Asian Journal of Andrology (2019) 21, 3–5
www.asiaandro.com; www.ajandrology.com

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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

PSA screening – for whom and when?

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Asian Journal of Andrology (2019) **21**, 3–5; doi: 10.4103/aja.aja_37_17; published online: 5 September 2017

Reasons for and against screening of prostate cancer have been discussed widely over the last decade. In 2014, the European Randomized Trial for Screening of Prostate Cancer (ERSPC) has reported a relative reduction of the cancer-specific survival of 27% in participants who definitely followed the screening protocol. This relative advantage has proven to be stable from year 7 to year 13 after the beginning of screening. Still, the disadvantages of overdiagnosis and overtreatment are the downsides of a population-based screening approach. But given the overall advantage of screening, a risk-adapted prostate-specific antigen (PSA) screening using a baseline PSA value at ages 45–50 may significantly reduce the number needed to diagnose maintaining the benefits of screening. PROBASE is a randomized risk-adapted screening trial currently ongoing in Germany to answer this important question.

Prostate cancer in industrialized countries is still the most frequent cancer in men and represents the third most cause of cancer-related deaths.[1] The huge difference between prevalence and mortality brings early detection into discussion. Still, in Germany, more than 13 000 men die from the disease.[2] An ideal would be a screening tool only detecting the aggressive cancers. However, current screening tools are restricted to digital rectal examinations, serum prostate-specific antigen (PSA), and prostate biopsies in cases of suspect findings.[3] The widespread use of PSA has led to a stage shift toward more clinically insignificant tumors.[4]

The ideal screening tool can detect a cancer at a stage when it is curable, is noninvasive, can reduce cancer-specific mortality, and is readily available. PSA has been tested in multiple randomized and nonrandomized trials (**Table 1**). The largest study, the European Randomized Screening Trial in Prostate Cancer (ERSPC), has shown a consistent 27% relative mortality reduction after 13 years in the participated men.[5] The American Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) had methodological problems with a very high contamination of the control arm and, therefore, cannot be evaluated correctly as to whether the trial can yield valid results to recommend or not recommend screening.[6] Since the United States Prevention Services Task Force (USPSTF) included the PLCO trial in their decision-making, in 2012, they have recommended against PSA as screening tool. Meanwhile, the USPSTF is about to change the recommendation and their plea is to inform men and recommend screening for risk groups.

Taken together, the problem of prostate cancer screening is not solved. The advantage of a population-based PSA screening in terms of a significant reduction in prostate cancer mortality is meanwhile proven by the ERSPC trial. However, there is still a considerable number of men unnecessarily diagnosed with clinically insignificant prostate cancers or with a false-positive PSA value, leading to unnecessary diagnostics and treatment.

DISADVANTAGES OF PSA SCREENING

Remarkably, none of the studies cited in **Table 1** have been able to show an advantage for screening in overall survival; the reduction in cancer-specific mortality was proven, for example, by the ERSPC trial. In ERSPC, at least 20% of participants have already died from noncancer-related reasons.[5] So in the given setting, it is rather unlikely that an advantage in the reduction of overall mortality will ever be proven. In addition, many papers including a Cochrane review did not show an advantage of PSA screening in terms of reduction of cancer-specific mortality.[7–9] In addition, the risk of overdiagnosis and overtreatment is highlighted by these papers multiple times. In more than half of men, rectal bleeding, hematuria, and hemospermia are seen. But only rarely, these bleedings lead to long-term complications.[10] On the other hand, infections by unnecessary biopsies, sometimes also with multiresistant bacteria, are an increasing problem.[11] Psychological problems with false-positive PSA values also count.[12] Even in men with a negative biopsy, psychological problems can persist for a longer time.[13] More important, however, are problems with overtreatment. The number needed to detect is about 27 detected prostate cancers to prevent one death from prostate cancer after a time period of 13 years.[5] This is in part due to the low prognostic power of clinical risk parameters in detecting clinically significant prostate cancer of only 75%–85%. In doubt, a radical curative treatment is recommended.[14] The rate of overtreatment (curative treatment for clinical insignificant cancers) is about 50% according to ERSPC data.[15] A review describes large differences of overtreatment from 1.7% to 67%.[16]

In a large difference to breast cancer, cervical cancer, or colorectal cancer, the primary treatment after detection of early stages of disease in prostate cancer results in tremendous side effect profiles (incontinence, impotence by surgery or radiotherapy). At last, the costs of a population-based PSA screening approach are very high due to low discriminative power of PSA.[17–20]

ADVANTAGES OF PSA SCREENING

Since the second largest trial (PLCO) has been proven not to be valid enough to evaluate the power of a population-based PSA screening due to a very high rate of PSA screening in the control arm of the trial (about 90% of participants had PSA values taken over 1–3 years period), all

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Received: 14 June 2017; Accepted: 15 June 2017

Table 1: Prostate-specific antigen screening trials

Trial	*Age (year)*	*Screening population (n)*	*Control (n)*	*Randomized*	*Follow-up (year, median)*	*Reduction in mortality*	*Relative risk*
ERSPC[5]	55–69	72 891	89 352	Yes	13	Yes	0.79 (ns)
PLCO[6]	55–74	38 340	38 345	Yes	13	No	1.09 (ns)
Quebec[33]	45–80	31 133	15 353	Yes	11	Yes	0.38*
Stockholm[34]	55–70	1782	24 422	No	15	No	1.10 (ns)
Norrköping[35]	50–69	1494	7532	Partially	20	No	1.16 (ns)

*P<0.5. ERSPC: European Randomized Trial for Screening of Prostate Cancer; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ns: not significant

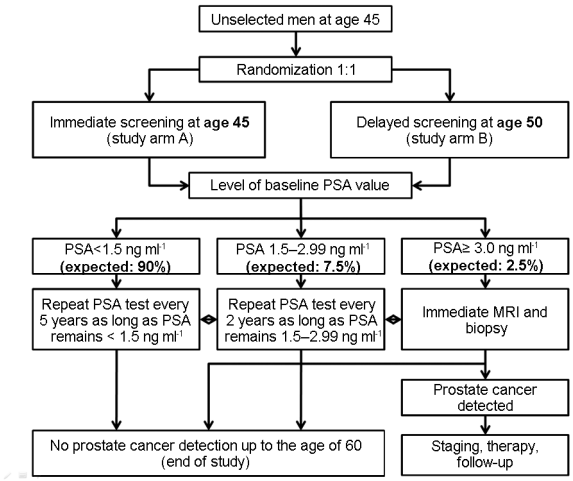

Figure 1: Design of the PROBASE risk-adapted screening trial. PSA: prostate-specific antigen; MRI: magnetic resonance imaging.

interpretations are now restricted to the ERSPC study.[21] With longer follow-up, the ERSPC trial has shown a reduced number of men needed to screen, diagnose, and treat in order to achieve a significant advantage in cancer-specific mortality.[5,22] In some parts of the ERSPC trial (e.g., Sweden), the reduction of cancer-specific mortality was as high as 44%. With longer follow-up, the absolute number of avoided deaths from prostate cancer increased from 0.71/1000 men (9-year follow-up) to 1.28/1000 men (13-year follow-up).[22] There are simulation models to calculate the risk reduction over the whole live span of >70% of participants who are still alive in the ERSPC trial which result in a 5-fold higher risk of reduction of mortality with a reduction of the number needed to screen to 98 and the number needed to detect to 5.[12]

In addition to the obvious effects of screening, the relative risk of developing prostate cancer metastasis of 42% is remarkable in ERSPC as well.[23] In view of the patients, this may be an even more important advantage since especially bone metastasis produces large clinical problems with the necessity for expensive treatments. In addition, ERSPC showed that, even at the time of diagnosis, the rate of metastasis could be reduced by 40% and this may contribute to the large difference in later metastasis.[24] In the last years, opportunistic PSA screening in the US has led to a stage shift to earlier stages, but of course for the price of higher rates of overdiagnosis.[25,26]

If PSA screening is highly standardized like in the Gothenburg part of the trial with 2-year intervals, the advantages of PSA screening can be further maximized. The opportunistic PSA screening in the control arm could only show an absolute reduction in cancer-specific mortality from 0.2% (as opposed to 0.73% in the screening arm).[27]

IMPROVEMENT OF PSA SCREENING BY NEW STAGING TOOLS SUCH AS MULTIPARAMETER MAGNETIC RESONANCE IMAGING

The development of mpMRIs for the more precise diagnosis of prostate cancer may also have an influence on future screening strategy.[28] In the Gothenburg part of the ERSPC trial, mpMRIs have been retrospectively analyzed and showed a higher accuracy of screening by lowering the PSA cutoff by adding the MRI information.[29]

BASELINE PSA AND RISK-ADAPTED PROSTATE CANCER SCREENING

Summarizing the pros and cons of a population-based PSA screening, the disadvantages overrule the advantages. A population-based prostate cancer screening based on PSA only in the screening groups at age 54 years cannot be recommended due to a too high rate of overdiagnosis and overtreatment. A possible solution is based on an observation which was made by analyzing a Swedish observational cohort of about 30 000 men in whom PSA values were analyzed >25 years after they had been enrolled in the trial.[30,31] Based on these data, a baseline PSA value could be defined which is specified by age. The data propose a nearly 10-fold risk of metastasis from prostate cancer in 45-year-old men if the PSA is >1.6 ng ml^{-1} as opposed to >0.6 ng ml^{-1}. About 90% of 45-year-old men will have a baseline PSA value of <1.5 ng ml^{-1} with a very low risk of developing and dying of prostate cancers 25 years later. About 2% are in a high-risk group (PSA >3 ng ml^{-1}) with a 44% risk of dying from prostate cancer, leaving an intermediate group of about 8%. Based on these assumptions, a randomized trial was constructed in Germany to prove the hypothesis of a baseline PSA being predictive of prostate cancer risk (PROBASE trial, www.probase.de). The primary end point of this trial is to prove the noninferiority of starting risk-adapted PSA screening with 50 years as opposed to 45 years by diminishing the side effects of screening like overdiagnosis. In this trial, a mpMRI is added to the diagnostic tools but has currently no influence on the decision to perform a biopsy (**Figure 1**).[32]

CONCLUSIONS

A population-based PSA screening for prostate cancer cannot be recommended.

The USPSTF recommendation was revised and reads now: "the decision about whether to be screened for prostate cancer should be an individual one. The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)-based screening for prostate cancer.... Recommendation Grade C." Screening for men aged 70 years and older is not recommended by the USPSTF.

A risk-adapted screening based on a PSA value taken at age 45 years may potentially solve a lot of problems of overdiagnosis. If active surveillance is discussed in addition to radiotherapy and surgery, the problem of overtreatment is diminished as well. Men at age 55 years may also benefit from a baseline PSA value; however, the prognostic information in cases of elevated values is diluted by a possibly already developed benign prostatic hyperplasia (BPH). The concept of a baseline PSA for the detection of high-risk patients should be recommended at the age of 45 years. The PROBASE trial will be able to answer the question of whether this age cutoff may be postponed to 50 years of age. So, if a man at the age of 45 years is informed about the benefits and harms of PSA screening and consents to proceed, a baseline PSA value should be taken and further PSA intervals should be recommended according to his risk group. If the value at age 45 is <1.5 ng ml^{-1}, further testing is recommended 5 years later, and if the value is 1.5–2.9 ng ml^{-1}, the interval should be 2 yearly. If the value is 3 ng ml^{-1} or greater, the classical diagnostic tools such as systematic biopsies should be recommended. It is not yet clear whether a mpMRI can add valuable information to a more accurate diagnosis as compared to a systematic biopsy. In cases of tumor-negative biopsies and further rising PSA values, a repeat biopsy should certainly be based on a mpMRI.

COMPETING INTERESTS

The author declares no competing interests.

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