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TMPRSS2-ERG gene fusions are infrequent in prostatic ductal adenocarcinomas

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Ductal adenocarcinoma of the prostate is an unusual subtype that may be associated with a more aggressive clinical course, and is less responsive to conventional therapies than the more common prostatic acinar adenocarcinoma. However, given its frequent association with an acinar component at prostatectomy, some have challenged the concept of prostatic ductal adenocarcinoma as a distinct clinicopathologic entity. We studied the occurrence of the *TMPRSS2-ERG* gene fusion, in 40 surgically resected ductal adenocarcinoma cases, and in their associated acinar component using fluorescence *in situ* hybridization. A group of 38 'pure' acinar adenocarcinoma cases matched with the ductal adenocarcinoma group for pathological grade and stage was studied as a control. Compared with the matched acinar adenocarcinoma cases, the *TMPRSS2-ERG* gene fusion was significantly less frequently observed in ductal adenocarcinoma (45 *vs* 11% of cases, $P=0.002$, Fisher's exact test). Here, of the ductal adenocarcinoma cases with the gene fusion, 75% were fused through deletion, and the remaining case was fused through translocation. The *TMPRSS2-ERG* gene fusion was also rare in the acinar component of mixed ductal–acinar tumors when compared with the pure acinar adenocarcinoma controls (5 *vs* 45%, $P=0.001$, Fisher's exact test). In 95% of the ductal adenocarcinoma cases in which a concurrent acinar component was analyzed, there was concordance for presence/absence of the *TMPRSS2-ERG* gene fusion between the different histologic subtypes. In the control group of pure acinar adenocarcinoma cases, 59% were fused through deletion and 41% were fused through translocation. The presence of the *TMPRSS2-ERG* gene fusion in some cases of prostatic ductal adenocarcinoma supports the concept that ductal adenocarcinoma and acinar adenocarcinoma may be related genetically. However, the significantly lower rate of the gene fusion in pure ductal adenocarcinoma cases underscores the fact that genetic and biologic differences exist between these two tumors that may be important for future therapeutic strategies.
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Ductal adenocarcinoma of the prostate is an unusual subtype, accounting in its pure form for 0.4% of all prostate cancer, and occurring as a mixed tumor with the more common prostatic acinar adenocarcinoma in up to 5% of all radical prostatectomy cases.[1,2] First described nearly 40 years ago, these tumors are characterized classically by large periurethral ductal structures filled with papillary fronds or cribriform proliferations lined by columnar epithelium.[3] In contrast to the more common acinar adenocarcinoma, prostatic ductal adenocarcinomas are often grossly visible to urologists on cystoscopy because of their central location within the gland and their occasional protrusion from the prostatic verumontanum.[1] Historically, clinical evidence supporting the distinction of ductal adenocarcinoma from acinar adenocarcinoma, has been the fact that the ductal adenocarcinoma cases are typically more aggressive tumors than their acinar counterparts, presenting at higher clinical stage and less responsive to traditional hormonal, radiation and radical surgical therapies in a handful of prior studies.[4–7]

However, since the early description of ductal adenocarcinoma, it has become clear that there is a more clinical overlap between ductal adenocarcinoma

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and acinar adenocarcinoma than was originally thought. In radical prostatectomy specimens, ductal adenocarcinoma occurs with a concurrent conventional acinar component in the majority of cases, making these mixed tumors much more common than pure ductal adenocarcinoma.[5] Much like acinar adenocarcinoma, tumors with the morphologic features of ductal adenocarcinoma may occur in peripheral locations. Additionally, a number of recent studies have challenged early reports of the ductal adenocarcinoma's resistance to traditional therapeutic strategies.[2,8] Given the temporal and clinical overlap between these two variants of prostate cancer, some investigators have questioned whether ductal adenocarcinoma represents a truly distinct clinicopathologic entity, or whether these tumors are simply a morphologic variant in the spectrum of conventional acinar adenocarcinoma.[2]

Recently, a bioinformatics approach uncovered a gene rearrangement present in 40–60% of conventional prostatic acinar adenocarcinoma cases, making it the most common rearrangement identified in human cancer to date.[9] This rearrangement occurs between an androgen-regulated gene, *TMPRSS2* (transmembrane protease serine 2, 21q22.3) and an *ETS* transcription factor family member, most commonly *ERG* (v-ets erythroblastosis virus E26 oncogene homolog, 21q22.2), resulting in a gene fusion product.[10] This gene fusion can occur through a small deletion on chromosome 21 (seen approximately in two thirds of the acinar cases) or through a translocation.[11] In either type of the rearrangement, ERG is brought under the control of an androgen-regulated promoter and over expression of the protein ensues. Although the clinicopathologic significance of this genetic rearrangement has remained elusive, it is clear that *TMPRSS2-ERG* rearrangements are specific and sensitive for prostatic acinar adenocarcinoma.[12] The rearrangement may also be seen in concurrent high-grade prostatic intraepithelial neoplasia lesions, suggesting that it is a clonal and early pathogenic event in prostatic acinar adenocarcinoma.[13]

Despite the numerous studies of *TMPRSS2-ERG* gene fusions in prostatic acinar adenocarcinoma, no studies to date have examined the occurrence of this rearrangement in prostatic ductal adenocarcinoma. Indeed, documentation of the *TMPRSS2-ERG* gene fusion in ductal adenocarcinoma might help resolve the continuing debate over whether prostatic ductal adenocarcinoma represents a truly distinct clinicopathologic entity. Here, we studied the rate of *TMPRSS2-ERG* gene fusions in 40 cases of ductal adenocarcinoma, and in a control group of pathologic grade- and stage-matched acinar adenocarcinoma cases by fluorescence *in situ* hybridization (FISH). We report that although the *TMPRSS2-ERG* fusions do occur in ductal adenocarcinoma, they are considerably less frequent in these tumors than in their acinar counterparts, suggesting that significant genetic and potential biologic differences may exist between these two prostate tumor types. Such differences may be important for guiding future treatments of prostatic ductal adenocarcinoma.

Materials and methods

Tissue Selection

A tissue microarray was constructed manually from 40 radical prostatectomy specimens with ductal adenocarcinoma, retrieved from the surgical pathology and consultation files of the Johns Hopkins Hospitals from 1984–2005. In 52% (21/40) of the ductal adenocarcinoma cases, a concurrent acinar component was present and included in the tissue microarray. In each case, quadruplicate 0.6 mm cores were punched from the ductal adenocarcinoma component, the acinar component (when present) and the surrounding benign prostatic tissue, with up to 16 total cores from each patient represented on the array. The ductal and acinar adenocarcinoma components were considered geographically separate primaries when the ductal adenocarcinoma and acinar adenocarcinoma tumor foci were separated by at least 5 mm in all dimensions.

Fifteen 'pure' acinar adenocarcinoma cases (Gleason pattern 4) were also included on the ductal adenocarcinoma tissue microarray as an internal control group. To provide additional pure acinar adenocarcinoma controls, an additional 23 acinar adenocarcinoma cases were selected for matched pathologic stage from a second tissue microarray, constructed from a PSA-era prostatectomy cohort (cases dating from 1993 to 2000). Overall, the 38 pure acinar adenocarcinoma controls were matched with the ductal adenocarcinoma group for pathological stage (39% pT2, 58% pT3) and grade (68% Gleason 7, 31% Gleason 8–9) (Table 1).

Fluorescence *In Situ* Hybridization

FISH, using a break-apart probe for 5′ and 3′ *ERG*, was performed on the two tissue microarrays. Briefly, sections of 4 μm-thick, paraffin-embedded

Table 1 Clinicopathologic characteristics of ductal adenocarcinoma cases and acinar adenocarcinoma controls. U = Unknown

Total number of evaluable cases	*Ductal cases 38*	*Acinar controls 38*	P-*value*
Overall Gleason score, n (%):			
U	4 (10%)	0 (0%)	
7	21 (55%)	26 (68%)	0.570
8	11 (29%)	10 (26%)	
9	2 (5%)	2 (5%)	
Pathologic stage:			
TX	6 (16%)	1 (3%)	
T2	13 (34%)	15 (39%)	0.912
T3A	13 (34%)	16 (42%)	
T3B	6 (16%)	6 (16%)	

tissue microarrays were baked at 56°C for 2 h, then dewaxed and rehydrated using xylene and graded ethanol, respectively. Tissue microarrays were pretreated using Paraffin Pretreatment Reagent Kit III (Abbott Molecular Inc., Abbott Park, IL). Bacterial artificial chromosome (BAC) FISH probes were SpectrumGreen d-UTP direct-labeled BAC RP11-95I21 for 5′*ERG* and SpectrumOrange d-UTP direct-labeled BAC RP11-476D17 for 3′*ERG* (Nick transKit, Vysis, Abbott Park, IL). Tissue microarrays and BAC FISH probes were co-denatured at 94°C for 5 min and hybridized over night at 37°C in a humid chamber (StatSpin ThermoBrite, IRIS Inc, MA).

Fish Interpretation

FISH interpretation was performed by one of the two urologic pathologists (TLL and ML) with confirmation of positive cases by a third urologic pathologist (RA). For each case, a minimum of 50 cells was scored for the presence/absence of the *TMPRSS2-ERG* gene fusion through deletion or translocation as follows: a nucleus without *ERG* rearrangement shows two pairs of juxtaposed red and green signals (Figure 1, bottom row, right panel). A nucleus with *ERG* rearrangement through deletion shows absence of one or more green signals (Figure 1, bottom row, left panel), and a nucleus with rearrangement through translocation shows one or more pairs of the red and green signals split apart and separated spatially in different regions of the nucleus (Figure 2, bottom row, both panels). Any case with one of the above *ERG* signal abnormalities in ≥10% of the nuclei was scored as a fusion case and classified accordingly. Digitally scanned adjacent hematoxylin and eosin serial sections were available for side-by-side comparison with the FISH image to localize tumor cells, and a Gleason grade was assigned to each sampled core. Five cases of benign prostatic epithelium were scored on each tissue microarray as a negative control.

FISH scoring was conducted using a 100x oil immersion lens on an Olympus AX-70 fluorescence microscope (Olympus, Center Valley, PA) equipped with appropriate filters. For photomicrographs, images were captured using a Nikon E400 fluorescence microscope equipped with a Nikon DXM1200 camera (Nikon Instruments, Melville, NY) and the SPOT Advanced digital imaging software (Diagnostic Instruments, Inc., Sterling Heights, MI).

Statistical Analysis

The findings were analyzed using the Stata 9.2. (StataCorp, College Station, TX) software package. An appropriate pathologic grade and stage matching of the ductal adenocarcinoma cases and the acinar adenocarcinoma controls was tested using the Kruskal–Wallis test for non-parametric one-way analysis of variance by ranks. Fisher's exact test was used to compare frequency of the *TMPRSS2-ERG* fusion in ductal adenocarcinoma cases *vs* acinar adenocarcinoma controls.

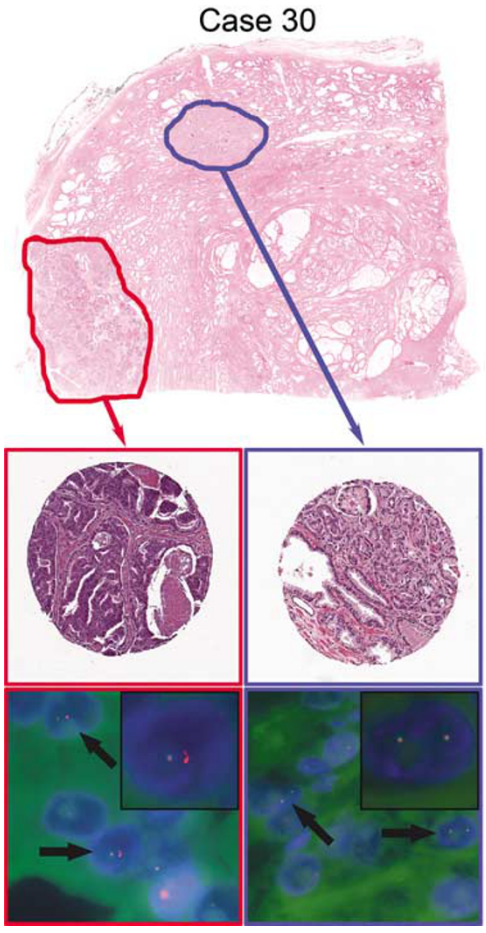

Figure 1 *Top panel*: low-power photomicrograph of the H&E stained radical prostatectomy slide with ductal adenocarcinoma focus circled in red and acinar adenocarcinoma focus circled in blue (Case 30). The ductal and acinar tumors are separated spatially and appear to be discrete tumor foci. *Middle panels*: digitally scanned images of an H&E stained section of the 0.6 mm cores punched for the tissue microarray from each tumor area (40× magnification). *Bottom panels*: *ERG* break-apart FISH images from ductal and acinar tumor foci (all 1000× magnification). Case 30 shows the *TMPRSS2-ERG* fusion through deletion in the ductal adenocarcinoma (left panel), with one juxtaposed red–green (yellow) signal in each nucleus and absence of the second green signal (arrows, inset). The acinar component of Case 30 (right panel) shows no evidence of *TMPRSS2-ERG* fusion with two pairs of juxtaposed red–green signals in each nucleus (arrows, inset).

Results

Here, of the 40 ductal adenocarcinoma cases, 38 were evaluable by FISH for *ERG* gene rearrangements (95%). Overall, 11% (4/38) of the ductal adenocarcinomas showed the *TMPRSS2-ERG* gene fusion, with 75% (3/4) showing the deletion and 25% (1/4) showing the translocation (Table 2,

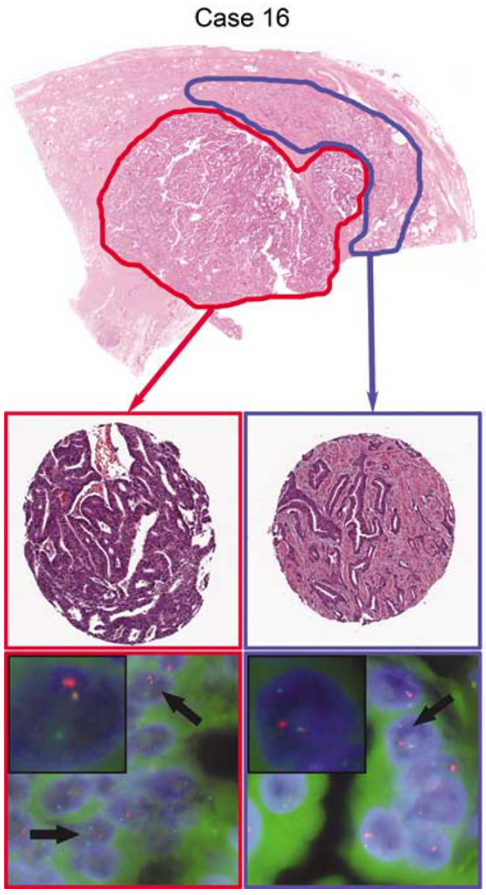

Figure 2 *Top panel*: low-power photomicrograph of the H&E stained radical prostatectomy slide with ductal adenocarcinoma focus circled in red and acinar adenocarcinoma focus circled in blue (Case 16). The ductal and acinar adenocarcinoma foci are commingled spatially and likely represent a single primary tumor. *Middle panels*: digitally scanned images of an H&E stained section of the 0.6 mm cores punched for the tissue microarray from each tumor area (40× magnification). *Bottom panels*: *ERG* break-apart FISH images from ductal and acinar tumor foci (all 1000× magnification). Case 16 shows the *TMPRSS2-ERG* fusion through translocation in both the ductal and acinar tumor foci, with one juxtaposed red–green (yellow) signal in each nucleus and the second pair of red and green signals split apart and separated spatially in different regions of the nucleus (arrows, inset).

Figures 1 and 2). No cases of duplication/polyploidy of the fusion were observed in the ductal adenocarcinoma group. In 55% (21/38) of the evaluable ductal adenocarcinoma cases, a concurrent acinar component was present for evaluation as well. Although represented on separate cores in the tissue microarray, the ductal adenocarcinoma and acinar adenocarcinoma components were geographically separate primaries (separated by at least 5 mm in all dimensions), in the radical prostatectomy specimen in only 19% (4/21) of the cases (Figure 1). In 67% (14/21) of the cases, the two morphologies commingled and appeared to represent a single primary tumor (Figure 2), and in 14% of the cases (3/21), it was not possible to tell whether the components were separated spatially. In all the 21 cases, the sampled acinar component consisted primarily of

Table 2 Frequency of *TMPRSS2-ERG* rearrangement in ductal adenocarcinoma cases compared to pure grade- and stage-matched acinar adenocarcinoma controls

	Ductal cases	*Acinar controls*	P-*value*
Total cases	38	38	
Rearrangement	4 (11%)	17 (45%)	0.002
Deletions	3 (75%)	9 (53%)	NA
Double deletion	0 (0%)	1 (6%)	NA
Translocation	1 (25%)	7 (41%)	NA

poorly formed or cribriform glands diagnostic of Gleason pattern 4 carcinoma (Gleason score 7–8). As seen in the ductal adenocarcinoma component, *TMPRSS2-ERG* gene fusion was also rare in the acinar component of mixed ductal–acinar adenocarcinomas (1/21 cases, 5%). In 95% of the ductal adenocarcinoma cases in which a concurrent acinar component was available for analysis (20/21), there was concordance for presence/absence of the *TMPRSS2-ERG* gene fusion between the different histologic subtypes (Table 3). The only discordant case (Case 30, Table 3, Figure 1) showed gene fusion through deletion in the ductal adenocarcinoma component and had no evidence of gene rearrangement in the cribriform acinar adenocarcinoma component. The ductal adenocarcinoma and acinar adenocarcinoma components appeared to be spatially separate primaries in this case (Table 3, Figure 1). In 95% (19/20) of the concordant cases, no gene rearrangement was detected, whereas in the remaining concordant case, a gene fusion through translocation was detected in the ductal adenocarcinoma as well as in the poorly formed glands of the acinar adenocarcinoma (Case 16, Table 3, Figure 2). In this case, the ductal adenocarcinoma and acinar adenocarcinoma components were commingled spatially.

Here, in the control group of 38 grade- and stage-matched pure acinar adenocarcinoma cases, 45% (17/38) had the gene fusion with 53% (9/17) showing the deletion, 6% (1/17) showing a duplicated deletion (deletion with polyploidy) and 41% (7/17) showing the translocation (Table 2). All sampled tumor cores from the acinar adenocarcinoma control cases showed predominantly poorly formed or cribriform carcinoma glands and all were graded as primary Gleason pattern 4 carcinoma (Gleason score 7–8). Compared with the matched acinar adenocarcinoma control cases, the *TMPRSS2-ERG* gene fusion was significantly less frequently observed in ductal adenocarcinoma ($P = 0.002$, Fisher's exact test), as well as, in the acinar adenocarcinoma component of mixed ductal–acinar adenocarcinoma tumors ($P = 0.001$, Fisher's exact test).

Discussion

Perhaps the most compelling reason to subclassify prostatic carcinoma into ductal and acinar variants

Table 3 *TMPRSS2-ERG* fusion status for ductal adenocarcinoma cases and their mixed acinar adenocarcinoma component and the spatial relationship between components

Case #:	*Pathologic stage*	*Overall Gleason score*	*Ductal component*	*Acinar component*	*Spatial relationship*
1	TX NX MX	U	D		
2	TX NX MX	U	N		
3	TX NX MX	U	N		
4	T3A N0 MX	7	N		
5	T3A N0 MX	7	N		
6	T2 N0 MX	7	N	N	Commingled
7	TX NX MX	U	N	N	Unknown
8	T3B N0 MX	7	N	N	Commingled
9	T2 N0 MX	7	N	N	Commingled
10	T3A N0 MX	7	D		
11	T3B N0 MX	8	N		
12	T3A N0 MX	8	N	N	Unknown
13	T3A N0 MX	8	N		
14	T3B N0 MX	7	N		
15	T3A N0 MX	7	N	N	Separate
16	T3A N0 MX	7	T	T	Commingled
17	T2 N0 MX	7	N	N	Commingled
18	TX N0 MX	7	N	N	Commingled
19	T3A N0 MX	7	N		
20	T2 N0 MX	7	N		
21	T2 N0 MX	8	N	N	Commingled
22	T2 N0 MX	8	N	N	Commingled
23	T2 N0 MX	7	N		
24	T2 N0 MX	8	N	N	Unknown
25	T3A N0 MX	7	N		
26	T3A N0 MX	8	N		
27	T3B N1 MX	9	N	N	Commingled
28	TX N0 MX	7	N		
29	T3A N0 MX	7	N	N	Separate
30	T3A N0 MX	8	D	N	Separate
31	T2 N0 MX	7	N	N	Commingled
32	T2 N0 MX	7	N	N	Separate
33	T2 N0 MX	7	N		
34	T2 N0 MX	8	N	N	Commingled
35	T2 N0 MX	8	N	N	Commingled
36	T3B N1 MX	8	N	N	Commingled
37	T3B N0 MX	9	N	N	Commingled
38	T3A N0 MX	7	N		

D = fusion by deletion, T = fusion by translocation, N = normal.

is that ductal adenocarcinoma has been found to have a clinically more aggressive course than the typical Gleason pattern 3 acinar adenocarcinoma.[4–6] Although many of the original studies were conducted in pre-PSA era cohorts, a handful of more recent studies based on prostate needle biopsy with follow-up radical prostatectomy have shown similar results.[7] Only rare reports have suggested that ductal adenocarcinoma may have a less aggressive course than typical acinar adenocarcinoma.[14] However, because of the infrequent occurrence of ductal adenocarcinoma, studies with clinical follow-up of large cohorts, as seen in acinar adenocarcinoma, have not occurred. Although only acinar adenocarcinoma is included in Gleason's prostate carcinoma grading system, the current consensus is to treat ductal adenocarcinoma as if it is a Gleason $4+4=8$ carcinoma.[15] This is in part based on evidence from a needle biopsy study that suggested that the prognosis of surgically resected ductal adenocarcinoma cases was between that of a Gleason score 7 and Gleason score 8 acinar adenocarcinoma.[7]

Despite these important clinical differences between ductal and acinar adenocarcinoma, to our knowledge, the two tumor types have not been compared on a molecular-genetic level. Although ductal adenocarcinoma and acinar adenocarcinoma may occur together in as many as 5% of radical prostatectomies, no prior studies have examined whether there is a clonal relationship between these tumor components. Based on morphologic observations, the ductal and acinar tumor components in mixed prostate carcinoma cases are more often commingled intimately than geographically separate; a finding that would suggest that these components are likely genetically related, at least in a subset of cases.[16] In this study, we also found that in mixed ductal–acinar tumors, the two components were intermingled. Further, the very presence of the *TMPRSS2-ERG* rearrangement in 11% of the ductal adenocarcinoma cases suggests that at least some cases with the morphologic features of ductal adenocarcinoma may share some of the same early pathogenetic aberrations with acinar adeno-

carcinoma cases. Additionally, in 95% of the mixed ductal–acinar adenocarcinoma cases there was concordance for presence/absence of the *TMPRSS2-ERG* rearrangement between the ductal and acinar components of the tumor in a given case. As the vast majority of these cases did not have the *TMPRSS2-ERG* rearrangement, this data certainly does not prove a genetic relationship between the acinar and ductal tumor components; however, it is not inconsistent with this hypothesis.

To date, the role of the *TMPRSS2-ERG* gene rearrangement in the initiation and progression of prostate carcinoma remains unclear. Early studies of the rearrangement suggested that the presence of the gene fusion was associated with higher stage and Gleason grade disease, and shorter interval to biochemical recurrence.[17–20] However, recent larger studies in surgical cohorts have consistently found an inverse relationship between Gleason grade and rates of gene fusion, and no consistent relationship with prognosis, measured either by biochemical recurrence or overall survival has emerged.[21,22] *ERG* over expression in transgenic mouse models causes prostatic intraepithelial neoplasia, but not invasive cancer, suggesting that *TMPRSS2-ERG* fusion may not be sufficient for transformation to an invasive phenotype.[23] *In vitro* experiments using ERG over expression or knockdown in cell lines suggest that ERG may play a role in the activation of multiple cellular programs modulating tumor cell invasion, as well as in the activation of the oncogene *C-MYC.*[23–25] However, no dramatic role for the *TMPRSS2-ERG* fusion in prostate tumor initiation or progression has emerged.

Even in light of the inverse relationship with Gleason grade, the finding in this study that only 11% of the ductal adenocarcinoma cases showed the rearrangement is somewhat surprising. Most large studies of acinar adenocarcinoma have found the percent of rearranged cases to hover around 40–50%, with higher Gleason score cases showing a minimum of 25% fusion rates in one study.[17–19,21,22,26,27] In our PSA-era cohort of grade-matched pure acinar adenocarcinoma controls (Gleason 7–8), we found 45% of cases had the rearrangement, a somewhat higher fraction than reported by Fine *et al* for the same grade, but one that is comparable with the overall rates of fusion reported in most surgical cohorts. Compared with our grade-matched pure acinar adenocarcinoma controls, the finding of only 11% rearrangement in the ductal carcinoma group is highly significant. Given that a subset of our pure acinar adenocarcinoma controls were embedded in the same ductal adenocarcinoma tissue microarray block, and these cases showed a much higher rate of *TMPRSS2-ERG* rearrangement, it appears unlikely that the low rate of rearrangement in the ductal adenocarcinoma cases is an artifact related to FISH or tissue microarray preparation.

Ultimately, the biologic explanation for the low rate of *TMPRSS2-ERG* fusions in prostatic ductal carcinoma requires further study, and may not emerge until we have a better understanding of the role of the fusion in prostate cancer initiation and progression. At the very least, our findings support the emerging concept that *TMPRSS2-ERG* fusion is less common in prostate tumors that appear more aggressive by traditional pathologic measures (ie, Gleason grade). Whether this genetic difference ever translates into an independent predictor of clinical outcome remains unclear. Similarly, how this inverse relationship between Gleason grade and frequency of *TMPRSS2-ERG* rearrangement can be explained, by what we know about the biological activity of *ERG*, is not evident. Here, of note, the frequency of *TMPRSS2-ERG* rearrangement in the acinar component of the *mixed* tumors in our series was also significantly lower than the frequency observed in the pathologic grade-matched *pure* acinar adenocarcinomas (45 *vs* 5%). This may be additional, though indirect, evidence for a genetic relationship between the acinar and ductal components in mixed tumors. Further, this data suggests that the pathogenetic events leading to mixed ductal–acinar tumors may be distinct from those leading to pure acinar adenocarcinomas. Such differences may have important biologic and clinical relevance when the pathogenic role of the *TMPRSS2-ERG* gene rearrangement is more fully understood.

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Conflicts of interest

The authors have no disclosures/conflicts of interest to declare.

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