Studies of TMPRSS2-ERG Gene Fusions in Diagnostic Trans-Rectal Prostate Biopsies

To the Editor: The recent article by Mosquera et al. reports TMPRSS2-ERG fusions in 46% of 100 trans-rectal biopsies of the prostate (TRBP) from prostate-specific antigen screened men in the United States (1) and compares this to the lower prevalence of ERG translocations in cancer detected incidentally on trans-urethral resection of the prostate (TURP). We agree with the authors that the lower prevalence of ERG rearrangements observed in our and other studies of specimens obtained from watchful-waiting men (2) is unlikely to be due to genetic differences between U.S. and European patients. The authors have attributed this observation to the overrepresentation of men with clinically insignificant, indolent disease in the watchful-waiting group, which is based on the assumption that an isolated TMPRSS2-ERG fusion is associated with worse outcome. This remains controversial as a number of studies now suggest that the combination of TMPRSS2-ERG fusion and copy number gain or additional genetic aberrations such as PTEN loss is required for worse outcome (3). More studies, preferably multicenter, evaluating these prognostic markers in well-defined patient cohorts are urgently required. In our recent study of TRBP specimens from 48 patients who all ultimately progressed and developed fatal prostate cancer, we reported ERG rearrangements in 20 patients (41%; ref. 4), which is a very similar prevalence to Mosquera et al.’s cohort of patients (1) who have a relatively low chance of developing fatal disease: If the presence of an ERG rearrangement was associated with fatal disease, one would have expected our cohort of men to have been enriched for ERG-rearranged cancers when compared with Mosquera et al.’s study. Other explanations for the lower prevalence of ERG rearrangements in the watchful-waiting TURP cancers should therefore be considered. One explanation could be that cancers arising in the para-urethral region have a lower prevalence of ERG rearrangements, as has been described by Guo et al. (5), and therefore ERG-rearranged cancers arising peripherally are less likely to be detected incidentally by TURP. Also interestingly, we and Mosquera et al. report significantly less heterogeneity in TRBP (3 of 48 and 2 of 100 patients, respectively; refs. 1, 4) than would have been predicted from ETS gene studies of prostatectomies (3): It is therefore possible that the largest tumor focus (arising in the peripheral zone) that is most likely to account for the majority or all of TRBP cores has a uniform ERG status and is genetically distinct from cancers arising elsewhere. These observations have important implications for the development of ETS gene translocations as biomarkers for prostate cancer.

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Disclosure of Potential Conflicts of Interest

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References

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