Letters to the Editor

TMPRSS2-ERG gene fusions are infrequent in prostatic ductal adenocarcinomas

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To the Editor: We read with great interest the article by Lotan *et al*¹ recently published in this Journal on the subject of *TMPRSS2-ERG* gene fusions in prostatic ductal adenocarcinoma. In this article, Lotan *et al* noted the poorly understood role of *TMPRSS2-ERG* rearrangements in the initiation and progression of prostate carcinoma.

At present, there are large and important differences in the results of multiple articles studying the relationship between ETS fusion status and clinical outcome. Inconsistent results may be due to several factors, including study population, sample size, method of cancer detection, source of tissue, method of gene fusion detection, type of gene fusion sought after, primers used, follow-up, and different clinical end points. Often, this fundamental data are not well delineated in the methods sections, making comparisons even more difficult.

We would like to highlight one major factor that is inadequately addressed in the paper by Lotan *et al*¹: Cohort selection. Many studies have evaluated patients with PSA-screening-detected prostate cancer, who underwent radical prostatectomy.^{2–4} Other studies have focused on patients detected incidentally and placed on expectant therapy or watchful waiting.^{5,6} In the paper by Lotan *et al*,¹ the population was selected on the basis of a rare subtype of prostate cancer (ie, ductal adenocarcinoma). We and others have observed large frequency differences for *ERG*-rearranged prostate cancers depending on how they were selected.^{2–7} The selection of cases may help us understand these differences in *ERG* rearrangement frequencies, but to date we cannot offer a clear explanation. It is intriguing to speculate that the low frequency of the *TMPRSS2-ERG* fusion in incidentally identified prostate cancers by TURP is similar to ductal adenocarcinoma that may have been more often identified for symptomatic reasons. They both share a central localization within the prostate and are not detected by PSA screening.

Another issue related to cohort selection that needs to be better delineated in prostate cancer biomarker studies is clinical end point. The variability of end points in different studies makes results difficult to interpret. Some groups have reported a significant relationship between the presence of *ERG* rearrangement and worse clinicopathological indicators, whereas others have not found this

relationship. Still other groups describe an association with a better outcome. Most studies have used PSA biochemical failure as the study end point. In fact, it affects how a patient is treated and likely his perception of the disease. However, it is important to point out that biochemical recurrence is not a reliable predictor of disease progression or cancer-specific death.^{8–11}

The confusion caused by mixing study cohorts unfortunately surfaces in this paper. The study by Demichelis *et al*⁶ is grouped into the category of PSA biochemical studies showing association with clinical outcome. In fact, this study explored for associations with the development of metastatic disease or cancer-specific death. It represents a population-based cohort from a distinct catchment area of Örebro, Sweden. All cancers were detected incidentally without PSA screening and followed on a Watchful Waiting protocol. Therefore, the study assessed the natural history of fusion prostate cancer. Clearly, the Örebro cohort is distinct from a set of men selected through PSA elevation, at specific medical centers, and treated with radical prostatectomy. The Demichelis study was included among a group of studies that reported a relationship between the presence of the gene fusion and shorter interval to biochemical recurrence. However, in this study a statistically significant association between the gene fusion and prostate cancer death was observed.

The study by Lotan *et al*,¹ also failed to reference another population-based study from the United Kingdom by Attard *et al*⁵ that showed consistent finding with that of Demichelis *et al*.⁶

It is worth mentioning that in this article the cases were evaluated by FISH for *ERG* gene rearrangements using break-apart probes for 5'*ERG* and 3'*ERG*. This is an indirect test and cannot directly confirm the fusion of *TMPRSS2-ERG*. Recently, there is an increasing evidence of other 5' partners.^{12–14} Therefore, Lotan *et al* describe the occurrence of *ERG* rearrangements in prostatic ductal adenocarcinomas rather than the *TMPRSS2-ERG* fusion gene itself.

In conclusion, we like to point out that taking into account population selection, treatment, and follow-up is key for appropriate comparison among studies. Comparisons should be made between similar cohorts and end points.

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Response to Esgueva *et al*

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In Reply: It is with great interest and appreciation that we read the comments by Esgueva *et al*¹ in relation to our paper titled ‘TMPRSS2-ERG gene fusions are infrequent in prostatic ductal adenocarcinomas’ published in the March 2009 issue of the journal of *Modern Pathology*.²

We agree with the authors’ statement that studies assessing the relationship between *ERG* fusion and clinical outcome have so far yielded conflicting results.^{3–9} The main objective of our study was to evaluate the previously not-assessed incidence of *TMPRSS2-ERG* fusion in a well-characterized cohort of prostatic ductal carcinoma. Considering the well-documented aggressive behavior of prostatic ductal carcinoma, our finding of a relatively low incidence of *TMPRSS2-ERG* fusion in such tumors could be seen as indirect evidence arguing for its lack of association with aggressive outcome.

A comprehensive review of the previous literature on the relationship of fusion with outcome was neither attempted nor implied in our discussion, given the above well-defined focus of our study. In this regard, the omission of the study by Attard *et al*⁴ was definitely unintentional. By citing examples

from two groups of studies showing conflicting evidence on the association of *TMPRSS2-ERG* fusion with aggressive outcome, we simply attempted to illustrate the controversy rather than to provide a comprehensive categorization of the end points and cohort details of all previous studies.

The authors’ speculation regarding the possibility of symptomatic presentation as a potential common denominator between our cohort and the expectant management cohort of patients diagnosed on TURP in the report by Demichelis *et al*³ is intriguing but unlikely to be relevant in our cohort. As we detail in the ‘Materials and methods’ section of our paper, our cohort was diagnosed through PSA screening and/or through digital rectal examination. Furthermore, despite earlier reports, it is now well recognized that only a minority of prostatic ductal adenocarcinomas are completely limited to the central location, and similar to acinar prostatic carcinomas they are more likely to be discovered during PSA screening, as certainly was the case in our cohort.¹⁰

Finally, the break-apart FISH strategy that we adopted in our study is identical to the one used by two of the authors on the above commentary,