Peer Review File

Reviewer A

Comment 1: The commentary is well written and highlights the limitations of the ERSPC study which was appropriate in 1992 when it was designed, but with the advent of mpMRI has become underpowered.

Reply 1: Thank you for reviewing our manuscript.
Changes in the text: -

Reviewer B

Comment 1: This commentary discusses a post hoc subgroup analysis of the association between baseline prostate-specific antigen (PSA) level and prostate cancer (PCa) diagnosis, clinically significant PCa (csPCa) diagnosis, and PCa-specific mortality (PCSM) in the European Randomized Study of Screening for Prostate Cancer (ERSPC) intervention arm. The analysis found that higher baseline PSA was associated with higher risks of PCa and csPCa diagnosis across ages 55-69 yrs; men with PSA < 1 ng/mL had < 3% chance of PCa diagnosis within 16 yrs; 9/26 (35%) of PCa deaths within 16 yrs came from men with PSA < 2 ng/mL at age 60-61 and 0% of these deaths were from men who were still alive and undiagnosed with PSA < 2 ng/mL at age 68-70.
Summary statements about the ERSPC were incorrect or misleading. The ERSPC did not include a center in Portugal (Line 36). Although the ERSPC included two centers in France, they were excluded in results summarized by the authors (e.g., Lines 45-50). The summarized results were also restricted to a pre-specified core age group of 55-69 yrs (not mentioned by the authors). The authors' phrasing suggests all participants were consented before randomization (Line 38) but randomization was *before* consent in 3 countries.

Reply 1: The ERSPC trial did include a study site in Portugal, which can be referenced for example in the paper by Schröder titled "The European Randomized Study of Screening for Prostate Cancer (ERSPC): An Update" (DOI: https://doi.org/10.1159/000019894). However, it's worth noting that the Portuguese and French study centers were not utilized for the analysis. Our intention was to provide a comprehensive overview of the extensive scope of the ERSPC in the introduction, hence the use of an initial more general description. For enhancing the accuracy, the exclusion of Portuguese and French centers is now stated (lines 41-45).

Randomization and recruitment did differ between the countries. A description of the recruitment was added to the manuscript (lines 37-41)

Age group is now specified (line 50).

Changes in the text: lines 37-45 and 50

Comment 2: Summary statements introducing the post hoc subgroup analysis were not obviously consistent. Lines 28-33 highlight csPCa and Lines 52-56 highlight PCa diagnosis; the authors should consolidate and harmonize. Lorenz curves for PCSM for men ages 60-61 at first screen do not show "a repeat screening interval of 8 yr, respectively 16 yr" (Line 74); they show PCSM for these men 16 yrs after the first screen and, among the subgroup of these men with PSA 3 ng/mL (Lines 100-105) ignore the distinction between screen- vs interval-detected PCa in the analysis. The authors correctly note that the Gleason grading system in the subgroup analysis, and therefore the definition of csPCa, is outdated (Line 120).

Reply 2: Thank you for your remark. However, we do not think this is an inconsistency, but rather it displays the main problem of screening. Lines 28-33 summarize, as mentioned in the text, the aim of Remmers' analysis. Lines 52-56 summarize the original results of the 16-year outcome of the ERSPC trial. Remmers article focuses on clinically significant cancer, whereas the ERSPC trial reported the diagnosis of more PCa and consequently less PCa-specific mortality in the screening arm.

The introduction sentence for the Lorentz curve was deleted due to the inaccuracy.

Changes in the text: line 80.

Comment 3: The authors highlight "the crucial point of the study" (Line 107) as confirming the well-established low risk of PCSM in men with low baseline PSA. From this reviewer's perspective, the main point is not only that "follow-up screening can be minimized" (Line 125) but more specifically that these results support delaying rescreening for 8 yr or discontinuing screening in men with PSA < 2 ng/mL at age 60 yr.

Reply 3: The possible discontinuation of screening is now included in the last paragraph. However, Remmers specifically emphasizes that 'due to the limited size of the subgroup aged 60-61 years with a PSA <2.0 ng/ml, it is hard to generalize the results.' Therefore, we feel that stating this recommendation as the crucial point would not be ideal.

Changes in the text: line 130

Comment 4: Commentary language should be carefully reviewed for grammar and usage. E.g., "consecutively" reduced mortality (Line 47), "outmost" importance (Line 80), "time form diagnosis" (Line 91), "Contrary" (Line 105), "PSA baseline at initial screening visit" (Line 107), and numerous other ungrammatical or awkward phrasings.

Reply 4: Thanks for correcting. The passages have been corrected.

Changes in the text: various