Editorial Commentary

Prognostic properties of the baseline prostate-specific antigen value—insights from the European randomized study of screening for prostate cancer

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Comment on: Remmers S, Bangma CH, Godtman RA, *et al.* Relationship Between Baseline Prostate-specific Antigen on Cancer Detection and Prostate Cancer Death: Long-term Follow-up from the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2023;84:503-9.

Keywords: Screening; prostate-specific antigen (PSA); prostate cancer (PCa)

Submitted Nov 23, 2023. Accepted for publication Jan 24, 2024. Published online Mar 11, 2024.

doi: 10.21037/tau-23-606

View this article at: https://dx.doi.org/10.21037/tau-23-606

Screening for prostate cancer (PCa) continues to be challenging. Although PCa screening significantly reduces metastasized PCa and PCa-specific mortality, overdetection and overtreatment of indolent PCa remain a problem (1-3). Hence, improving risk stratification and subsequently better identification of men at low risk harboring relevant PCa are critical. The article by Remmers *et al.*, which was published in a recent issue of *European Urology*, investigated the risk of being diagnosed with clinically significant PCa (csPCa) (defined as a Gleason Score ≥7) and PCa-specific mortality based on the baseline prostate-specific antigen (PSA) in the "European Randomized Study of Screening for Prostate Cancer" (ERSPC) population (4).

The ERSPC trial is a randomized-controlled, multicenter trial in the European countries Finland, Sweden, Italy, Netherlands, Belgium, Switzerland, Spain, Portugal and France and recruited men between 1992 and 2001. Randomization differed between countries: men in the Netherlands, Belgium, Switzerland and Spain were invited by mail to participate in the study and were assigned to a screening and a control arm. In Finland, Sweden, and Italy, trial participants were selected from population registries and underwent randomization prior to the provision of written informed consent. Data from Portugal and France were not used in the final analysis of Remmers: the Portuguese study centers stopped participation in 2000 due to funding problems and unavailability of data. The French centers joined to the ERSPC study in 2001 and had consequently a shorter follow-up period. A PSA value ≥3.0 ng/mL triggered a prostate biopsy in the screening group at most trial centers. Transrectal or transperineal prostate biopsies with 6 to 12 cores were performed depending on the trial center. Treatment decisions were performed according to local policies and guidelines (5).

Over 160,000 men, aged 55–69 years, underwent randomization in the ERSPC trial. At 16-year follow-up, the cumulative PCa incidence was 13.3% in the screening arm and 10.3% in the control arm. Men in the PSA screening arm were more often diagnosed with PCa and showed consequently a significant reduced PCa mortality during follow-up. The relative risk of PCa-specific mortality was 0.80 at 16 years follow-up favoring the screening arm, resulting in a number needed to invite to screening of 570 to prevent one PCa death (2).

In the recently published paper, Remmers *et al.* assessed the prognostic value of the baseline PSA value regarding the subsequent detection of PCa and PCa-specific mortality utilizing data from the patients that attended at least one

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screening visit in the ERSPC trial. The authors stratified the results for age groups 55–59, 60–64, and 65–69 years (yr).

The analyzed cohort consisted of a total of 55,432 men (46.2% aged 55–59 yr, 30.5% aged 60–64 yr, and 23.3% aged 65–69 yr). During the 16-year follow-up, 7,120 men were diagnosed with any PCa (12.8%). The probability of csPCa were 3.7%, 5.1% and 5.7% for age groups 55–59 yr, 60–64 yr, and 65–69 yr. The probabilities of csPCa showed to differ significantly between men with an initial PSA ≥3.0 ng/mL (at most 14%) and men with a PSA <1.0 ng/mL (at most 1.5%).

The association between the baseline PSA value and the risk of PCa-specific mortality varied marginally between the age groups: The hazard ratio for PCa-specific death on doubling of baseline PSA was 2.46 in the age group of 55–59 yr, 2.23 in those aged 60–64 yr, and 2.04 in men aged 65–69 yr.

To assess the guideline recommendation of the European Association of Urology of postponing the next follow-up screening 8 years visit after initial PSA value <2.0 ng/mL at 60 years, the authors assessed the PCa-specific mortality of the subgroup of patients aged 60–61 yr. To display the association between baseline PSA value and PCa-specific mortality, the authors plotted a Lorenz curve. Initially developed in economics to characterize wealth distribution in a society, a Lorenz curve allows the visual interpretation of the cumulative disease burden in relation to a risk factor and its distribution among the population (6). The Lorenz curve for the men aged 60–61 yr displays that all PCa deaths within an 8-year follow-up interval happened in the 25% of patients with a baseline PSA >2.0 ng/mL. Furthermore, and of utmost importance, 92% of all PCa-specific deaths within a 16-year follow-up period occurred in patients with an initial PSA higher than the cohorts' median baseline PSA of 1.12 ng/mL.

The authors of the study concluded that men regardless of age with an initial PSA value <1.0 ng/mL are unlikely to reach a PSA biopsy threshold of ≥3.0 ng/mL, indicating a minimal risk of being diagnosed with relevant PCa during follow-up. They emphasized further that while the risk of being diagnosed with PCa was low in the <1.0 ng/mL subgroup aged 55–59 yr, half of the detected PCa during follow-up were clinically significant. Furthermore, the men who died from PCa after an initial low PSA at first screening round (10 of 12,825, <0.01%) had an aggressive course of the disease and passed away shortly after the diagnosis (median time from diagnosis to death: 1.7 yr). However, Remmers *et al.* concluded that lowering the PSA value that would trigger a biopsy would considerably raise the number needed to screen to 25,000 men and the number needed to treat to 724 to prevent one PCa-specific death. Therefore, lowering the PSA threshold would not contribute to a better benefit/risk ratio and should therefore be avoided. Nonetheless, the authors emphasized, since these men are less likely to have benign prostate enlargement, PCa must be excluded in any abrupt increase in PSA.

When analyzing the manuscript, it becomes evident that the subgroup of patients with a PSA ≥3.0 ng/mL were more frequently diagnosed with PCa. This could be expected since, in the majority of ERSPC centers, a PSA cut-off of 3.0 ng/mL also triggered a prostate biopsy. Consequently, the study's design influenced this particular outcome, leading to an increased number of performed biopsies in subgroup of men with PSA values ≥3.0 ng/mL. In contrast, the subgroup of men with a PSA <1.0 ng/mL were not biopsied and had fewer follow-up visits. However, the crucial point of the study is the association of the PSA value at initial screening visit and the PCa-specific mortality. Remmers *et al.* could confirm previous findings that men with a low baseline PSA value have a very low risk for PCa-specific deaths (7-10). Although few patients with an initial low baseline PSA value (31 of 23,613, 0.13%) still died of PCa after an initial PSA <1.0 ng/mL during long-term follow-up and showed a very aggressive course of the disease. Future research should also concentrate on this specific subgroup of men to enhance our understanding of factors that are prognostic for a highly aggressive course of disease. This focus may include areas such as family history, genetic predispositions and other relevant factors. Particularly in younger patients, these insights could provide a rationale for continuing PSA screening, even when initial baseline levels are low.

The paper has some limitations. Since the start of the ERSPC trial, the pathological Gleason grading system has been updated and the method of screening has changed substantially with the implementation of multiparametric magnetic resonance imaging (mpMRI).

Overall, Remmers *et al.* could confirm the excellent properties of PSA as a biomarker for long-term PCa prognosis. In men with initial low PSA baseline values the follow-up screening visits can be minimized or even discontinued to reduce overdetection and overtreatment of men at low risk dying from PCa. Still future research is needed to further improve risk stratification. Particularly, men with elevated PSA levels are at higher risk of being diagnosed with low risk PCa (Gleason Score =6) due to the higher likelihood of undergoing a prostate biopsy.

mpMRI, risk calculators and novel biomarkers should be further tested in clinical trials to improve the identification of high-risk patients, while limiting overdetection and overtreatment of low risk PCa.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-606/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-606/coif). T.P.S. reports study fees for the Master in Public Health, University Zurich, Basel and Bern from Monsol Foundation and payment for laboratory equipment from the Swiss Cancer Foundation. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Scherer TP, Poyet C. Prognostic properties of the baseline prostate-specific antigen value—insights from the European randomized study of screening for prostate cancer. Transl Androl Urol 2024;13(3):473-475. doi: 10.21037/tau-23-606

