Overexpression of Prostate-Specific TMPRSS2(exon 0)-ERG Fusion Transcripts Corresponds with Favorable Prognosis of Prostate Cancer

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Abstract Purpose: To gain insight in the mechanism and clinical relevance of TMPRSS2-ERG expression in prostate cancer, we determined the specific characteristics of fusion transcripts starting at TMPRSS2 exon 1 and at a more upstream and less characterized exon 0.

Experimental Design: We used quantitative PCR analysis to investigate expression of wild-type TMPRSS2(exon 0) and TMPRSS2(exon 1) and of ERG fusion transcripts. Expression was tested in normal tissue samples, in prostate cancer cell lines and xenografts, and in fresh-frozen clinical prostate cancer samples (primary tumors and recurrences). Expression in clinical samples was correlated with disease progression.

Results: TMPRSS2(exon 0) and TMPRSS2(exon 1) transcripts were similarly androgen regulated in prostate cancer cell lines, but the expression levels of TMPRSS2(exon 1) were much higher. Comparison of expression in different tissues showed TMPRSS2(exon 0) expression to be much more prostate specific. In androgen receptor–positive prostate cancer xenografts, TMPRSS2(exon 1) transcripts were expressed at similar levels, but TMPRSS2(exon 0) transcripts were expressed at very variable levels. The same phenomenon was observed for TMPRSS2-ERG fusion transcripts. In clinical prostate cancers, the expression of TMPRSS2(exon 0)-ERG was even more variable. Expression of TMPRSS2(exon 0)-ERG transcripts was detected in 55% (24 of 44) of gene fusion–positive primary tumors but only in 15% (4 of 27) of gene fusion–positive recurrences and at much lower levels. Furthermore, in primary tumors, expression of TMPRSS2(exon 0)-ERG transcripts was an independent predictor of biochemical progression-free survival.

Conclusion: The expression of TMPRSS2(exon 0)-ERG fusion transcripts in prostate cancer is associated with a less-aggressive biological behavior.

Recently, recurrent fusions of prostate-specific and androgen-regulated TMPRSS2 to the ETS genes ERG, ETV1, ETV4, and ETV5 have been reported as the most frequent genetic alterations in clinical prostate cancer (1–7). TMPRSS2-ERG fusion is detected in 40% to 70% of clinical prostate cancers. Fusion of ETV1, ETV4, and ETV5 to TMPRSS2 are much less frequent, but ETV1, ETV4, and ETV5 have multiple fusion partners. Expression of most of these partner genes is prostate specific and androgen regulated (1–5). Some clinical studies have shown TMPRSS2-ERG to be associated with a more aggressive prostate cancer phenotype (8–12). However, other studies did not find an association with outcome in patients treated by radical prostatectomy (13, 14) or even described TMPRSS2-ERG to be correlated with a more favorable outcome (15, 16).

TMPRSS2 has more than one first exon. Not only fusion transcripts starting at the well-known TMPRSS2 exon 1 but also transcripts that start from a more upstream and less characterized alternative first exon, here denoted exon 0, have been identified (14).

In the present study, we determined the specific characteristics of TMPRSS2 transcripts starting at exons 1 and 0 in benign prostate tissue and in prostate cancer. Moreover, we investigated clinical prostate cancer samples (primary tumors and recurrences) for expression of TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG. The expression of TMPRSS2(exon 0)-ERG fusion transcripts was correlated with a more favorable outcome.
Translational Relevance
The TMPRSS2-ERG gene fusion is the major genetic alteration in prostate cancer. The prognostic value of TMPRSS2-ERG in prostate cancer is still a subject to debate. We describe novel findings of a TMPRSS2 transcript starting at an alternative exon, denoted exon 0. We show that this transcript is much more prostate specific than the generally studied transcript starting at TMPRSS2 exon 1. Furthermore, we provide important evidence that the expression of the TMPRSS2(exon 0)-ERG fusion transcript correlates with a good prognosis of prostate cancer, whereas TMPRSS2(exon 1)-ERG transcripts do not show such a correlation. Our findings urge further investigation of the heterogeneity of TMPRSS2-ERG in prostate cancer. More systematic identification of specific fusion transcripts like TMPRSS2(exon 0)-ERG or alternatively spliced mRNAs might assist in a molecular classification of prostate cancers, which can be integrated in therapeutic decision making in the future.

(exon 1)-ERG fusion transcripts. In the primary tumors, we correlated fusion gene expression with time to biochemical progression after radical prostatectomy. Our data show different expression patterns of TMPRSS2(exon 0) and TMPRSS2(exon 1) transcripts. Furthermore, our findings indicate a more favorable prognosis of tumors with TMPRSS2(exon 0)-ERG expression.

Materials and Methods
Prostate cancer cell lines and xenografts. Prostate cancer cell lines LNCaP and DuCaP were grown in RPMI-1640 supplemented with 5% fetal calf serum and antibiotics. Androgen receptor–positive prostate cancer xenografts PCEW, PC82, PC295, PC310, PC329, PC346, and PC374, and androgen receptor–negative xenografts PC133, PC135, PC324, and PC339 were propagated by serial transplantation on male nude mice, as described (17, 18).

Clinical samples. Primary prostate tumors were obtained by radical prostatectomy and recurrent tumors by transurethral resection of the prostate. Hematoxylin/eosin-stained tissue sections were histologically evaluated by two pathologists (T. van der Kwast; G.J.H.L. van Leenders). Although introducing a bias, only samples that contained at least 70% tumor cells were selected for analysis. The clinical and pathological demographics of the patients with primary prostate tumors included in the statistical analysis (n = 67) are given in Supplementary Table S1. Tissues were snap frozen and stored in liquid nitrogen. Use of the samples for research purposes was approved by the Erasmus MC Medical Ethics Committee according to the Medical Research Involving Human Subjects Act (MEC-2004-261).

RNA isolation. RNAs from the prostate cancer cell lines LNCaP and DuCaP cultured in the absence or the presence of 10−7 mol/L R1881 were isolated using the RNeasy RNA extraction kit (Qiagen). RNA from clinical prostate cancer samples was isolated from frozen tissue sections using RNA-Bece (Campro Scientific). Xenograft RNA was isolated according to the LCL protocol.

Quantitative reverse transcriptase-PCR (RT-PCR). Total RNA was reverse transcribed using M-MLV reverse transcriptase (Invitrogen) and an oligo dT12 primer. cDNAs of 16 different tissues were purchased from Clontech. Quantitative RT-PCRs were done in Power SYBR Green PCR Master Mix (25 µL), containing 0.33 µmol/L forward and reverse primer in an ABI Prism 7700 Sequence Detection System (Applied Biosystems). Amplified products were quantitated relative to porphobilinogen deaminase (PBGD). Primer sequences of the primers used are summarized in Supplementary Table S2.

Statistical analysis. Associations between clinical and histopathologic variables and expression of TMPRSS2-ERG transcripts were evaluated by the Pearson’s χ2 test, the Mann-Whitney U test, or Kruskal-Wallis test, where appropriate. Expression of TMPRSS2-ERG transcripts was correlated with the primary end point, biochemical progression-free survival, defined as time from radical prostatectomy to date of biochemical recurrence. Biochemical recurrence was defined as (a) a prostate-specific antigen level of ≥0.2 ng/mL at two consecutive measurements with a 3-month interval if the prostate-specific antigen nadir was <0.1 ng/mL or (b) a prostate-specific antigen nadir of ≥0.2 ng/mL. Patients that died from causes other than prostate cancer or that were lost to follow-up were censored at the date of last prostate-specific antigen test. Patients were routinely followed thrice monthly during the first year after radical prostatectomy, semianually during the second year, and subsequently at 12-month intervals. In case of progression, patients were followed every 3 months. Kaplan-Meier curves were constructed to assess the probability of remaining free of biochemical recurrence as a function of time after surgery. The differences between the survival curves of the groups were tested using the log-rank test or Breslow method if appropriate. A Cox proportional regression analysis with forward stepwise elimination was done to assess the impact of various parameters on time to recurrence. In the multivariate analysis, the model included pathologic T stage, surgical margin status, the Gleason score of the primary tumor, and expression of indicated TMPRSS2-ERG fusion transcripts. Patients with unknown parameters were excluded from the analysis. Statistical analyses were done using the Statistical Package for Social Sciences, version 15.0 (SPSS), with a significance level of 0.05 (two-tailed probability).

Results
TMPRSS2-ERG gene fusion is present in 40% to 70% of primary prostate tumors. ERG and TMPRSS2 are located ~3 Mbp apart on chromosome 21q22.3 in the same orientation (Fig. 1A). The most common TMPRSS2-ERG fusion transcripts are composed of TMPRSS2 exon 1 or exons 1 and 2 linked to exon 4 of ERG. Less frequently, fusion of TMPRSS2 exon 1 or 2 to other ERG exons have been detected (12). Genomic databases describe that TMPRSS2 transcripts might also contain an alternative first exon, here denoted exon 0, which maps ~4-kbp upstream of exon 1 (Fig. 1A). TMPRSS2-ERG fusion transcripts might also contain TMPRSS2 exon 0 (14).

We determined the specific characteristics of transcripts starting at either exon 0 or exon 1 of TMPRSS2. First, the expression of both transcripts was investigated on a panel of cDNA from 16 different normal tissues. Although expression of TMPRSS2 (exon 1) mRNA was highest in the prostate, these transcripts were also detected in lung, kidney, pancreas, and colon samples. In contrast, TMPRSS2(exon 0) mRNA had a completely prostate-specific expression pattern (Fig. 1B). Subsequently, we did a quantitative RT-PCR analysis on RNA from prostate cancer cell lines DuCaP and LNCaP cultured in absence or presence of the synthetic androgen R1881. Both TMPRSS2 transcripts were induced by androgens (Fig. 1C). Notably, in the cell lines, expression of TMPRSS2(exon 0) transcripts was much lower than expression of TMPRSS2(exon 1).
Testing of RNAs from eleven human prostate cancer xenografts for expression of TMPRSS2 starting at either exon 0 or 1 showed that six androgen receptor–positive xenografts, PCEW, PC82, PC295, PC329, PC346, and PC374, expressed TMPRSS2 (exon 1) at less-variable levels (Fig. 1D). Xenograft PC310 showed no expression of TMPRSS2 because of a deletion of the wild-type allele (17). Five xenografts expressed TMPRSS2 (exon 0) with a much more variable level of expression. None of the androgen receptor–negative xenografts expressed TMPRSS2.

Previously, we have shown that five androgen-dependent xenografts, PCEW, PC82, PC295, PC310, and PC329, contained

Fig. 1. Characterization of TMPRSS2 and TMPRSS2-ERG transcripts starting at exon 0 or 1. A, a schematic representation of the TMPRSS2-ERG locus on chromosome band 21q22.3. The most frequent gene fusion events are indicated. The enlarged genomic region containing TMPRSS2 shows exons 0 and 1 and repeat sequences. B, tissue-specific expression of TMPRSS2(exon 0) and TMPRSS2(exon 1) mRNA assessed by quantitative RT-PCR analysis on a cDNA panel from 16 different normal tissues. Mean of duplicate experiment relative to PBGD with SD. C, androgen-regulated expression of TMPRSS2(exon 0) (left) and TMPRSS2(exon 1) (right) mRNA in androgen receptor–positive prostate cancer cell lines LNCaP and DuCaP. LNCaP and DuCaP cells were grown in the absence and presence of synthetic androgen R1881 (10⁻⁹ mol/L) for 24 h. Mean of duplicate experiments relative to PBGD with SD are depicted. Note that the level of TMPRSS2(exon 0) expression is much lower in the cell lines than in the normal prostatic tissue (B). D, quantitative RT-PCR analysis of TMPRSS2(exon 0) and TMPRSS2(exon 1) (left) and TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG (right) transcripts in 11 human prostate cancer xenografts. Mean of duplicate experiments relative to PBGD with SD.
TMPRSS2(exon 1)-ERG mRNA (17). Quantitative RT-PCR analysis for [TMPRSS2(exon 1)-ERG and TMPRSS2(exon 0)-ERG] fusion transcripts showed that three xenografts, PC82, PC295, and PC329, expressed TMPRSS2(exon 0)-ERG at different levels (Fig. 1D). However, the other two xenografts that expressed TMPRSS2-ERG transcripts, PCEW and PC310, did not express the TMPRSS2(exon 0)-ERG fusion transcript at all. The expression levels of TMPRSS2(exon 1)-ERG transcripts in the five xenografts did not show a large variation (Fig. 1D). The difference in TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG expression was similar to that observed for wild-type TMPRSS2(exon 0) and (exon 1) transcripts.

Next, we determined the expression of TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG transcripts in a cohort of 126 fresh-frozen clinical prostate cancer samples (81 primary tumors and 45 recurrent tumors; Fig. 2A). TMPRSS2-ERG transcripts were detected in 54% (44 of 81) of the primary tumors and in 60% (27 of 45) of the recurrences. In the primary tumors, 20 (25%) of 81 of the cases exclusively expressed TMPRSS2(exon 1)-ERG transcripts, three samples (4%) exclusively expressed TMPRSS2(exon 0)-ERG, and 21 (26%) expressed both transcripts. Analysis of wild-type TMPRSS2 in benign prostatic tissue excluded preferential expression of TMPRSS2(exon 1) or TMPRSS2(exon 0) transcripts in one of the tumors.

![Fig. 2. Expression of TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG transcripts in clinical prostate cancer samples. A, distribution of both TMPRSS2-ERG fusion transcripts in primary and recurrent tumors. Primary tumors, n = 81; recurrent tumors, n = 45. B, box plot of TMPRSS2(exon 0)-ERG and TMPRSS2(exon 1)-ERG mRNA expression levels in primary tumors and recurrences. Open circle, outliers; asterisk, extremes.](image-url)
the different prostate zones (data not shown). In the recurrent tumors, exclusive expression of TMPRSS2(exon 1)-ERG was detected in 23 (51%) of 45 of the cases, whereas none expressed exclusively TMPRSS2(exon 0)-ERG and only four cases (9%) expressed both transcripts. Expression levels of TMPRSS2(exon 0)-ERG transcripts were significantly higher in primary tumors than in recurrent tumors \( (P = 0.015) \), and variation in expression was much larger in the primary tumors than in the recurrences (Fig. 2B). In contrast, the percentage of tumors expressing TMPRSS2(exon 1)-ERG transcripts was the same range for primary and recurrent tumors, and the expression levels of these transcripts did not differ between both tumor types \( (P = 0.74) \).

We correlated the expression of TMPRSS2(exon 0)-ERG with clinical outcome in the primary prostate cancer cohort \( (n = 81) \) to see whether it was of prognostic value. We excluded from the analysis 10 patients that were known to harbor fusion or overexpression of other ETS genes and four patients whose primary treatment was not a radical prostatectomy. Despite the very long follow-up available (median, >10 years), only 11 of the remaining 67 patients died from prostate cancer, precluding statistical analysis. Instead, we used time to prostate-specific antigen recurrence after radical prostatectomy as an end point. The patients’ demographics are summarized in Supplementary Table S1. No differences were seen in clinical and histopathologic characteristics between patients expressing TMPRSS2-ERG and negative patients, although TMPRSS2-ERG-negative patients had higher Gleason scores with borderline significance \( (P = 0.053) \); Supplementary Table S3). The median time to prostate-specific antigen progression was not significantly different between the two groups: 73.2 versus 122.1 months \( [95\% \text{ confidence interval (95\% CI)}, 32.7-113.7 \) versus \( 70.6-173.6; \) \( P = 0.45 \); Fig. 3A].

Within the TMPRSS2-ERG–positive population, the only difference between patients that exclusively expressed TMPRSS2(exon 1)-ERG transcripts and patients that expressed the TMPRSS2(exon 0)-ERG subtype was that the former had higher pathologic stages than the latter \( (P = 0.009) \); Supplementary Table S4). The median time to prostate-specific antigen progression for patients expressing TMPRSS2(exon 0)-ERG transcripts was significantly longer than for patients that exclusively expressed TMPRSS2(exon 1)-ERG transcripts: 158.2 versus 50.5 months \( [95\% \text{ CI}, 98.9-217.5 \) versus \( 32.6-68.4; \) \( P = 0.012 \); Fig. 3B).

Using a Cox proportional hazards model, positive surgical margins, Gleason score \( \geq 7 \), pathologic stage of \( \geq pT3a \), and the absence of TMPRSS2(exon 0)-ERG transcripts were all associated with a worse biochemical progression-free survival. Importantly, multivariate analysis with forward stepwise selection showed expression of TMPRSS2(exon 0)-ERG fusion transcripts to be an independent predictor of progression-free survival (hazard ratio, 0.34; 95% CI, 0.14-0.84; \( P = 0.019 \); Table 1).

### Discussion

This study addresses two important aspects of TMPRSS2-ERG expression in prostate cancer. First of all, a remarkable difference in expression characteristics was detected between TMPRSS2(exon 1) and TMPRSS2(exon 1)-ERG transcripts on the one hand and TMPRSS2(exon 0) and TMPRSS2(exon 0)-ERG transcripts on the other hand. Secondly, the clinical data indicated a more favorable prognosis for prostate cancer patients expressing TMPRSS2(exon 0)-ERG transcripts.

It is estimated that almost half of all genes in the human genome contain more than one first exon as an important mechanism to regulate gene expression (19). Here, we showed that TMPRSS2 transcripts starting at exon 0 were much more prostate specific than those starting at exon 1 (Fig. 1B) and that the expression level of transcripts containing exon 0 was much more variable (Fig. 1D). TMPRSS2 exon 0 is located in a retroviral repeat element, ERVL-B4 (Fig. 1A). This repeat does not contain a standard long terminal repeat promoter element; however, other retroviral repeat sequences might function as cryptic promoters (19, 20). Within the same retroviral repeat, the TMPRSS2 sequence present in a TMPRSS2-ETV4 fusion transcript is located (6). Although a different 5′-untranslated region might affect translation efficacy, the major proteins translated from the fusion transcripts seem identical N-truncated ERG proteins, which are translated from an ATG codon in the ERG exon 4 part of the fusion transcripts.

It could be speculated that the prostate-specific TMPRSS2(exon 0) transcripts are expressed in tumors with a more differentiated phenotype. Recurrent tumors represent late-stage prostate cancer.

<table>
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<th>Variable</th>
<th>n</th>
<th>Median time to PSA recurrence (mo)</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
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<td>Positive</td>
<td>30</td>
<td>43.9</td>
<td>31.0-56.8</td>
<td>&lt;0.001</td>
<td>7.5 (3.0-18.5)</td>
<td>&lt;0.001</td>
<td>7.7 (3.0-19.4)</td>
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<td>Negative</td>
<td>31</td>
<td>122.1</td>
<td>49.5-194.7</td>
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<td>≥7</td>
<td>26</td>
<td>68.2</td>
<td>41.5-94.9</td>
<td>0.037</td>
<td>2.1 (1.0-4.5)</td>
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<td>Extraprostatic</td>
<td>43</td>
<td>65.0</td>
<td>37.4-92.5</td>
<td>&lt;0.001</td>
<td>5.7 (1.9-16.8)</td>
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<td>158.2</td>
<td>146.7-169.7</td>
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<td>Yes</td>
<td>21</td>
<td>158.2</td>
<td>98.9-217.5</td>
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<td>68.2</td>
<td>36.8-99.6</td>
<td>1.0</td>
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Abbreviations: HR, hazard ratio; pT stage, pathologic T stage; PSA, prostate-specific antigen.
cancer that normally has a less differentiated phenotype. In our study, 55% of the recurrences had a Gleason score of 2+8 compared with 15% of the primary tumors. An alternative explanation is that expression from exon 0 is stimulated by the stromal compartment, which will be different in primary tumors and recurrences. Obviously, there are no stromal cells present in in vitro cultures of prostate cell lines, which showed very low expression levels of TMPRSS2(exon 0) (Fig. 1).

The prognostic significance of TMPRSS2-ERG gene fusion remains subject of debate, although a growing number of studies has been published on this matter (8–13, 16). Because technology used to investigate TMPRSS2-ERG varies (FISH or quantitative RT-PCR) and compositions of patient cohorts differ considerably, it is difficult to draw general conclusions from available data. In the present study on a selected and rather limited group of well-defined patients with a very long median follow-up, there was no difference in time to prostate-specific antigen recurrence after radical prostatectomy between patients that expressed TMPRSS2-ERG and patients without expression of the fusion gene.

In two studies on watchful waiting cohorts, it was shown that patients having TMPRSS2-ERG fusion had a higher incidence of metastases or cancer-specific death than gene fusion–negative patients (8, 9); however, this was not confirmed in a large surgically treated cohort (13). Attard et al. (8) showed by FISH analysis that patients with an interstitial deletion of genomic sequences between TMPRSS2 and ERG (so called “class Edel”) had poorer cancer-specific and overall survival than gene fusion–negative patients or than patients with TMPRSS2-ERG fusion without loss of the genomic region between the two genes. Other studies have correlated TMPRSS2-ERG with biochemical progression after radical prostatectomy, like in the present study. Before the identification of TMPRSS2-ERG, Petrovic et al. (15) found that patients with high expression levels of ERG had longer prostate-specific antigen recurrence-free survival than patients without ERG overexpression. Recently, similar results were reported by Saramaki et al. (16), using FISH analysis of TMPRSS2-ERG. However, other studies claimed a negative correlation between TMPRSS2-ERG and prostate-specific antigen recurrence (10–12). Perner et al. indicated that patients with TMPRSS2-ERG rearrangement through deletion showed a trend for higher prostate-specific antigen recurrence rate than patients without fusion (11). Wang et al. (12) provided evidence that specific TMPRSS2-ERG splice variants were associated with early prostate-specific antigen recurrence.

Information on TMPRSS2(exon 0)-ERG transcripts in prostate cancer is still scarce. Thus far, this transcript was only identified by Lapointe et al. (14). However, the clinical implications of this specific fusion transcript subtype were not investigated. The low expression frequency of TMPRSS2 (exon 0)-ERG transcripts in late-stage prostate cancer and the favorable prognosis for patients expressing this fusion transcript in primary tumors, as shown in our study, urges further investigation of the heterogeneity of TMPRSS2-ERG in prostate cancer. More systematic identification of specific fusion transcripts like TMPRSS2(exon 0)-ERG or alternatively spliced mRNAs (12) might assist in a molecular classification of prostate cancers, which can be integrated in therapeutic decision making in the future.

**Disclosure of Potential Conflicts of Interest**

The authors declare no conflict of interest.

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