated with *TMPRSS2-ERG* fusion prostate cancer (9). In the current study, cribriform growth pattern, blue-tinged mucin, and macronucleoli were confirmed to be associated with a positive fusion status. The presence of collagenous micronodules, which was previously not independently significant (*P* = 0.056; ref. 9), has now been associated with *TMPRSS2-ERG* fusion prostate cancer. In the most recent United States and Canadian Academy of Pathology meetings, there have been controversial findings regarding the morphologic correlates of *TMPRSS2-ERG* fusion prostate cancer. Fine et al. did not find any correlation (13) whereas Nigwekar et al. found a significant association between perineural invasion, blue-tinged mucin, and intraductal tumor spread with a positive gene fusion status (14).

Cross-evaluation of the FISH assay by two independent groups of pathologists showed complete agreement. Minor discrepancies in Gleason grading and the presence or absence of morphologic features were observed. However, only one H&E slide per case was available, limiting complete evaluation

of each case. The results show that FISH and morphologic evaluation of *TMPRSS2-ERG* fusion prostate cancer could potentially be standardized. A future study will focus on the validation of these findings.

Although it is beyond the scope of this report, we identified four cases of *TMPRSS2-ERG* gene fusion HGPIN that shared the same fusion pattern with prostate cancer in the same biopsy, and three cases of *TMPRSS2-ERG* gene fusion heterogeneity corresponding to separate areas of prostate cancer within the same tissue core (data not shown). These observations are consistent with the most recent work on *TMPRSS2-ERG* fusion HGPIN and *TMPRSS2-ERG* fusion prostate cancer heterogeneity by our group and others (5, 15, 16). *TMPRSS2-ERG* interfocal clonal heterogeneity occurs in 41% of prostate cancers that are at least pT2c (15). Hence, FISH analysis would be necessary in bilateral prostate cancer–positive cores if one result was negative. We have also shown that *TMPRSS2-ERG* gene rearrangement, observed in ∼20% of HGPIN lesions (4, 10, 16), is always indicative of *TMPRSS2-ERG* fusion prostate cancer (16).

Given their significant clinical implications, these are findings that merit consideration when *TMPRSS2-ERG* fusion status assessment on prostate biopsies is implemented, and in view of the development of a urine-based screening test for fusion transcripts (17–19).

Clinically, two factors may play a significant role in predicting the *TMPRSS2-ERG* fusion status in prostate cancer, race and PSA density. Non-Caucasian patients were less likely to have a positive fusion status, and this association was significant ($P = 0.02$). Preliminary data from a collaborative study with our group (20), including a larger number of non-Caucasians, show that *TMPRSS2-ERG* fusion prostate cancer is more common in Caucasians compared with African American and Asian patients ($P = 0.034$). Furthermore, the mechanism of *TMPRSS2-ERG* fusion through deletion, which has been associated with worse prognosis (2), is more common in prostate cancer of African American patients ($P = 0.098$). Interestingly, we have seen that one of the best predictors for a positive *TMPRSS2-ERG* fusion status is a lower PSA density (Table 5).

In summary, we have assessed *TMPRSS2-ERG* fusion status in a large series of prostate needle core biopsies from the United States. We have confirmed prevalence similar to a previously reported series in prostatectomy specimens and also confirmed the morphologic features of *TMPRSS2-ERG* fusion–positive prostate cancer.

Disclosure of Potential Conflicts of Interest

Acknowledgments

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