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European Association of Urology

Letter to the Editor

Reply to Kathryn L. Penney, Massimo Loda, and Meir J. Stampfer's Letter to the Editor re: Melissa Assel, Anders Dahlin, David Ulmert, et al. Association Between Lead Time and Prostate Cancer Grade: Evidence of Grade Progression from Long-term Follow-up of Large Population-based Cohorts Not Subject to Prostate-specific Antigen Screening. Eur Urol 2018;73:961–7

We would like to thank Penney et al for their interest in our paper [1]. We agree that neither grade progression during active surveillance nor increasing prevalence of high-grade cancer with age provides compelling evidence in support of the hypothesis of grade progression. We also agree that population-level evidence on grade progression cannot address "whether a given low-grade lesion becomes high-grade cancer, or whether a new focus of high-grade arises in a prostate that already contains a low-grade cancer".

Penney et al go further, suggesting that our findings are an artifact of changes in the way that tumors are graded following publication of the 2005 International Society of Urological Pathology (ISUP) guidelines. There are three lines of evidence against this interpretation. First, it is prima facie implausible that grade shift would explain the effect size we observed. We report that close to 80% of tumors diagnosed shortly after an elevated prostate-specific antigen are low grade compared to only 20% diagnosed at 30 yr. To explain such a difference in terms of shifts in Gleason grading, fully 75% of tumors categorized as low grade according to ISUP 2005 would have to be classed as high grade after 2005. The grade shift associated with ISUP 2005 was nowhere close to this magnitude. Second, we report that results are almost unchanged when defining high-grade disease as grade group 3 or higher (Supplementary Table 3 [1]). This casts doubt on the grade shift hypothesis because most of the grade shift was between groups 1 and 2. Most critically, we can confirm that all tumors in the Västerbotten Intervention Project (VIP) cohort were regraded according to ISUP 2005. The results were virtually identical between the VIP and Malmö cohorts, with both showing a positive association between lead time and grade.

We also disagree with the claim by Penney et al claim that "if Gleason grade does progress, then radical treatment of low-grade disease has a stronger rationale". The value or otherwise of radical treatment versus conservative management for low-grade disease is best determined by clinical trials [2] and long-term follow-up of active surveillance cohorts [3], not theoretical considerations of tumor biology.

In conclusion, there is no reason to believe that shifts in grading explain our reported association between lead time and prostate cancer grade. Such an association suggests grade progression over time, although whether this occurs at the lesion or organ level is unknown. The phenomenon of grade progression has no direct implications for treatment choices at the time of diagnosis.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Assel M, Dahlin A, Ulmert D, et al. Association between lead time and prostate cancer grade: evidence of grade progression from long-term follow-up of large population-based cohorts not subject to prostate-specific antigen screening. Eur Urol 2018;73:961–7.
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