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Platinum Opinion

Wise Prostate-specific Antigen Testing Means a Limited, Risk-adjusted, and Personal Approach

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The European Randomized Study of Screening for Prostate Cancer (ERSPC), the only sufficiently powered trial, showed, besides a 20% reduction in prostate cancer mortality in the intervention arm, that many men needed to be screened and to be treated to avoid one prostate cancer death [1]. Since that publication, it has been stated many times that prostate cancer screening can be performed more efficiently and should lead to less overdiagnosis than was initially designed. An early stopping age and limiting the number of tests to three or four are (cost-)effective ways to improve the balance between harms and benefits [2].

Another relatively easy way to improve prostate cancer screening is to take previous prostate-specific antigen (PSA) test results into account when scheduling a next test, thereby taking an individual's (re-assessed) risk into account. In particular, the Malmö study in Sweden provided evidence supporting reduced screening for men with low PSA [3,4]. Archived blood samples that had been collected around 1980 in the Malmö Preventive Project were analyzed and the men were followed for more than 25 yr. The risk of prostate cancer death was associated with PSA. Men aged 45–49 yr and 51–55 yr with PSA below the median for their age group (0.68 and 0.85 ng/ml) had a risk of metastasis of only 0.09% and 0.28%, respectively, during 15 yr of follow-up. Men aged 60 yr with PSA <1.0 ng/ml had a 0.5% probability of metastatic prostate cancer after 25 yr. Partly based on this study, the European Association of Urology (EAU) recommends a "risk-based" screening strategy consisting of, conservatively, a 5-yr screening interval for men age 50–59 yr with an initial PSA result <1.0 ng/ml, and stopping screening for men aged 60–70 yr if their PSA is <1.0 ng/ml [5].

A more recent large study from Sweden showed the probability of having a biopsy or a cancer diagnosis within various intervals after the previous test by PSA level [6]. Fewer than 3% of men with an initial PSA $\leq$1.0 ng/ml had PSA >3 ng/ml at the next test within 1–8 yr and a very low probability of having Gleason $\geq$7 cancer. The ERSPC recently showed similar results: men with PSA <1.0 ng/ml at their first test had a 1.2–1.5% probability of having clinically significant cancer in 16 yr of follow-up, whereas the probability for men with PSA >3.0 ng/ml was 13.3–13.8% [7].

In this issue of *European Urology*, a study by Bjerner et al. [8] shows that in a cohort from Norway there was also strong association between baseline PSA and prostate cancer death over the subsequent 16 yr. Data for men with baseline PSA <4.0 ng/ml, measured in blood drawn as part of routine medical care between 1995 and 2005, were analyzed. In total, 176 099 men aged between 40 and 70 yr were included. Some 53% of the prostate cancer deaths occurred in the 16% of men with the highest baseline PSA (2.0–3.9 ng/ml) and 83% of the prostate cancer deaths occurred in the 48% of men with baseline PSA of 1.0–3.9 ng/ml. This study therefore replicates the association between PSA and long-term prostate cancer death previously found, but the ample size is much larger and the data are more recent.

Interestingly, we now have several studies showing similar results from different settings: retrospective blood sample analyses in a period when screening was not common (the Malmö study), PSA results as part of routine medical care in Sweden and Norway, and PSA test results from the ERSPC trial. As the authors of the present study describe, participants in the Malmö study were not aware of their PSA result and therefore did not intervene at PSA values close to the threshold. In this present study in Norway (as well as in the study in Sweden), the reasons for a PSA test are not known and are probably a combination of oppor-

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tunistic screening and presence of symptoms. Men with higher PSA values could have had repeat tested in the following years, leading to early diagnosis of cancer and treatment. Therefore, the association between PSA and prostate cancer was higher in the recent study in Norway, and the association between PSA and prostate cancer death lower than in the Malmö study.

This present study in Norway is a good example of how data from clinical settings can be used. By not limiting the analysis to baseline PSA and including subsequent PSA test results, additional useful information for determining the optimal screening intervals and stopping age can be obtained.

By extending the screening interval for men with low PSA, this type of risk-based screening will certainly substantially reduce the number of screening tests needed. The question is whether this approach will also reduce the number of biopsies and overdiagnosis. Men with PSA <1 ng/ml are not very likely to have PSA above the biopsy threshold within a period of 8 yr [6,7]. In the Swedish study and in the ERSPC trial, almost half of men with PSA <1.0 ng/ml who were diagnosed with prostate cancer had Gleason $\geq$7 disease [6,7]. Therefore, it is likely that less screening for this group will not have a large effect on overdiagnosis. Reducing overdiagnosis seems more feasible using risk calculators and magnetic resonance imaging before biopsy [9].

Running trials and pilot programs for organized prostate cancer testing (OPT)as in Sweden, in which screening intervals are based on the previous test result, will be very helpful in determining the optimal screening protocol [9,10]. However, the ultimate challenge is to make prostate cancer screening programs really "risk-adjusted and personal". The balance between the, sometimes low, risk of dying from prostate cancer in the future and the immediate harms is a delicate one and needs personal weighting.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.

[2] Getaneh AM, Heijnsdijk EAM, Roobol MJ, de Koning HJ. Assessment of harms, benefits, and cost-effectiveness of prostate cancer screening: a micro-simulation study of 230 scenarios. Cancer Med 2020;9:7742–50.

[3] Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. BMJ 2010;341:c4521.

[4] Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40–55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023.

[5] Van Poppel H, Roobol MJ, Chapple CR, et al. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology position and recommendations for 2021. Eur Urol 2021;80:703–11.

[6] Palsdottir T, Nordstrom T, Karlsson A, Gronberg H, Clements M, Eklund M. The impact of different prostate-specific antigen (PSA) testing intervals on Gleason score at diagnosis and the risk of experiencing false-positive biopsy recommendations: a population-based cohort study. BMJ Open 2019;9:e027958.

[7] 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. In press. https://doi.org/10.1016/j.eururo.2023.03.031.

[8] Bjerner J, Bratt O, Aas K, et al. Baseline serum prostate-specific antigen value predicts the risk of subsequent prostate cancer death—results from the Norwegian Prostate Cancer Consortium. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2023.04.028.

[9] Bratt O, Auvinen A, Godtman RA, et al. Screening for prostate cancer: evidence, ongoing trials, policies and knowledge gaps. BMJ Oncol 2023;2:e000039.

[10] Alterbeck M, Jarbur E, Thimansson E, et al. Designing and implementing a population-based organised prostate cancer testing programme. Eur Urol Focus 2022;8:1568–74.