



Platinum Priority – Collaborative Review – Prostate Cancer

Editorial by Ian M. Thompson and Donna P. Ankerst on pp. 662–663 of this issue

Risk-Based Prostate Cancer Screening

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Article info

Article history:

Accepted November 15, 2011

Published online ahead of
print on November 24, 2011

Keywords:

Mass screening
Early detection of cancer
Prostate-specific antigen
Prostate neoplasms
Nomograms
Risk factors

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Abstract

Context: Widespread mass screening of prostate cancer (PCa) is not recommended because the balance between benefits and harms is still not well established. The achieved mortality reduction comes with considerable harm such as unnecessary biopsies, overdiagnoses, and overtreatment. Therefore, patient stratification with regard to PCa risk and aggressiveness is necessary to identify those men who are at risk and may actually benefit from early detection.

Objective: This review critically examines the current evidence regarding risk-based PCa screening.

Evidence acquisition: A search of the literature was performed using the Medline database. Further studies were selected based on manual searches of reference lists and review articles.

Evidence synthesis: Prostate-specific antigen (PSA) has been shown to be the single most significant predictive factor for identifying men at increased risk of developing PCa. Especially in men with no additional risk factors, PSA alone provides an appropriate marker up to 30 yr into the future. After assessment of an early PSA test, the screening frequency may be determined based on individualized risk. A limited list of additional factors such as age, comorbidity, prostate volume, family history, ethnicity, and previous biopsy status have been identified to modify risk and are important for consideration in routine practice. In men with a known PSA, risk calculators may hold the promise of identifying those who are at increased risk of having PCa and are therefore candidates for biopsy.

Conclusions: PSA testing may serve as the foundation for a more risk-based assessment. However, the decision to undergo early PSA testing should be a shared one between the patient and his physician based on information balancing its advantages and disadvantages.

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1. Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in men, accounting for 14% (903 500) of total new

cancer cases and 6% (258 400) of total cancer deaths in men in 2008 [1].

PCa has a variable natural history, ranging from indolent to strikingly aggressive with a long preclinical phase. Because we are still awaiting a breakthrough in the

Table 1 – Summary of recommendations for prostate cancer screening

Organization	Year	Recommendation	Notes
European Association of Urology [111]	2011	<ul style="list-style-type: none"> Widespread screening is not appropriate. Offer early detection to well-informed men. Baseline PSA determination at age 40 yr has been suggested on which subsequent screening interval may then be based. Screening interval of 8 yr might be enough in men with initial PSA ≤ 1 ng/ml. Further PSA testing is not necessary in men >75 yr of age and a baseline PSA ≤ 3 ng/ml because of their very low risk of dying from PCa. 	Updates previous recommendation of 2008, which predates the ERSPC and PLCO publications.
American Urological Association [112]	2009	<ul style="list-style-type: none"> Offer early detection to asymptomatic men ≥ 40 yr of age who wish to be screened and who have an estimated life expectancy >10 yr. Future screening intervals should be based on this baseline PSA level. A physician should assess the individual patient's health status to determine the appropriateness of PSA testing at any given age. 	Updates previous recommendation by lowering age to screening from 50 to 40 yr (to obtain baseline).
American Cancer Society [113]	2010	<ul style="list-style-type: none"> Asymptomatic men who have at least a 10-yr life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened. Men at average risk should receive this information beginning at 50 yr of age. African American men and men who have a first-degree relative diagnosed with PCa before age 65 yr should receive this information beginning at age 45 yr. Men with multiple family members diagnosed with PCa before age 65 yr should receive this information beginning at age 40 yr. 	Updates previous recommendation emphasizing informed and shared decision making.
National Comprehensive Cancer Network [114]	2010	<ul style="list-style-type: none"> Offer baseline digital rectal examination and PSA testing at age 40 after providing counseling on the pros and cons of early detection. If African American, if there is a family history of PCa, or if the PSA level is >1.0 ng/ml, repeat annually. Otherwise, repeat at age 45 and annually starting at 50. Screening in men >75 yr should be considered individually. 	Updates previous recommendation by lowering age to screening from 50 to 40 yr (to obtain baseline).

ERSPC = European Randomized Study of Screening for Prostate Cancer; PSA = prostate-specific antigen; PLCO = Prostate, Lung, Colorectal, and Ovary Trial; PCa = prostate cancer.

treatment of advanced disease, earlier detection of clinically significant disease currently seems to afford the best opportunity of stemming the tide. In general, there are two approaches to early detection: screen everyone within a certain age range (eg, breast cancer and cervical cancer) or screen selectively based on risk factors (eg, lung cancer).

For PCa screening, evidence of mortality reduction was shown by prostate-specific antigen (PSA)-based screening in the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the overlapping Göteborg trial [2–4]. Although several associations in Europe and the United States have updated their guidelines regarding PCa screening (Table 1), widespread mass screening is not recommended because the achieved mortality reduction comes with considerable harm such as unnecessary biopsies, overdiagnoses, and subsequent overtreatment [3,5,6]. Therefore, patient stratification with regard to PCa risk and aggressiveness is necessary to identify those men who are at risk and may actually benefit from early detection [7,8]. In other words, a risk-based strategy is necessary to prevent unnecessary PSA testing and widespread overdiagnoses.

With the current screening algorithm applied in the ERSPC, the relative mortality reduction after a median follow-up of 9 yr is modest at 20–30% [2,3]. A recent study from the ERSPC group showed that noncompliance with the screening protocol and aggressive interval cancers were attributed to a significant proportion of the PCa deaths in the intervention arm [9]. With a risk-based strategy, we may improve the screening effect. First, those with intermediate and high risk may be screened with a shorter interval, which may lead to fewer aggressive interval

cancers. Second, the compliance might increase among those at high risk if they were informed of their risk status, resulting in fewer nonattendees after being screened once. This review critically examines the current evidence regarding risk-based PCa screening.

2. Evidence acquisition

To apply a risk-based screening strategy, one must first identify the risk factors. Thus in this review we considered articles that evaluated factors predicting the presence of PCa. It is important to realize that some markers predict the risk of either current or future PCa, and others have predictive value in both cases. We also highlighted some of the most frequently used prediction tools that assess the chance of having PCa.

A search of the literature was performed using the Medline database by combining the following terms: *prostate cancer, diagnosis, screening, risk factors, predictive tools, and nomograms*. A total of 367 records, including original articles, review articles, and editorials, were retrieved. Subsequently, the search results were restricted to the English language, with preference given to articles published within the last 10 yr. In total, 152 articles evaluating risk factors and 42 studies reporting on prediction tools were selected based on title and abstract. Further studies were retrieved based on manual searches of reference lists and review articles. We reviewed the list of references to ensure completeness. The articles with the highest evidence were included, reviewed, and summarized, with the consensus of all the authors of this paper.

3. Evidence synthesis

3.1. Demographics and medical history

3.1.1. Age

The association between increasing age and PCa risk is very strong [10–13]. However, across the relatively narrow age range typically encountered in many screening programs, age may not be an independent predictor of risk. Schröder et al. showed that age (per year or per decade) was not a statistically significant predictor for PCa in men 55–70 yr at the initial screen, unlike PSA, previous negative biopsy (yes or no), and prostate volume, which were predictive [14].

We do not yet have clear evidence of when to start and when to stop screening. In the ERSPC study, mortality reduction after 9-yr follow-up is shown in the age groups 55–59 yr and 65–69 yr but not in the age group 60–64 yr [3]. In contrast, the Göteborg trial showed that the most apparent mortality reduction after 14 yr of follow-up was achieved in men 60–64 yr of age at study entry, although the trial was not powered for such subgroup analysis [4]. These observations suggest that screening benefit for each age group may alter with longer follow-up. Therefore, we do not have a clear idea of when to start screening at this time. As for the upper age cut-off, most programs stop screening at age 70, but there are still men who are diagnosed after age 70 and eventually die from PCa [15].

3.1.2. Ethnicity

Race-related differences in PCa risk may reflect multiple factors, including exposure differences, particularly dietary differences, differences in access to care and detection, and genetic differences. The highest incidence rates for PCa in the world are among African American men. For the period 1988–1992, race-specific US incidence rates ranged from 24.2 per 100 000 for Koreans, 89.0 per 100 000 for Hispanics, 134.7 per 100 000 for whites, and 180.6 per 100 000 for African Americans [16]. African American and Hispanic men commonly are diagnosed at a significantly younger average age (mean: 63.7 and 65.2 yr, respectively) compared with white men (mean: 68.1 yr) [17].

Because of their increased risk of PCa [16] and high-grade disease [18] as well as PCa-specific death [10,19], more intensive screening of African Americans is likely warranted.

3.1.3. Family history

A family history of PCa is an important risk factor for developing the disease. The foremost evidence was demonstrated in two meta-analyses, reporting a relative risk (RR) of approximately 2–3.5 [20,21]. The risk depends on the degree of relatedness and number of affected degrees. Among first-degree relatives, risk was significantly higher for men with an affected brother compared with those with an affected father [20,21].

More recently, Brandt et al. used the nationwide Swedish Family-Cancer Database to estimate age-specific risks of PCa according to the number and type (father or brother) of affected first-degree relatives and according to the relative's age at diagnosis [22]. The study included 26 651

PCa patients of whom 5623 were familial, and therefore it is the largest study of familial PCa published to date. The authors found that the hazard ratios (HRs) of PCa diagnosis increased with the number of affected relatives and decreased with increasing age. The highest HRs were observed for men <65 yr of age with three affected brothers (HR: approximately 23) and the lowest for men between 65 and 74 yr of age with an affected father (HR: approximately 1.8). The pattern of the risk of death from familial PCa was similar to the incidence data, with the highest risk of dying in men with an affected father and two affected brothers (HR: 9.7).

These findings imply that among men with a strong family history (two or more first-degree relatives with PCa diagnosed at <65 yr of age), a heightened surveillance and a lower biopsy threshold are warranted because of a HR >6.5 [22]. Conversely, we must remember that most of the studies just mentioned were performed before or at the beginning of the PSA era; therefore, family history may become less predictive because most cancers today are screen detected.

3.1.4. Comorbidity

Comorbidity has been associated with incident and fatal PCa, but the exact role of obesity [23], diabetes [24–26], and metabolic syndrome [27–29] in the development and progression of PCa and PCa-specific mortality has not been elucidated.

Interestingly, a recent analysis of the Prostate, Lung, Colorectal, and Ovary Trial demonstrated benefit from screening only in men in good health [30]. In a study of 1482 men diagnosed with nonmetastatic PCa, a two-fold increase in other-cause mortality was shown with each point increase in the Charlson score [31]. Another competing risk analysis among 19 639 men diagnosed with localized PCa reported that, in general, a higher comorbidity score is associated with higher overall mortality and lower PCa-specific mortality [32]. Altogether, these findings may suggest that PSA screening is less effective among men with high comorbidity scores.

3.1.5. Previous negative biopsy

A previous negative biopsy is associated with a lower risk of a subsequent positive result for men with the same PSA level, with a greater number of negative biopsies decreasing the risk [33]. It is important to recognize that men who undergo biopsy are typically at increased risk of PCa by definition because the trigger for biopsy is usually an increased PSA and/or an abnormal digital rectal examination (DRE). Thus, although a previous negative biopsy lowers risk compared with no previous biopsy, these men may still have a risk greater than those without an indication for biopsy and therefore can be considered as a population of men at increased risk for PCa [34,35].

3.2. Prostate-specific antigen and clinical risk factors

3.2.1. Prostate-specific antigen

The clinical usefulness of PSA as a marker for PCa was described in the early 1990s [36,37]. Catalona et al. showed that serum PSA with a cut-off value of 4.0 ng/ml was useful

for screening of PCa [36]. Six years later, the same group suggested a PSA cut-off of 2.5 ng/ml, which was widely accepted after demonstrating a detection rate of PCa in the PSA range 2.5–4.0 ng/ml of 22% [38]. Data from the Prostate Cancer Prevention Trial (PCPT) showed there is no cut-off of PSA in which sensitivities and specificities are reasonably matched but rather a continuum of PCa risk at all values of PSA. If one considers a biopsy Gleason score >7 as a parameter of aggressiveness, cut-off values of 4 and 2 ng/ml would miss 59.6% and 24.4% of such lesions, respectively [39].

Over the years, PSA has evolved as a useful marker for assessing the risk of future PCa. Table 2 summarizes the studies linking PSA and the subsequent risk of developing PCa. The initial observation was made by Stenman et al. [40]. Based on 44 men with PCa selected among 21 172 Finnish men, the authors reported associations between baseline PSA and the risk of clinically detected cancer within 6–10 yr.

Gann et al. measured PSA levels in entry blood samples from the Physicians' Health Study and analyzed 366 men who eventually were diagnosed with PCa and 1098 controls. Concentrations were also found to be raised 5–6 yr before diagnosis among the 366 men with palpable PCa [41].

More recently, data from the Baltimore Longitudinal Study of Aging showed that a PSA greater than the age-adjusted median in men 40–60 yr of age was associated with a RR of 3.6 of being diagnosed with PCa at a median follow-up of 13 yr [42].

Studies from Washington University showed similar results. Antenor et al. reported that a baseline PSA greater than the age-adjusted mean was associated with a RR of 22 for PCa during a 10-yr period in men 40–49 yr and a RR of 12 in those 50–59 yr [43]. Loeb et al. found that among men in their 40s who were at risk and being screened for PCa, those with a PSA of 0.7–2.5 ng/ml were at a 14.6-fold higher risk of being diagnosed with PCa within 10 yr compared with those

Table 2 – Prostate-specific antigen and subsequent risk of developing prostate cancer

Study	Study design	No. of men	Age at baseline PSA, yr	No. of cases	Results
Stenman et al. [40]	Nested case control	21 172	45–84	44	At a specificity of 92% with a PSA cutoff of 2.5 µg/l, 95% of the cancers developing within the first 5 yr and 52% developing in 6–10 yr tested positive.
Gann et al. [41]	Nested case control (Physicians' Health Study)	22 071	40–84	366	With a cut-off for PSA of 4.0 ng/ml, sensitivity for the entire 10-yr follow-up was 46%. Sensitivities for detection of total, aggressive, and nonaggressive cancers occurring in the first 4 yr were 73%, 87%, and 53%. Overall, specificity was 91%.
Fang et al. [42]	Prospective study (Baltimore Longitudinal Study of Aging)	796	40–60	88	The 25-yr disease-free probability for men 40–49.9 yr was 89.6% and 71.6% when the PSA level was less than and greater than the median, respectively. The 25-yr disease-free probability for men 50–59.9 yr was 83.6% and 58.9% when the PSA level was less than and greater than the median, respectively.
Antenor et al. [43]	Prospective study (Washington PSA study)	26 111	40–60	2122	Men 40–49 yr with initial PSA above the median (0.7 ng/ml) were at a 22-fold higher relative risk for PCa than men with initial PSA below the median. In men 50–59 yr with initial PSA above the median (0.9 ng/ml), the relative risk of cancer detection was 12-fold higher.
Loeb et al. [44]	Prospective study (Washington PSA study)	13 943	40–60	661	A baseline PSA level between the median and 2.5 ng/ml was associated with a 14.6-fold and 7.6-fold increased risk of PCa in men 40–49 and 50–59 yr, respectively. A greater baseline PSA value was also associated with a significantly greater PSA velocity, more aggressive tumor features, a greater biochemical progression rate, and a trend toward a greater cancer-specific mortality rate.
Lilja et al. [45]	Nested case control (Malmö Prevention Project)	21 277	33–50	1312	At a median follow-up of 23 yr, baseline PSA measured in men ≤50 yr was strongly associated with subsequent PCa (AUC: 0.72; AUC for advanced cancer: 0.75).
Vickers et al. [48]	Nested case control (Malmö Prevention Project)	1167	60	126	PSA at 60 yr of age was associated with PCa metastasis (AUC: 0.86) and death from PCa (AUC: 0.90). Ninety percent of deaths from PCa occurred in men with concentrations in the top quarter (>2 ng/ml). Conversely, men 60 yr of age with concentrations at the median or lower (≤1 ng/ml) had 0.5% risk of metastasis by 85 yr of age and 0.2% risk of death from PCa.
Roobol et al. [51]	Prospective study (ERSPC)	1327	55–65	3	In men with an initial PSA ≤1.0 ng/ml, 8 cancers were detected based on 2344 subsequent PSA determinations and a PSA ≥3.0 ng/ml as biopsy threshold in an 8-yr period after the initial screening.
van Leeuwen et al. [52]	Observational study	86 484	55–74	5861	Using men with a PSA <2.0 ng/ml as reference, men in the intervention arm of the ERSPC with a PSA of 2.0–4.0 ng/ml had a 6.8-fold risk of being diagnosed versus the 3.7-fold risk in the clinical population in Northern Ireland. For PSA groups 4.0–10.0 and 10.0–20.0 ng/ml, the rate ratios were 12.6 versus 8.6 and 21.7 versus 21.5, respectively.

PSA = prostate-specific antigen; PCa = prostate cancer; AUC = area under the curve; ERSPC = European Randomized study of Screening for Prostate Cancer.

with a baseline PSA <0.7 ng/ml (the median). This risk was 7.6-fold higher in men in their 50s with a PSA of 0.9–2.5 ng/ml compared with those with a PSA of 0.9 ng/ml (the median) [44].

Several studies from the Malmö Preventive Project (MPP) also demonstrated the use of PSA to stratify risk. A single PSA at or before age 50 predicts clinically significant PCa up to 30 yr later [45–47]. Lilja et al. examined 21 277 men from the MPP, 33–50 yr of age at the time of participation, and reported a strong association of baseline PSA with subsequent PCa and advanced cancer (area under the curve [AUC] 0.72 and 0.75, respectively). Based on their findings, the authors suggest that men with PSA levels below the median (approximately 0.6 ng/ml) might be expected to benefit little from subsequent annual or even biennial PSA checkups. However, as mentioned in the article, there is insufficient data to suggest that these men need no further screening [45].

Vickers et al. observed that PSA level at age 60 predicts a lifetime risk of clinically detected PCa, metastasis, and death from the disease [48]. The authors reported that although only a minority of the men with a PSA >2 ng/ml develop fatal PCa, 90% (78–100%) of deaths from PCa occurred in these men. Conversely, men age 60 with PSA at the median or lower (≤ 1 ng/ml) were unlikely to have clinically relevant PCa (0.5% risk of metastasis by age 85 and 0.2% risk of death from PCa).

Data from the ERSPC showed similar association between baseline PSA and risk of having (clinically significant) PCa during follow-up [14,49–52]. Based on 1327 men with an initial PSA ≤ 1.0 ng/ml and 2344 subsequent PSA determinations, Roobol et al. found that a 8-yr screening interval instead of 4 yr would lead to a considerable decrease in the number of screening visits, with a minimal risk of missing aggressive cancer at the curable stage [51].

In a recent study comparing the intervention arm of the ERSPC with the population in Northern Ireland, where screening is not routinely performed, van Leeuwen et al. reported a number needed to treat of 724 for men who had a PSA level of 0.0–1.9 ng/ml; the number needed to treat was 60 for men with a PSA level of 10–19.9 ng/ml. In men with a baseline PSA of 0.0–1.9 ng/ml, the authors showed only minor profit in PCa-specific mortality of only 0.05 per 10 000 person-years in favor of the screened men [52].

There are some arguments against an early PSA test (before age 50). First, it is unknown how the recommendations from the MPP will be implemented in routine practice in terms of compliance. For example, men with a PSA below the median at ages 44–50 yr and who are asked to return for screening around ages 55–60 may experience the screening interval of 10 yr as too long. It is quite possible for these men to have unnecessary tests during that interval due to the need for self-reassurance [53]. However, men may have a false sense of security if they decide not to return for a repeat screen because they are told to be at low risk initially, although 19% of men with advanced PCa in the MPP had an initial PSA below the median at ages 44–45 [45]. Considering what we know about the natural history of early PCa, it must at present be considered uncertain if and at what time potentially lethal cancers can be detected in a curable stage.

Second, information on PSA values at certain ages and their prediction of aggressive PCa later can be used to decide for whom screening should be focused, but other, preferably prospective, data are required to design a screening program. We need to determine how to deal with these findings in terms of applying further diagnostic steps and follow-up schemes. Nevertheless, PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of PCa to date [7,14,54].

3.2.2. Digital rectal examination

Catalona et al. reported that DRE in conjunction with PSA enhanced early detection of PCa [55]. Men with a positive DRE-driven biopsy may more often present with poorly differentiated PCa [56]. A possible explanation may be ascertainment bias because men with an abnormal/suspicious DRE are more likely to be biopsied.

However, it is important to note that in routine clinical practice, men with a suspicious DRE are typically candidates for prostate biopsy. Therefore, DRE has limited value as a predictor of future risk because it typically triggers a biopsy.

3.2.3. Prostate volume

Several studies have suggested a correlation between high-grade cancers and men with smaller prostates [57–59]. A prostate volume less than approximately 40 cm³ has been proposed to identify an increased risk of developing future PCa [57,60]. However, in clinical practice, prostate volume might be a difficult variable to measure and therefore seems to have a limited role in screening purposes.

Interestingly, in a very recent study, Roobol et al. assessed a new risk calculator incorporating prostate volume based on DRE instead of ultrasound, and they found little difference between the new and the original model. The AUCs for predicting significant PCa were 0.85 in the DRE-based risk calculator and 0.86 in the original ultrasound-based risk calculator [61]. Replacing ultrasound measurements by DRE estimates may therefore enhance implementation of prostate volume into risk stratification in routine practice.

3.2.4. Prostate-specific antigen velocity

PSA velocity has been suggested to be useful in distinguishing men with and without PCa [62,63] and in identifying men with clinically significant disease [64,65] and men at risk of having life-threatening PCa [66,67]. Several studies from the D'Amico group reported that men with a PSA velocity >2.0 ng/ml during the year before the diagnosis had a significantly higher risk of dying from PCa [68,69].

However, the apparent predictive value of PSA velocity might simply reflect that PSA and PSA velocity are highly collinear [70]. Analyses in prospective studies showed that PSA velocity does not appear to add diagnostic value for PCa detection beyond that of a single PSA in the setting of screening [18,71–75].

3.2.5. Markers related to prostate-specific antigen

A number of potential PSA subforms have been identified that might provide additional predictive value in determining the risk of PCa, such as free PSA, BPSA (benign PSA), and

p2PSA ($[-2]proPSA$) [76]. However, it is most unlikely that a single biomarker will be able to identify men at risk. Therefore, several authors have examined the predictive value of combinations of PSA molecular subforms. In a prospective multicenter study including 892 men with a PSA of 2–10 ng/ml, Catalona et al. investigated the relationship of serum PSA, free-to-total PSA, and PHI (Prostate Health Index = $[p2PSA/free\ PSA] \times \sqrt{PSA}$) with biopsy results. The authors reported that at 80–95% sensitivity, the specificity (16% and 45%, respectively) and AUC (0.70) of PHI exceeded those of PSA and free-to-total PSA. An increasing PHI was associated with a 4.7-fold increased risk of PCa and a 1.61-fold increased risk of aggressive PCa (greater than or equal to Gleason score 4 + 3) [77]. Other authors showed similar results [78–80].

Next to PSA subforms, reports suggest that human kallikrein-related peptidase 2 (hk2), a secreted serine protease from the same gene family as PSA [81], could be more strongly associated with PCa than PSA [82–84]. A number of studies from the group of Vickers and Lilja showed that combining a kallikrein panel including hk2 could substantially reduce the number of unnecessary prostate biopsies [85–87].

Although some of these (combinations of) PSA-related markers are promising, further research is needed to determine whether these are valuable in assessing the long-term risk of PCa. In a recent study, combining multiple kallikrein markers into a multivariate model did not improve the long-term predictive accuracy of PSA for all men, although enhancements were observed when focusing on men with increased PSA [45].

3.3. Other risk factors

Since the identification, molecular characterization [88], and commercialization [89] of the prostate cancer gene 3 (PCA3), numerous studies have been published to investigate the

performance of the PCA3 test as a prebiopsy diagnostic test and to compare its performance with the serum PSA test [90]. To date, the PCA3 test is not capable of replacing the PSA test in clinical practice; it may, however, improve the diagnostic accuracy in addition to standard risk factors. Nevertheless, an appropriate cut-off level with acceptable performance characteristics is hard to define [90,91]. There is no evidence of the long-term predictive value of PCA3 in assessing future PCa.

Some genetic markers showed promising results and may become important in risk prediction in the future [92,93]. However, the influence of single nucleotide polymorphisms, such as the KLK3, on cancer risk has been disputed [94,95].

Studies of protein-based and DNA-based urinary markers on their potential use for assessing PCa risk have produced conflicting results [96]. These markers are not routinely examined. Prospective studies in a multivariate setting, including larger sample sizes and avoiding attribution bias caused by preselection on the basis of serum PSA, are required.

3.4. Prediction tools

Studies of multivariate prediction tools for assessing *future* risk of PCa are lacking, and therefore we discuss some of the most frequently used tools predicting the presence of *current* PCa (Table 3). These tools require PSA and therefore usually aim at reducing unnecessary biopsies and over-diagnoses. Their strength is that they can provide predictions that are evidence based and at the same time individualized. With multivariate risk calculators, it is possible to identify men at increased risk of having PCa and therefore are candidates for biopsy [97]. Screening is obviously inseparable from biopsy because there is no point in screening if there are no consequences for screen-positive participants.

Table 3 – Overview of most frequently used risk calculators

Risk calculator	Site	No. of patients	Characteristics of patients	Mean No. of cores	Cancer detection, %	Variables used in model	Accuracy in model	No. of external validations and their references	Accuracy in external populations
PCPT	Multicenter United States	2219	PSA ≤ 3.0 ng/ml; age ≥ 55 yr; many men likely to have been previously screened	6	21.9	PSA, family history, outcome of DRE, and prior biopsy	0.70	7 [98–103]	0.57–0.74
ERSPC	Rotterdam, The Netherlands	3616	Age 55–75 yr; unscreened men	6	24.5	PSA, outcome of DRE, TRUS volume and outcome, and prior biopsy	0.79	2 [107,108]	0.71–0.78
Step 4 and step 5		2896	Previously screened (step 4) and biopsied (step 5)	6	18.9		0.68	3 [105–107]	0.71–0.80
Sunnybrook	Canada	3108	Referred population, PSA ≤ 50	8	42.0	Age, ethnicity, family history, AUA symptom score, PSA, %fPSA, DRE	0.74	1 [103]	0.67

PCPT = Prostate Cancer Prevention Trial; PSA = prostate-specific antigen; DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer; TRUS = transrectal ultrasound; AUA = American Urological Association; %fPSA = percent free PSA.

3.4.1. Prostate Cancer Prevention Trial risk calculator

The PCPT risk calculator (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>) depends on PSA, family history, outcome of DRE, and prior biopsy [18]. The original study reported an AUC of 0.70 for the calculator, slightly higher than the 0.68 reported for PSA alone [18]. One of the reasons for this small size of benefit may be the impact on the predictive value of PSA level on systematically biopsied patients, as opposed to the use of a cut-off level. The omission of prostate volume may explain the modest increase in AUC observed over PSA alone.

The PCPT risk calculator has been validated in external populations, with accuracies between 0.57 and 0.74 [98–103]. Because the PCPT was based on an unreferred population, caution should be used when applying the risk calculator to counsel patients referred for suspicion of PCa because it underestimates the risk of high-grade disease [100]. In addition, Nguyen reported lower accuracy in contemporary screened men with extensive biopsy schemes [101].

3.4.2. European Randomized Study of Screening for Prostate Cancer risk calculator

The ERSPC risk calculator comprises six steps (based on six different logistic regression models) and is Internet based (www.prostatecancer-riskcalculator.com) [8,104]. Step 3 estimates the chance of positive biopsy in previously unscreened, step 4 previously screened but not biopsied, and step 5 previously screened and biopsied men, according to PSA, ultrasound-assessed prostate volume, outcome of DRE, outcome of transrectal ultrasound, and prior biopsy status [8,104]. Applying threshold for prediction PCa may result in a considerable reduction of unnecessary biopsies at both initial and repeat screening [8].

Studies of external validation of the ERSPC risk calculator reported AUCs between 0.71 and 0.80 [105–108]. Based on Swedish and Finnish cohort of ERSPC, van Vugt et al. reported that the calculator discriminated well between those with and without PCa among initially screened men but overestimated the risk of a positive biopsy [108]. In head-to-head comparisons, the ERSPC risk calculator outperformed the PCPT model [105–107]. Although based on the European population, validation in referred patients from a North American cohort showed that the ERSPC risk calculator (AUC: 0.71) was superior to the PCPT model (AUC: 0.63) and PSA (AUC: 0.55) [107].

3.4.3. Sunnybrook risk calculator

The Sunnybrook risk calculator (http://sunnybrook.ca/content/?page=OCC_prostateCalc), combining age, family history of PCa, ethnicity, urinary voiding symptom score, DRE, PSA, and percent free PSA, reached an AUC of 0.74 for any PCa and 0.77 for high-grade cancer, significantly greater than the conventional screening method of PSA and DRE only (0.62 for any cancer and 0.69 for high-grade cancer) [109].

In a prospective head-to-head comparison in 2130 patients who underwent a prostate biopsy, Nam et al. demonstrated that the Sunnybrook calculator performed better than the PCPT model (AUC 0.67 vs 0.61 for any cancer;

0.72 vs 0.67 for predicting aggressive disease) [103]. However, the decision curve analysis [110] carried out in the study demonstrated that neither calculator was of clinical benefit because of it does not help decide which probability threshold should be considered acceptable [103].

4. Conclusions

To date, PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of developing PCa. Especially in men with no additional risk factors, PSA alone provides an appropriate marker up to 30 yr into the future. After assessment of an early PSA test, the screening frequency may be determined based on individualized risk. Although retrospective data strongly point toward the potential of risk-stratifying men, outcomes such as unnecessary testing, overdiagnosis, and mortality reduction remain unknown, and an individualized follow-up scheme after a single PSA needs to be determined. The decision to undergo early PSA testing should be a shared decision between the patient and his physician based on information balancing its advantages and disadvantages. A limited list of additional factors such as age, comorbidity, prostate volume, family history, ethnicity, and previous biopsy status have been identified to modify risk and are important for consideration in routine practice.

In men with a known PSA, risk calculators may hold the promise to identify those who are at increased risk of having PCa and are therefore candidates for biopsy.

Author contributions: Xiaoye Zhu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zhu, Roobol, Schröder, Vickers.

Acquisition of data: Zhu.

Analysis and interpretation of data: Zhu.

Drafting of the manuscript: Zhu.

Critical revision of the manuscript for important intellectual content: Zhu, Albertsen, Andriole, Roobol, Schröder, Vickers.

Statistical analysis: Zhu.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Schröder, Roobol.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Peter C. Albertsen is an advisor to GlaxoSmithKline, Ferring Pharmaceuticals, Blue Cross and Blue Shield, and Sanofi-Aventis. Gerald L. Andriole is an advisor to Aeterna Zentaris, Amgen, Augmenix, Cambridge Endo, Caris, EMD Serono, Envisioneering, Ferring Pharmaceuticals, France Foundation, GenProbe, GlaxoSmithKline, Johnson & Johnson, Myriad Genetics, NCI, NIDDK, Nema Steba, Onconome, Ortho Clinical Diagnostics, Veridex LLC, and Viking Medical. Monique J. Roobol is an advisor for GlaxoSmithKline, Beckman, and GenProbe. Fritz H. Schröder is an advisor to GlaxoSmithKline, Ferring Pharmaceuticals, and Schering. None of the other authors have anything to disclose.

Funding/Support and role of the sponsor: None.

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