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# When Is It Too Early To Start Prostate Cancer Screening? Reflections on the PROBASE Study Using Magnetic Resonance Imaging for Men Aged 45 Yr with Elevated Prostate-specific Antigen

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We congratulate Boschheidgen and colleagues [1] on their paper reporting results from the first screening round of the PROBASE trial in this issue of *European Urology*. The question of whether and how to screen for prostate cancer continues to challenge epidemiologists, with Lithuania being the only country to date to have an organised national screening programme [2]. An acceptable screening programme must balance detection of prostate cancer at a curable stage against the harms of screening, which include costs both to the patient and to society from overdiagnosis and potential overtreatment [3], as well as the costs for running the screening programme. Magnetic resonance imaging (MRI) can reduce the harms of overdiagnosis in men with elevated prostate-specific antigen (PSA) [4] and is of interest as a new primary screening tool [5–7].

Because cancer is very uncommon among men aged 45 yr, the protocol was appropriately cautious, using a confirmatory PSA test for those with an initial result of ≥3 ng/ml, followed by MRI for men with two PSA levels ≥3 ng/ml. The most striking finding is the very low incidence of elevated PSA of ≥3 ng/ml. Only 344/23 411 (1.5%) men had an initially elevated PSA result and only 186/23 411 (0.8%) had PSA ≥3 ng/ml on repeat testing . For comparison, a single PSA test in a largely unscreened but older population in the UK CAP study showed that 11% had PSA ≥3 ng/ml [8].

The 186 men identified as having a high risk of prostate cancer were offered MRI and biopsy. One in five men (37/156) did not proceed to MRI and one in four (35/149) did not proceed to biopsy after MRI. Were these young men reluctant to proceed with more extensive testing because of the potential impact of treatment or low possibility of having significant disease? The median PSA density among the men who had MRI but not biopsy was lower than that for the men diagnosed with cancer.

Is MRI of use in younger men? Despite the low prevalence of elevated PSA in the study, MRI had 91% negative predictive value (NPV) when read by an expert reader, and no cases of significant cancer were missed among patients with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 1 or 2. The yield of 29% for significant cancer among men with elevated PSA is similar to that found in other studies for men with elevated PSA [4].

Is 45 yr an appropriate age to start offering screening? In this trial, 0.20% of screened men (47/23 411) were diagnosed with prostate cancer, of which only 70% (33/47) cases were deemed clinically significant. This is probably too low a yield for a public health programme. A second screen in these men (perhaps at 5 and 10 yr) would be of value for assessing whether the PSA at age 45 yr could predict future risk, with men at the lowest risk able to defer further testing for 10 yr or so.

The study raises several issues. The first relates to the quality of the MRI and the local MRI reading. MRI reports by the local reader were only moderately reliable in comparison to the expert reader ($\kappa$ = 0.41). Between 29% and 56% of local reports differed from the expert reader across the four different sites. These findings suggest the need

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for dedicated readers and an ongoing improvement programme. None of the men with only PI-RADS 1 or 2 lesions on expert reading has significant cancers. All centres will have a learning curve, with reports that a plateau is reached after some months [9], and this should be considered when the biopsy strategy is based on MRI.

The ability to accurately reassure young participants that they do not need further testing for many years is critical. When using a threshold of PI-RADS 4/5 for detection of clinically significant cancer, the local report had NPV of 80%, compared to 91% for the expert reader. These findings support the position that dedicated screening centres for advanced imaging studies are more appropriate than a hospital specialist approach.

The study also suggests that PSA density might discriminate between men with clinically significant and insignificant disease. Median PSA density was 0.13 ng/ml/cm$^3$ for men with grade group 1 disease or benign findings, compared to 0.18 ng/ml/cm$^3$ for those with significant cancer.

The authors acknowledge that a strategy of using only two cores per lesion may have led to undersampling, which may be accentuated by the likelihood of these men having smaller lesions, although younger men also tend to have smaller prostates. Determination of an index lesion for every prostate, even when the PI-RADS score for that lesion is 2, is an interesting idea. This approach yielded similar numbers of cores among those with and without a PI-RADS 4/5 lesion, but future strategies to reduce the biopsy burden may well incorporate a PSA density cutoff for men with equivocal MRI findings.

In summary, the PROBASE study is evaluating the value of a prostate cancer screening programme starting at the age of 45 yr. The low yield for significant cancers suggests that a higher age of 50 or 55 yr for initiation of screening is more acceptable from a public health perspective. However, in comparison to a deferred digital rectal examination screen, an expertly read MRI and biopsy for men at high risk because of PSA $\geq$3 ng/ml on two occasions did find clinically significant cancer in one of three men, suggesting that this strategy is appropriate when expert readers are used.

***Conflicts of interest***: The authors have nothing to disclose.

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