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European Association of Urology

Platinum Opinion – Guidelines

Early Detection of Prostate Cancer: European Association of Urology Recommendation

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Abstract

Background: The recommendations and the updated EAU guidelines consider early detection of PCa with the purpose of reducing PCa-related mortality and the development of advanced or metastatic disease.
Objective: This paper presents the recommendations of the European Association of Urology (EAU) for early detection of prostate cancer (PCa) in men without evidence of PCa-related symptoms.
Evidence acquisition: The working panel conducted a systematic literature review and meta-analysis of prospective and retrospective clinical studies on baseline prostate-specific antigen (PSA) and early detection of PCa and on PCa screening published between 1990 and 2013 using Cochrane Reviews, Embase, and Medline search strategies.
Evidence synthesis: The level of evidence and grade of recommendation were analysed according to the principles of evidence-based medicine. The current strategy of the EAU recommends that (1) early detection of PCa reduces PCa-related mortality; (2) early detection of PCa reduces the risk of being diagnosed and developing advanced and metastatic PCa; (3) a baseline serum PSA level should be obtained at 40–45 yr of age; (4) intervals for early detection of PCa should be adapted to the baseline PSA serum concentration; (5) early detection should be offered to men with a life expectancy $\geq$10 yr; and (6) in the future, multivariable clinical risk-prediction tools need to be integrated into the decision-making process.
Conclusions: A baseline serum PSA should be offered to all men 40–45 yr of age to initiate a risk-adapted follow-up approach with the purpose of reducing PCa mortality and the incidence of advanced and metastatic PCa. In the future, the development and application of multivariable risk-prediction tools will be necessary to prevent over diagnosis and over treatment.

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1. Introduction

The American Urological Association (AUA) has recently released new guidelines for the early detection of prostate cancer (PCa) [1]. In brief, the new guideline (1) does not recommend prostate-specific antigen (PSA) screening in men <40 yr of age, (2) does not recommend PSA screening in men 40–54 yr of age at average risk, (3) does recommend shared decision making for men 55–69 yr of age, (4) does recommend a screening interval ≥2 yr, and (5) does not recommend PSA screening in men >70 yr of age or in men with a life expectancy of <10–15 yr.

Based on the current evidence in the literature, the European Association of Urology (EAU) has a different recommendation for the early detection of PCa. The updated EAU guidelines do not recommend widespread mass screening for PCa but do strongly recommend early detection in well-informed men [2]. A baseline PSA determination at 40–45 yr of age has been suggested upon which the subsequent screening interval can then be based. Furthermore, the EAU guidelines do not use a specific chronological age as a threshold for screening, but screening in men with a life expectancy >10 yr is recommended independent of chronological age. After reevaluation of the literature, the EAU came to following statements.

2. Statement 1: Early detection of prostate cancer reduces prostate cancer–related mortality

The purpose of screening for PCa is to reduce PCa-specific and overall mortality and to improve men's future quality of life because of the prevention of locally advanced or metastatic disease [3]. PSA screening reduces PCa-related mortality by 21–44% [4,5], but a recent Cochrane analysis states that PCa screening did not significantly decrease PCa-specific mortality when including the results of five randomised trials with a total of 341 342 participants [6]. It was also noted that any reduction in PCa-related mortality might take up to 10 yr, so screening in men with a life expectancy of at least 10 yr might be beneficial. The benefit increases, however, with longer life expectancy.

2.1. Statement 1: Scientific background

Currently, five prospective randomised trials on PCa screening are available, and these include a total of 341 342 participants aged 45–80 yr [6]. All trials involved testing of serum concentrations of PSA, digital rectal examination (DRE) at different intervals, and thresholds for further evaluation. Besides the European Randomised Study of Screening for Prostate Cancer (ERSPC) [4] and the Göteborg randomised population-based PCa screening trial [5], no trials demonstrated a survival benefit for the screening arm. In fact, a meta-analysis of all studies did not demonstrate a significant affection of PCa-specific mortality between men randomised to screening or control (relative risk [RR]: 1.00; 95% confidence interval [CI], 0.96–1.03). However, all of these randomised studies have been too small [7,8], have been criticised for methodologic problems [9,10], or have been inconclusive because of a high rate of contamination [11].

To understand the EAU strategy, one must understand the most important results of the two positive trials. The ERSPC study involved 182 160 men between the ages of 50 and 74 yr, with a predefined core group of 162 388 men aged 55–69 yr. After a median follow-up of 11 yr, the RR reduction of death from PCa was 21% (RR: 0.79; 95% CI, 0.68–0.91; $p = 0.001$) and 29% after adjustment for noncompliance [4]. It must be noted that the cumulative hazard of death from PCa started to separate at approximately 7 yr. Increasing mortality was observed with longer follow-up, such that in men with a follow-up of 10–11 yr, the RR of PCa death was 0.62 (95% CI, 0.45–0.85; $p = 0.003$) in the screening arm (a reduction of 38%). However, it also should be noted that the RR reduction for death from PCa was significant only for men 65–69 yr of age. Besides this significant reduction in PCa mortality, it was demonstrated (1) that a diagnosis of PCa was significantly greater in the screening group (RR: 1.30; 95% CI, 1.02–1.65), (2) that localised PCa was more commonly diagnosed in the screening group (RR: 1.79; 95% CI, 1.19–2.70), and (3) that the proportion of men with locally advanced PCa (RR: 0.80; 95% CI, 0.73–0.87) or aggressive Gleason score 8–10 PCa was significantly lower in the screening group. The numbers needed to be screened and to be diagnosed to prevent 1 PCa-related death were 1055 and 37, respectively.

The ERSPC reached the following major conclusions:

- The benefit of screening becomes more evident as follow-up increases, with a RR reduction of 38% in men with a follow-up of 10–11 yr.
- A reduction in PCa-related mortality must be balanced against potential disadvantages of early detection of PCa (biopsy-related complications, overdiagnosis, overtreatment, and treatment-related complications).
- There was no indication of a mortality reduction in men ≥70 yr of age, so this upper age limit or life expectancy ≥10 yr warrants careful consideration in future screening programmes.

The Göteborg randomised population-based PCa screening trial started in 1995 and included 32 298 men aged 50–64 yr who underwent biannual PSA testing [5]. Men with a PSA serum concentration >3.4 ng/ml between 1995 and 1998 and >2.5 ng/ml thereafter were invited for further workup, including DRE, transrectal ultrasound (TRUS), and laterally directed sextant prostate biopsies. During a median follow-up of 14 yr, the risk of death from PCa in the screening arm was 0.56 (95% CI, 0.39–0.82; $p = 0.002$) compared with the control arm. There was a significant difference between attendees and nonattendees, with an RR for death from PCa of 0.44 (95% CI, 0.28–0.68; $p = 0.0002$) compared with the control group, whereas no benefit in terms of PCa-specific mortality could be observed for nonattendees compared with the control group (RR: 1.05; 95% CI, 0.62–1.78; $p = 0.84$) [12]. PCa incidence was significantly higher in the screening group at 12.7% versus 8.2% for the control group ($p = 0.0001$). Moreover, most of

the cancers diagnosed in the screening group were early stage PCa, and the number of men with advanced PCa was significantly lower in the screening group than in the control group ($p = 0.0003$). These findings correlated with a significantly higher rate of endocrine treatment in the control group than in the screening group (1.8% vs 1.0%). In contrast, diagnosis of PCa did not automatically result in surgically radical treatment and overtreatment. About 40% of men diagnosed with PCa in the placebo arm were placed on active surveillance protocols. The numbers needed to be screened and to be diagnosed to prevent 1 PCa-related death were 293 and 12, respectively.

Several factors might have contributed to the much higher mortality reduction compared with ERSPC and other studies. First, patients in the Göteborg study were much younger (median age: 56 yr vs >60 yr), and therefore the probability of having locally advanced and incurable PCa was less likely. Second, the PSA threshold of 3.0 ng/ml was lower. Third, the screening was 2 yr compared with 4 yr in ERSPC. Fourth, the biopsy rate was much higher in cases of a positive screening result (93% vs 30–40% in the Prostate, Lung, Colorectal and Ovarian [PLCO] trial). Finally, the follow-up in the Göteborg study was much longer than in ERSPC and PLCO.

The Göteborg study reached the following major conclusions:

- Most of the benefit from screening occurs after 10 yr of follow-up.
- PSA screening in all men ≥70 yr of age appears to be questionable.
- Early diagnosis of PCa does not necessarily result in overtreatment but enables a risk-adapted therapeutic approach, with the majority of men being eligible for active surveillance.
- Screening might result in the detection of fewer locally and systemically advanced PCa cases, which enables less aggressive treatment with fewer side effects [13].
- PSA screening might result in a substantial risk of overdiagnosis and necessitates careful identification of cohorts that benefit most from screening when balancing the advantages and the harms.

Based on the findings of both clinical trials, it is evident that PSA testing and early detection reduce death from PCa, but both trials raise concerns that screening programmes in an unselected male population are associated with a substantial degree of overdiagnosis and subsequent overtreatment. Consequently, it is necessary to identify clinically relevant risk factors for PCa that can stratify men by their risk of future clinically apparent PCa.

3. Statement 2: Early detection of prostate cancer reduces the risk of being diagnosed and developing advanced and metastatic prostate cancer

The risk of being diagnosed with metastatic PCa was reduced by 30% and 48.9% in the ERSPC and the Göteborg branch of ERSPC, respectively, after a follow-up of 12 yr and 10 yr, respectively [14,15]. In the Göteborg branch of ERSPC, 24 of 810 men (2.96%) in the screening arm and 47 of 442 men (10.6%) in the control arm were diagnosed with metastatic PCa. Despite the significant risk reduction, it has to be considered that the number of events is low and that a 1.83-fold increased risk of being diagnosed with PCa in the screening arm must be considered.

In the ERSPC, a total of 666 men were diagnosed with metastatic disease after a median follow-up of 12 yr (256 cases and 410 cases were identified in the screening and control arms, respectively). The cumulative incidence of metastases was statistically significant at 0.67% and 0.86% ($p < 0.001$), respectively, which translates into an RR reduction of 30% (95% CI, 0.60–0.82; $p < 0.001$). The absolute risk reduction was 3.1 cases per 1000 men randomised. It became evident that the risk of developing metastatic disease started to diverge at years 4 and 5 after initiation of screening. The risk of being diagnosed with PCa increased to 37.6 per 1000 men in the screening arm, which was 55.6% higher than the control arm, indicating a fair amount of overdiagnosis. The number needed to invite (NNI) and the number needed to diagnose to avoid 1 case of metastatic disease were 328 and 12, respectively.

Recently, Etzioni et al. [16] tried to quantify the link between PSA screening and the decline in distant metastases incidence through the use of a single-cohort microsimulation model. The adapted model simulates life histories for the US population of men aged 50–84 yr. The authors describe a constant incidence of locally advanced disease at the 1987 level in the absence of screening. With the use of screening, the distant stage incidence decreased from 77 cases per 100 000 men in 1990 to 37 cases per 100 000 men in 2000, resulting in an 80% drop in the incidence of advanced disease.

The risk of overtreatment is not necessarily increased if patients are informed about the treatment options appropriately. As already outlined, about 40% of all men identified with PCa in the Göteborg study were followed by active surveillance. In another study, Kim et al. [17] reported that about 96% of all men with screen-detected low-risk PCa are candidates for active surveillance, resulting in an individualised, risk-adapted approach.

4. Statement 3: A baseline serum prostate-specific antigen level should be obtained at 40–45 yr of age

A baseline serum PSA level ≥1.0 ng/ml at 45 yr of age and a baseline serum PSA level ≥2.0 ng/ml at 60 yr of age are associated with a significantly increased risk of PCa-related mortality and diagnosis of advanced or metastatic disease even 25 yr after the initial PSA was obtained.

4.1. Statement 3: Scientific background

The median PSA serum level and the 95th percentile for healthy men aged 30–49 yr has been reported to range between 0.6 and 0.78 ng/ml [18–20], and it has been shown to be 0.7–1.23 ng/ml for men aged 50–59 yr. The median PSA level in men aged 60–64 yr and 65–69 yr is about

1.20 ng/ml and 1.43 ng/ml, respectively [19,20]. Several studies have indicated that a baseline PSA level above the median PSA for age group might be a better indicator of PCa development than other clinical risk factors, such as race, family history, or suspicious DRE [20–24].

Loeb et al. [20] reported on 13 943 men aged <60 yr in a PCa screening programme from 1991 to 2001. Age, family history, race, DRE, and baseline PSA were recorded at study entry. In addition, PSA level at diagnosis of PCa, PSA velocity, clinical stage, and biopsy Gleason score were documented. It turned out that the baseline PSA level was a significant predictor of PCa diagnosis. The median baseline PSA level was significantly higher for men aged 40–49 yr who were diagnosed with PCa than those without PCa (2.7 ng/ml vs 0.7 ng/ml; $p < 0.0001$). The same finding holds true for men aged 50–59 yr (2.4 ng/ml vs 0.9 ng/ml; $p < 0.0001$). Men aged 40–49 yr with a baseline PSA level between 0.7 and 2.5 ng/ml had a 14.6-fold increased risk of PCa, whereas the risk increased 7.6-fold in men aged 50–59 yr with a baseline PSA level of 0.9–2.5 ng/ml. The baseline PSA level in men <60 yr of age was also associated with a significantly higher frequency of non–organ-confined PCa, Gleason score ≥7, lymph node metastases, biochemical recurrence, and PCa-specific mortality.

The Västerbotten Intervention Project identified 654 incident cases of PCa, for which 540 men had a prospectively collected blood sample for PSA measurements available [25]. For better statistical analysis of subgroups, the patients were divided into one group aged <59 yr and one group aged >59 yr at the time of recruitment. For each PCa patient, two controls were randomly selected who were alive and free of PCa. The median PSA concentration was 3.6 ng/ml in cases versus 1.1 ng/ml in controls. The mean time between venipuncture and diagnosis of PCa was 7.1 ± 3.7 yr. Among men with a baseline PSA concentration <1.0 ng/ml, only 3.9% were diagnosed with PCa, and only 1.2% of men developed high-risk PCa. Compared with this reference group, men with PSA serum concentrations between 1 and 2 ng/ml had an odds ratio (OR) of PCa diagnosis of 9.1 (95% CI, 5.0–16.5), men with PSA serum levels of 2–3 ng/ml had an OR of 23.3 (95% CI, 12.3–49.9), and men with PSA serum concentrations of 3–4 ng/ml exhibited an OR of 43.9 (95% CI, 22.1–87.3). Although this longitudinal study could not identify a cut-off value for PSA to predict later PCa diagnosis, it identified a cut-off of 1.0 ng/ml as being associated with a negative likelihood ratio of 0.08, which virtually rules out the development of high-risk PCa in the future.

In a similar approach, Lilja et al. [26] evaluated 21 277 men 33–50 yr of age who had a blood sample drawn between 1974 and 1986 in the Malmö Preventive Project. Because PSA screening is not recommended in Sweden, the cohort represents the natural history of the association between baseline PSA concentration and the development of PCa. The median time between PSA measurement and PCa development was 23 yr for the three groups (any PCa, palpable PCa, and advanced PCa). Among men aged 44–50 yr, 95% and 94% of all PCa cases and advanced PCa cases, respectively, were diagnosed after 60 yr of age. There was a strong and statistically highly significant association between baseline PSA and the later diagnosis of PCa ($p < 0.0005$; area under the curve [AUC]: 0.719; 95% CI, 0.704–0.736). The median PSA was 1.01 ng/l versus 0.62 ng/ml for any PCa, 1.02 ng/ml versus 0.62 ng/ml for palpable PCa, and 1.15 ng/ml versus 0.63 ng/ml for advanced PCa. The long-term risk of being diagnosed with PCa increased significantly from 1–5% for men with PSA <0.5 ng/ml to 8–15% for men with PSA between 0.75 and 1.25 ng/ml; 81% and 69% of all advanced PCa cases were diagnosed in men with PSA levels above the median or in men with PSA in the top tertile. Interestingly, the group of men who developed advanced PCa represented a heterogeneous group of patients, with some being diagnosed with PCa after 75 yr of age and another substantial fraction being diagnosed with PCa before 60 yr of age. The major clinical implications of this finding are (1) that a high-risk group of men with regard to the development of PCa can be identified with a baseline PSA obtained at 40 yr of age and (2) that future biomarkers might identify men who will benefit from immediate treatment and men who can be allocated to active surveillance protocols.

Based on the data of the Malmö Preventive Project, Vickers et al. [27] attempted to develop a strategy for early detection of PCa resulting from the baseline PSA level determined at 40–55 yr of age. The authors identified that the baseline PSA concentrations were significantly associated with the detection of PCa metastases 30 yr later. It was demonstrated that the risk of developing metastases within 15 yr increased 3-fold (1.6%) and 10-fold (5.2%) for men with PSA levels in the highest 10th at 45–49 yr of age and 50–55 yr of age, respectively, compared with men aged 40–44 yr (0.6%). It was also shown conclusively that screening seems to be indicated even in men with PSA serum levels below the median because 28% of men with PCa metastases at a median follow-up of 27 yr exhibited PSA serum concentrations below median. In addition, the authors demonstrated that PCa death was significantly associated with baseline PSA level: 44% of all PCa-related deaths occurred in men with a PSA concentration in the highest 10th of the distribution of serum concentrations at 45–49 and 50–55 yr of age.

Even for men 60 yr of age, the baseline PSA serum concentration is significantly associated with the risk of being diagnosed with PCa at 85 yr of age (AUC: 0.76; 95% CI, 0.71–0.81; $p < 0.001$), of developing PCa metastases at 85 yr of age (AUC: 0.86; 95% CI, 0.79–0.92; $p < 0.001$), and of dying from PCa at 85 yr of age (AUC: 0.90; 95% CI, 0.84–0.96; $p < 0.001$) [28]. These data are derived from a cohort of 1167 men born in 1921 who provided blood samples in 1981–1982 that were matched to cancer registries updated in 2006 when these men had either died or reached their 85th birthday. It was shown that men with a baseline PSA ≥2 ng/ml had a 26-fold increased risk of dying from PCa than men with PSA serum levels <2.0 ng/ml. Considering a PSA of 2.0 ng/ml as a potential risk-adapted threshold for screening purposes, 62% of all PCa cases and 80% and 90% of PCa metastases and PCa-related death, respectively, would have been predicted correctly.

Recently, a case control study nested within the Danish Diet, Cancer and Health cohort measured PSA in the serum

of 27 179 men aged 50–64 yr at the time of enrolment between 1993 and 1997 [29]. In total, 911 PCa cases were identified 14 yr after cohort entry, and the cases were matched with cancer-free controls. Baseline total PSA and the free-to-total PSA ratio were significantly associated with the risk of developing PCa up to 14 yr later. The incidence rate ratio for PCa was 150 (95% CI, 72–310) among men with a total PSA in the highest quintile. Furthermore, the risk of developing aggressive PCa (cT3a or higher, Gleason score ≥8, or N1 or M1) was significantly elevated for men with PSA levels in the highest quintile.

5. Statement 4: Intervals for early detection of prostate cancer should be adapted to the baseline prostate-specific antigen serum concentration

Screening intervals should be 2–4 yr for men with PSA serum concentrations >1.0 μg/l at 45–59 yr of age, whereas it could be up to 8 yr in men with PSA serum concentrations below this threshold value [30,31]. Using this approach, it will be possible to reduce the potential harms of screening by targeting a high-risk group of men. On the one hand, shorter intervals are preferable to avoid the risk of missing significant cancers. On the other hand, longer intervals might be preferable to reduce the substantial risk of overdiagnosis and reduce costs associated with frequent screening [32–34].

5.1. Statement 4: Scientific background

In an analysis of 1703 men aged 55–65 yr with a PSA level ≤1.0 ng/ml who underwent two screening rounds in the Rotterdam section of the ERSPC, only 8 PCa cases were diagnosed at 8 yr, resulting in an overall PCa detection rate of 0.47% [30]. These data are similar to findings of other groups that reported a PCa detection rate of 0.08% and 0.9% after follow-up of 4 yr and 7.6 yr, respectively [31,33]. Based on these data, a screening interval of approximately 8 yr seems to be justified in men with a baseline PSA <1.0 ng/ml.

In another subanalysis of the ERSPC, a total of 43 987 men aged 55–74 yr were randomised into the intervention arm between 1993 and 1999 and were compared with a total of 42 503 age-matched controls in Northern Ireland [34]. After a median follow-up of 9.1 yr and 8.8 yr for the intervention and control groups, respectively, PCa mortality increased with increasing baseline PSA, with a minimal absolute difference in PCa-specific mortality of 0.05 per 10 000 person-years in men with a baseline serum PSA of 0.0–1.99 ng/ml and a maximum absolute difference of 8.88 per 10 000 person-years in men with a baseline serum PSA of 10–19.9 ng/ml. These differences are reflected by the NNI and the number needed to treat (NNT) to save one man from PCa death. The NNI and NNT were 24 642 and 724, respectively, in men with a baseline serum PSA <2.0 ng/ml, and they were 133 and 60, respectively, in men with a baseline serum PSA of 10.0–19.9 ng/ml. The benefits of early detection of PCa were minimal in men with a PSA serum concentration <4.0 ng/ml, with a minimal absolute difference in PCa-related mortality of 0.52 per 10 000 person-years, and a high risk of excess incidence, with a rate ratio of 3.66 (95% CI, 3.09–4.33; $p < 0.001$). The benefit was greatest in men with moderately elevated PSA serum levels of 4.0–9.9 ng/ml and 10.0–19.9 ng/ml. Therefore, men with low baseline serum PSA levels do not need to undergo frequent screening at 2- to 4-yr intervals, whereas men with moderately elevated PSA serum concentrations will benefit from the 4-yr screening interval performed in the ERSPC.

Within the ERSPC, the screening intervals differed among centres, with a 4-yr screening interval at the majority of centres and a 2-yr interval in the Göteborg arm [4,5]. During the study period, men in Göteborg had a maximum of six screenings, with a median follow-up of 12 yr, whereas men in Rotterdam had a maximum of three screenings, with a median follow-up of 11.2 yr. It was shown that the screen-detected PCa incidence rate ratio was 3.64 (95% CI, 2.92–4.53) in Göteborg and 3.08 (95% CI, 2.67–3.55) in Rotterdam. In addition, the proportional incidence rate ratio of advanced PCa was 0.40 (95% CI, 0.22–0.71) and 0.69 (95% CI, 0.50–0.96) in Göteborg and in Rotterdam, respectively [35]. The 2-yr screening intervals, therefore, resulted in an RR reduction of PCa-specific mortality of up to 44% and an RR reduction of advanced PCa of up to 43%. However, it has to be recognised that the diagnosis of PCa and the incidence of low-risk PCa also increased significantly with the biannual screening, leading to potential overdiagnosis and overtreatment. This study was the first to demonstrate that some men need more intense screening than others, making the development of individualised screening programmes necessary.

According to age-specific PSA profiles, 73% and 59% of men aged 45–49 yr and 51–55 yr, respectively, exhibit PSA serum concentrations below the suggested threshold level. In men aged 60–64 yr and 65–70 yr, the median PSA concentrations are 1.20 and 1.43 μg/l, respectively, so the threshold levels have to be adapted accordingly [28]. A PSA serum concentration ≥2.0 ng/ml is associated with a 26-fold increased risk of dying from PCa, so this threshold value might be used for men ≥60 yr of age [28]. Based on the data of the Malmö Preventive Project [26,27], it seems reasonable to use a PSA serum concentration ≤1.0 μg/l as a threshold for more intensive versus less intensive screening in men <60 yr of age.

The risk of PCa-related metastases within 25 yr of PSA testing is expected to be no higher than 0.4%, whereas it increases to 7.61% and 4.02% if the PSA concentration is in the highest 10th and the highest quarter, respectively, for men aged 45–49 yr [27]. The cumulative incidence of metastases within 25 yr increases to 11.44% and 6.20% if the PSA concentration is in the highest 10th and the highest quarter, respectively, for men aged 51–55 yr. In addition, the cumulative incidence of death from PCa is significantly associated with baseline PSA level. The risk of death is 0.55% in men with a PSA below median at 45–49 yr of age and increases to 5.14% and 2.67% at 25 yr if the PSA serum concentration is in the highest 10th and the highest quarter, respectively. Similarly, the risk of PCa-related death increases from 0.80% in men with a PSA below median to

9.03% and 5.07% if the PSA is in the highest 10th and the highest quarter, respectively.

6. Statement 5: Prostate-specific antigen screening should be offered to men with a life expectancy of ≥10 yr

The current EAU guidelines on the diagnosis and treatment of PCa recommend screening in men who have a life expectancy ≥10 yr [2]. There is limited evidence of the effect of screening for PCa in elderly men. A recent analysis suggests that early detection of cancer in men >70 yr of age might not be cost-effective [36].

6.1. Statement 5: Scientific background

Bergdahl et al. [37] analysed the incidence of PCa in 13 423 men who participated in the Göteborg randomised screening trial and who were 69 yr of age when they received the last invitation for screening. The median follow-up after termination of screening was 4.8 yr in the screening arm and 4.9 yr in the control arm. A total of 173 and 371 PCa cases were diagnosed in the screening and control arms, respectively. A marked stage shift towards advanced-, intermediate-, and high-risk PCa was shown with increasing time intervals from termination of screening; 139 of 173 detected PCa cases (80.3%) were intermediate-risk tumours and 286 of 371 detected PCa cases (77.1%) were high-risk tumours and therefore represented significant disease with a need for treatment.

In another study, the long-term natural history of untreated, low-risk PCa was evaluated in a cohort of 223 men diagnosed between 1977 and 1984 and followed until 2010 [38]. A total of 90 patients (40.3%) progressed to locally advanced disease, and 18% of men progressed to metastatic disease. The mean time until development of metastases and PCa death was 9.2 yr and 9.5 yr, respectively; 53.5% and 24.1% of patients who were aged ≤70 yr and >75 yr at the time of diagnosis experienced local progression, respectively, and 24% and 9.2% of the men aged ≤70 yr and >75 yr died from PCa. In multivariate analysis, the RR of death from PCa rose significantly after 5 yr of follow-up in men aged <70 yr with Gleason score 7–10 disease and increasing tumour stage. The RR of dying from PCa was 0.44 (95% CI, 0.15–1.30), 0.29 (95% CI, 0.06–1.49), and 0.19 (95% CI, 0.02–1.70) after a follow-up period of 5–9 yr, 10–14 yr, and 15–20 yr, respectively. The study demonstrates that local progression and death from PCa can develop even in elderly men with organ-confined disease at the time of diagnosis, so early detection and active treatment seems to be justified in men with a long life expectancy independent of chronological age. The only drawback of the study is the fact that no correlation between outcome and PSA at diagnosis could be made because all patients were identified in the pre-PSA era.

A recent analysis of the Cancer of the Prostate Strategic Urologic Research Endeavour database revealed that the likelihood of being diagnosed with high-risk PCa by Cancer of the Prostate Risk Assessment classification 6–10 increased significantly with increasing age ($p < 0.001$) [39]. Of these men, 26% of those aged ≥75 yr presented with high-risk disease at the time of diagnosis. Overall and PCa-specific survival were associated with age using univariate analysis, but when controlling for each treatment modality alone (radical prostatectomy, external-beam radiation therapy, brachytherapy, androgen-deprivation therapy, watchful waiting), neither age nor comorbidity was an independent predictor of mortality. In a similar approach, Albertsen et al. [40] conducted a 10-yr competing risk analysis of 19 639 men aged ≥66 yr with clinically localised PCa who were identified by the Surveillance Epidemiology and End Results programme and who did not receive local therapy. PCa-specific and overall mortality were stratified by patient age, PCa Gleason score, clinical stage, and Charlson Comorbidity Index (CCI). CCI had a negative impact on overall survival, with 60%, 51%, and 41% of men with a CCI of 0, 1, or ≥2, respectively, were still alive after a median follow-up of 6 yr. Depending on age and comorbidity, men without comorbidities and with organ-confined Gleason score 5–7 PCa have a 2–4% probability of dying from PCa within 5 yr after diagnosis, whereas the risk increases to 12–48% in men with significant comorbidities but the same age. These data indicate that not age by itself but rather comorbidities are the major factor that should be considered when discussing screening or treatment of PCa. It seems necessary to consider patient age and comorbidities with the use of validated instruments such as the CCI to assess life expectancy. The CCI has been validated in men with PCa and has been shown to harbour a relatively high predictive accuracy that can be used in daily routine.

7. Statement 6: In the future, multivariable clinical risk-prediction tools need to be integrated into the decision-making process

PSA screening results in a significant reduction in PCa-related mortality, diagnosis, and development of advanced and metastatic PCa [4,5], but there is a substantial risk of overdiagnosis and overtreatment when PSA screening is used with inappropriate frequency. In our daily routines, we need to be able to identify those men who might harbour or develop clinically significant disease and who will benefit from early detection.

Currently, we know that increasing age, ethnicity, and family history represent established risk factors for diagnosis of PCa. To date, PSA is the single most important parameter for identifying men with an increased risk of PCa. To improve the accuracy of PSA screening, we might use multivariable clinical risk-prediction tools that have already been developed but that are used only to a minimal extent in daily routine.

The Prostate Cancer Prevention Trial (PCPT) risk calculator was developed from men recruited in the placebo arm of the PCPT and integrates PSA, PSA velocity, DRE, age, race, biopsy, and family history of PCa. The risk calculator has been externally validated and has been shown to be superior to PSA in predicting PCa diagnosis and distinguishing between low- and high-grade PCa [41,42].

The ERSPC risk calculator includes the AUA symptom score, PSA, TRUS, and DRE to predict the risk of PCa [43]. The risk calculator has been externally validated and was shown to discriminate between the presence and absence of PCa, but it overestimated the risk of a positive biopsy [44]. It was also shown that the ERSPC risk calculator outperforms the PCPT risk calculator for both European and North American cohorts [45].

The Sunnybrook risk calculator includes PSA, percentage of free PSA, age, race, family history, International Prostate Symptom Score, and DRE [44]. The risk calculator predicts the risk of PCa and the presence of high-risk disease with high accuracy and has been shown to outperform the PCPT risk calculator when analysed in a prospective multi-institutional evaluation [42].

Besides risk calculators, clinical parameters to assess the risk of PCa such as new serum or urinary biomarkers might be used in the future to further improve prediction tools. Besides prostate cancer antigen 3 (*PCA3*) and *TMPRSS-2ERG*, specific genetic allele mutations associated with PCa have been identified that might be implicated in prostate carcinogenesis [46,47]. Currently, however, it is unknown how to incorporate these findings in early detection practices.

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Analysis and interpretation of data: Heidenreich, Abrahamsson, Artibani, Catto, Montorsi, Van Poppel, Wirth, Mottet.
Drafting of the manuscript: Heidenreich.
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