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. The huge difference between prevalence and mortality brings early detection into discussion. Still, in Germany, more than 13,000 men die from the disease. 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. The widespread use of PSA has led to a stage shift toward more clinically insignificant tumors.

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. 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. 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. 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. 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. On the other hand, infections by unnecessary biopsies, sometimes also with multiresistant bacteria, are an increasing problem. Psychological problems with false-positive PSA values also count. In men with a negative biopsy, psychological problems can persist for a longer time. 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. 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. The rate of overtreatment (curative treatment for clinical insignificant cancers) is about 50% according to ERSPC data. A review describes large differences of overtreatment from 1.7% to 67%.

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.

**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
In addition to the obvious effects of screening, the relative risk of developing prostate cancer metastasis of 42% is remarkable in ERSPC as well.21 With longer follow-up, the absolute number of avoided deaths from prostate cancer increased from 0.71/1000 men (9-year follow-up) to 0.73% in the screening arm (13-year follow-up).22 There are simulation models to calculate the risk reduction over the whole life span of >70% of participants who are still alive in the ERSPC trial which result in a 5-fold higher risk of avoidance 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.21 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 cancer 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.

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**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*     | 55–69      | 72,891                   | 89,352     | Yes        | 13                       | Yes                    | 0.79 (ns)    |
| PLCO*      | 55–74      | 38,340                   | 38,345     | Yes        | 13                       | No                     | 1.09 (ns)    |
| Quebec22   | 45–80      | 31,133                   | 15,353     | Yes        | 11                       | Yes                    | 0.38*        |
| Stockholm34 | 55–70      | 17,822                   | 24,422     | No         | 15                       | No                     | 1.10 (ns)    |
| Norköping30 | 50–69      | 14,942                   | 7,532      | 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
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 PROBAS 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 years. 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.

REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374–403.
2. Zentrum für Krebsregisterdaten. Available from http://www.krebsdaten.de/Krebs/DE/Home/homepage_node.html. [Last accessed in 2016 Dec 22].
3. Interdisziplinäre Leitlinie der Qualität S3 zur Frühkenntnisse, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. Available from: http://www.awmf.org/leitlinien/detail/III/043-O220L.html. [Last accessed on 2016 Dec 22].
4. Antenor JA, Han M, Roehl KA, Nadler RB, Catalona WJ. Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. J Urol 2004; 172: 90–3.
5. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014; 384: 2027–35.
6. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012; 104: 125–32.
7. Djuzbegovic M, Beyth RJ, Neuberger MM, Stofs TL, Vieweg J, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. BMJ 2010; 341: c4543.
8. Ilic D, O’Connor D, Green S, Witt TJ. Screening for prostate cancer: an updated Cochrane systematic review. BJU Int 2011; 107: 882–91.
9. Ilic D, Neuberger MM, Djuzbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013; CD004720.
10. EAU Guideline of Prostate Cancer. Available from: http://www.uroweb.org/guideline/prostate-cancer/. [Last accessed in 2017].
11. Ayl M, Dynákov R, Nordström T, Jalal S, Weibull CE, et al. Rapid increase in multidrug-resistant enteric bacilli blood stream infection after prostate biopsy – A 10-year population-based cohort study. Prostate 2015; 75: 947–56.
12. Heijnsdijk EA, van der EM, Auvinen A, Hugosson J, Cliatto S, et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012; 367: 595–605.
13. Macfie AI, Metcalfe C, Lane JA, Donovan JL, Avery KN, et al. Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result. Br J Cancer 2010; 102: 1335–40.
14. Han M, Partin AW, Zahirak M, Plantadosi S, Epstein JI, et al. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003; 169: 517–23.
15. Draisma G, Boer R, Otto SJ, van der Cruisken IW, Damhuis RA, et al. Lead times and overdetection due to prostate-specific antigen screening; estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; 95: 868–78.
16. Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Persson DF, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol 2014; 65: 1046–55.
17. Roth JA, Guliati R, Gore J, Cooperberg MR, Etzioni R. Economic analysis of prostate-specific antigen screening and selective treatment strategies. JAMA Oncol 2016; 2: 890–9.
18. Heijnsdijk EA, de Carvalho JM, Auvinen A, Zappa M, Nelen V, et al. Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. J Natl Cancer Inst 2014; 107: 366.
19. Shteynshlyuger A, Andriole GL. Cost-effectiveness of prostate specific antigen screening in the United States: extrapolating from the European study of screening for prostate cancer. J Urol 2011; 185: 828–32.
20. Landsorp-Vogelar I, Knudsuen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev 2011; 33: 88-100.
21. Grubb RL 3rd, Pinsky PF, Greenlee RT, Izmirlian G, Miller AB, et al. Prostate cancer screening in the prostate, lung, colorectal and ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008; 101: 130–5.
22. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Cliatto S, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360: 1320–8.
23. Schröder FH, Hugosson J, Carlsson S, Tammela T, Määtännen L, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012; 62: 745–52.
24. Bussoni C, Auvinen A, Roobol MJ, Carlsson S, Moss SM, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2015; 68: 885–90.
25. Etzioni R, Guliati R, Toikikov A, Weyer EM, Peron DF, et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. Cancer 2012; 118: 5955–63.
26. Fleshner N, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol 2017; 14: 26–37.
27. Ansurd Godtman R, Holmberg E, Lilja H, Stranne J, Hugosson J. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. Eur Urol 2015; 68: 354–60.
28. Vargas HA, Akin O, Shukla-Dave A, Zhang J, Zakian KL, et al. Performance characteristics of MR imaging in the evaluation of clinically low-risk prostate cancer: a prospective study. Radiology 2012; 265: 478–87.
29. Grenabo Bergdahl A, Wilderång U, Aus G, Carlsson S, Damber JE, et al. Role of magnetic resonance imaging in prostate cancer screening: a pilot study within the Göteborg randomised screening trial. Eur Urol 2016; 70: 566–73.
30. Lilja H, Ulmert D, Björk T, Becker C, Serio AM, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate Kallikreins measured at age 44 to 50 years. J Clin Oncol 2007; 25: 431–6.
31. Vickers AJ, Ulmert D, Sjoberg DD, Bennett CJ, Björk T, 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.
32. Arsov C, Becker N, Hadaschik BA, Hohenfellner M, Herkommer K, et al. Prospective randomized evaluation of risk-adapted prostate-specific antigen screening in young men: the PROBASE trial. Eur Urol 2016; 70: 873–5.
33. Labrie F, Canadas B, Cusan L, Gomez JL, Bélainger A, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1998 Quebec prospective randomized controlled trial. Prostate 2004; 59: 311–8.
34. Kjellman A, Akre O, Norming U, Törnblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. J Urol 2009; 181: 1615–21.
35. Sandblom G, Varenhorst E, Rosell J, Löfman O, Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011; 342: d1539.

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