RE: Prostate-Specific Antigen Screening Trials and Prostate Cancer Deaths: The Androgen Deprivation Connection

We were intrigued to read the article by Haines and Miklos (1) in which they reviewed published data from the three large randomized prostate-specific antigen (PSA) screening trials: Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, European Randomized Study of Screening for Prostate Cancer (ERSPC), and the Göteborg trial. The authors note “that in both European trials far more patients received hormonal treatment in the control than the screening arm”, with a concomitant “increase in prostate cancer deaths in control patients” (1). The authors thus claim that, instead of PSA screening effectively reducing prostate cancer deaths in the screening arm, androgen deprivation therapy (ADT) given to patients in the control arm increased prostate cancer deaths, calling their hypothesis an “androgen deprivation connection.”

Haines and Miklos raise a worrying concern. However, their claim is fundamentally flawed and their argumentation is not supported by available evidence.

The authors claim that there is no evidence of cure or benefit from early treatment. The Scandinavian SPCG-4 trial, not cited by the authors, indeed demonstrated a survival advantage for radical prostatectomy over watchful waiting (2).

Next, the authors cite the outcome of the PLCO (3) as “no benefit from early diagnosis and treatment.” However, absence of effect does not equal proof of no effect. PLCO reflected widespread PSA use, with 44% of men prescreened in the screening arm (4) and 46% to 85% screened in the control arm during the trial (5), thus reducing the contrast between arms and power (6,7).

Next, the authors argue that similar prostate cancer mortality rates in the screening arms of the PLCO, ERSPC, and GÖTEBORG trials (rates = 41, 41, and 44 per 10,000, respectively) but a large difference in the control arms (rates = 38, 52, and 78 per 10,000, respectively) show that only the control arm was affected by the trial. The logic here fails in the premise of assuming similar baseline mortality across the trials. Owing to randomization, comparability is assured only across the arms within a trial, not between trials with different target populations.

Further, Haines and Miklos argue that the similarity of prostate cancer incidence and mortality between the screening vs control arms of the PLCO trial (incidence = 4250 vs. 3815; mortality = 158 vs. 145) is evidence for validity, whereas, in fact, it is just an indication of the lack of any substantial difference in screening activities between arms. This also explains the apparent difference in treatments between the trial arms. To assess the effect of screening and not case management, similar treatment should be provided for men in both trial arms—but with the important proviso of similar disease and patient characteristics. Therefore, only a trial with more frequent detection of early disease treated with curative intent has the potential to show a mortality benefit. This intermediate in the screening process—a shift in stage and treatment—is misrepresented as bias by Miklos and Haines. In both ERSPC and GÖTEBORG, the proportion of men who received curative treatment was similar among men with low- and intermediate-risk tumors in the screening group compared with the control group (8,9).

To support their ADT hypothesis, Haines and Miklos cite four studies and conclude that “hormonal intervention increases prostate cancer deaths” (1). In addition, they claim that “current belief [is] that primary ADT treatment is beneficial for men with localized tumors” (1). These statements are erroneous.

First, “current belief” in the urological community is not that primary ADT is beneficial for men with localized tumors. No guidelines recommend that.

Second, an observation of increased prostate cancer deaths among men on ADT does not imply a causal relationship. Instead, men with advanced disease are specifically selected for ADT because their increased risk of prostate cancer death due to the lethal nature of their symptomatic disease stage is an indication for hormonal treatment.

The observational studies cited by the authors are thus prone to confounding by indication (selection bias due to case mix)—that is, ADT is offered to patients with worse prognosis, also within a broad prognostic category. Treatment effects thus also reflect patient selection.

The scientific question of whether ADT impacts prostate cancer mortality is best resolved by a randomized controlled trial. In a meta-analysis of 11 such trials, including the large EORTC and RTOG studies, ADT given to men with unfavorable risk disease was, if anything, associated with lower prostate cancer–specific mortality (relative risk = 0.69; 95% confidence interval = 0.56 to 0.84) (10). The randomized SPCG-6 and -7 trials have similarly demonstrated statistically significantly reduced prostate cancer mortality from administering ADT plus standard care to men with locally advanced disease (11,12).

In conclusion, we find no evidence to support any “androgen deprivation connection” in the European screening trials.

SIGRID CARLSSON
MONIQUE J. ROOBOL
FRITZ H. SCHRODER
JONAS HUGOSSON
ANSSI AHVINEN

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**Affiliations of authors:** Department of Surgery (Urology), Memorial Sloan-Kettering Cancer Center, New York, NY (SC); Department of Urology, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden (SC, JH); Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands (MJR, FHS); Tampere University, School of Health Sciences, Tampere, Finland (AA).

**Correspondence to:** Sigrid Carlsson, MD, PhD, Department of Surgery (Urology Service), Memorial Sloan-Kettering Cancer Center, 307 E 63rd St, 10065, New York, NY 10065 (e-mail: carlssos@mskcc.org).

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