
Can We Screen and Still Reduce Overdiagnosis?

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Autopsy Studies of Subclinical Prostate Cancer

To be able to fully grasp the potential problem of overdiagnosis, it is important to understand the natural history of prostate cancer. In a very nice overview of van der Kwast et al., different types of prostate cancer in relation to their clinical presentation and symptoms are given (Fig. 2.1) [1].

To be able to address the problem of overdiagnosis, first the proportion of indolent cancers needs to be identified. Autopsy studies of non-prostate cancer-related deaths and observational natural history studies might provide some insight into this problem. A Greek autopsy study showed that subclinical cancers were found in 13.8% (60–69 years), 30.5% (70–79 years), and 40% (80–89 years) men [2]. More recent autopsy studies showed that in 1056 White and Black men in the United States, the proportion of latent prostate cancer was as high as 44–46% (50–59 years), 68–72% (60–69 years), and 69–77% (70–79 years), with the vast majority having potentially indolent Gleason score 6 or less cancers (84–93%) [3]. These men obviously would

not benefit from a diagnosis of prostate cancer in their lifetime.

Natural History of Untreated Low-Risk Prostate Cancer

Johansson et al. followed up 223 Swedish men with localized prostate cancer who were diagnosed in the pre-PSA era (1977–1984) without initial active treatment [4]. In 2004, it was reported that most observed men had an indolent course in the first 15 years, but progression and death from prostate cancer increased sharply from 15 to 20 years in those men still alive. In 2013, an updated analysis of the series was reported after 30 years of follow-up [5]. After the death of 99% of men in the cohort, it was found that only 17% of men died of prostate cancer (which means 83% died of competing causes), and prostate cancer deaths occurred mostly between 15 and 25 years from diagnosis [5].

Albertsen et al. described another cohort of 767 men (ages 55–74) diagnosed with localized prostate cancer around 1971–1984 and observed for more than 20 years [6]. At 20 years, the prostate cancer mortality rate was 30 per 1000 person-years in Gleason 6 cancer, 65 per 1000 person-years in Gleason 7 cancer, and 121 per 1000 person-years in Gleason 8–10 cancers. More than 70% of men died of other causes with Gleason score 6 at 20 years [6]. It should be noted

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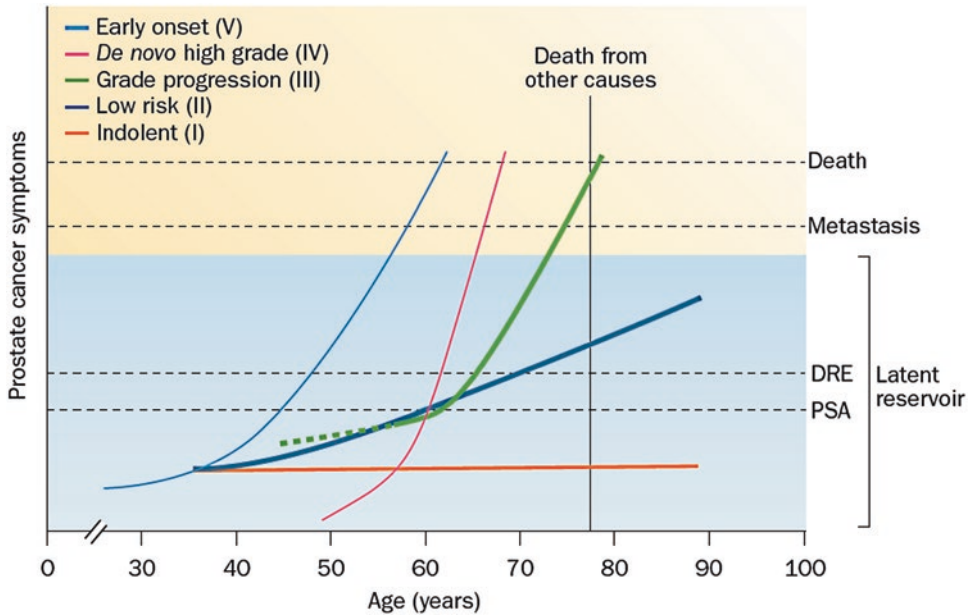


Fig. 2.1 Scheme depicting the age-related natural history of five hypothetical forms of prostate cancer (presented by the curved lines I–V) in relationship to their clinical signs and symptoms, visualizing their sojourn time in the latent reservoir (gray-colored zone). The X-axis represents patient age. Signs and symptoms of prostate cancer are represented by the horizontal lines. Indolent (curve I) and low-risk (curve II) cancers are thought to remain in the latent reservoir, although low-risk prostate cancer can grow in size and become PSA detectable and DRE detectable over time. When grade progression occurs in initially low-risk prostate cancers (curve III), these tumors can escape from the latent reservoir and become clinically

detectable. It is thought that a small fraction of de novo poorly differentiated late-onset prostate cancers (curve IV) develop rapidly with a short sojourn time in the latent reservoir, precluding their timely detection by PSA screening. The size of the curved lines indicates their frequency in a population. A very small fraction of early-onset prostate cancers (curve V) with growth kinetics comparable to those of late-onset prostate cancers with grade progression (curve III) represent a biologically distinct subset of prostate cancers. Abbreviation: DRE digital rectal examination (From Van der Kwast and Roobol [1]. Used with permission, Springer Nature)

that both cohorts represented an era without PSA testing, and it is expected that most of these patients were diagnosed at a later stage as compared with prostate cancer detected nowadays. Therefore, the early localized prostate cancers that were diagnosed in more recent years might have a more indolent course than those in the natural history studies.

The control arms of the two randomized trials of surgery versus observation also provided insights in the natural history of localized prostate cancer, the Scandinavian Prostate Cancer Group 4 (SPCG4) [7] in pre-PSA era and Prostate Cancer Intervention Versus Observation Trial (PIVOT) [8] in the early PSA era. SPCG4 randomized 699 men with prostate cancer (cT1–T2) in 1989–1999 to radical prostatectomy or watch-

ful waiting [7]. Only 5% of patients had cT1c and 75% had palpable disease (cT2) at time of diagnosis. The prostate cancer mortality in the observation group was about 20% at 15 years, and in the low-risk subgroup, the cancer mortality was only 10% at 15 years.

PIVOT randomized 731 men with prostate cancer (cT1–T2) in 1994–2002 to radical prostatectomy or observation [8]. About half of the patients had cT1c and 90% had Gleason scores 6–7. Prostate cancer mortalities of both arms were less than 20% at 15 years, and in the low-risk subgroup, the cancer mortality was less than 5% at 15 years.

In summary, localized prostate cancer shows an excellent 15-year cancer-specific survival without initial curative-intent treatment, and only

younger (<65 years old) patients might benefit from detection and radical treatment.

Estimation of the Extent of Overdiagnosis

Overdiagnosis on a population level can be estimated by either epidemiological or clinical criteria. Epidemiological studies can estimate overdiagnosis using two approaches, the so-called lead-time approach or calculating excess incidence created by active screening [9]. In clinical studies, overdiagnosis is often expressed as the number or percentage of low-risk prostate cancers that are being detected. The different approaches have a wide variable estimation of overdiagnosis and are, in addition, difficult to translate to an individual [9–11].

The ERSPC study first reported 20% reduction of prostate cancer mortality by PSA-based screening in 2009 at a median follow-up time of 9 years [12]. A 30% reduction in metastatic prostate cancer was also shown [13]. However, the excess incidence of predominantly low-risk prostate cancer cases was significant. This is expressed in the so-called numbers needed to screen and numbers needed to diagnose (in excess to a clinical situation) in order to prevent one death from prostate cancer with 1410 and 48 men, respectively. With additional follow-up, these numbers reduced to 781 and 27 men, respectively [14]. Mathematical simulation models on the basis of the Rotterdam section of ERSPC data showed that compared to a situation without screening, applying a 4-year interval and PSA-based screening algorithm from ages 55 until 70 would lead to 40% of prostate cancers detected to be overdiagnosed [15]. Three alternative screening strategies (1) screening from ages 55 to 70 with 1-year intervals, (2) screening from ages 55 to 70 with 2-year intervals, and (3) screening from ages 55 to 75 with 4-year intervals showed percentages of potentially overdiagnosed prostate cancers of 49%, 48%, and 57%, respectively [15] (Fig. 2.2).

The higher rate of overdiagnosis when screening men at higher age is confirmed by other mod-

eling studies. Gulati et al. using a contemporary cohort of US men that modeled the effects of 35 screening strategies that vary by start and stop ages, screening intervals, and thresholds for biopsy referral concluded that less intensive screening in older men (higher PSA threshold for biopsy referral) reduces the risk for overdiagnosis [16].

This is confirmed by a recent cost-effective analysis, the Microstimulation Screening Analysis (MISCAN) model, based on ERSPC data. There it was shown that a screening algorithm with 2-year intervals between the ages 55 and 59 (3 screenings) had the best incremental cost-effective ratio [17]. However, if a better quality of life for the posttreatment period could be achieved (i.e., applying active surveillance for low-risk prostate cancer), men at older age up to 72 could also be included in a screening program [17].

Next to detecting prostate cancers that are very likely to have an indolent course based on their clinical characteristics at time of diagnosis, there is obviously another factor that is closely related to overdiagnosis, i.e., life expectancy. As is shown above, a low-risk prostate cancer at time of diagnosis can become potentially life threatening if its host lives long enough.

Finding the balance between two difficult-to-predict individual-level outcomes is needed. This balance is graphically displayed in Fig. 2.3 where it is obvious that we need to be able to predict both course of disease and life expectancy to be able to screen for prostate cancer while keeping the proven benefits and avoiding the harms.

The next sections of this chapter hence focus on who and how to screen for prostate cancer.

Who to Screen?

There are certain patient groups that have been associated with higher risks of potentially aggressive prostate cancer in population studies, and they included those with positive family history, ethnically Black men, and those with genetic predisposition to prostate cancer.

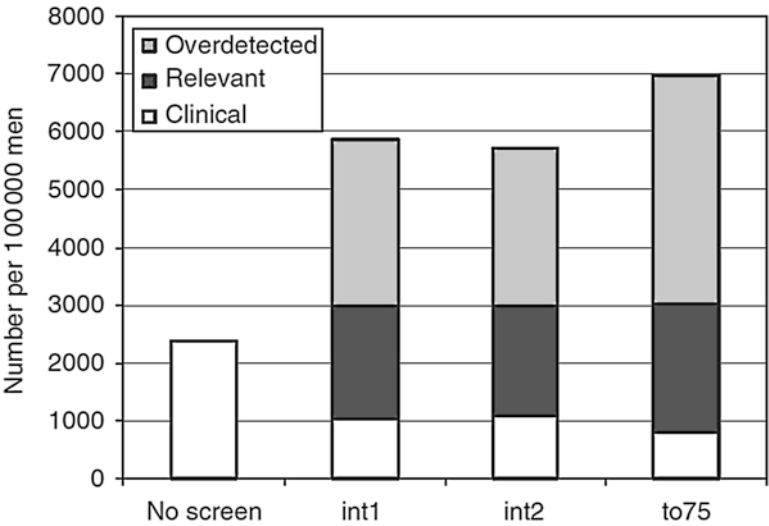
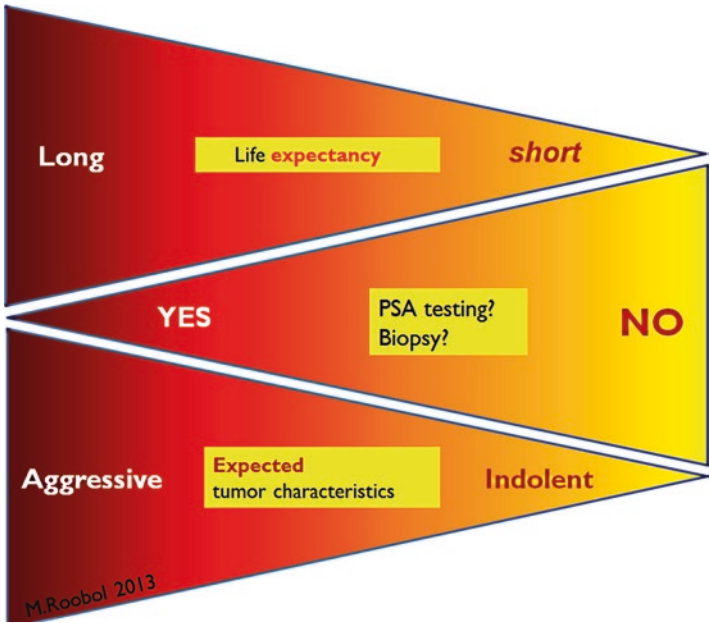


Fig. 2.2 Number of cancers detected per 100,000 men in 25 years for three screening scenarios (1-year interval ages 55–70, int1; 2-year interval ages 55–70, int2; 2 to 4-year interval ages 55–75: int4 to 75) for clinically detected cancers (interval cancers), relevant cancers (screen-detected cancers that would have given rise to

clinical symptoms later in life), and overdetected cancers (screen-detected cancers that would never give rise to clinical symptoms and would not lead to death caused by prostate cancer) (From Heijnsdijk et al. [15]. Used with permission, Springer Nature)

Fig. 2.3 Prostate cancer screening in association with life expectancy and disease course



Family History of Prostate Cancer

Meta-analyses on family history and prostate cancer risk demonstrated a relative risk (RR) of 2.5 in men having a lifetime risk and positive

family history of prostate cancer and up to 3.5–4.4 in those with two affected first-degree relatives [18]. Those with a brother having prostate cancer had an even higher risk of prostate cancer than those with a father having prostate cancer

(RR 3.1 vs 2.4) [19]. The effect of family history was also associated with earlier disease onset (before 65 years old) (RR 2.9 vs 1.9) [20]. In the Swiss arm of the ERSPC, men with positive family history of prostate cancer had a 60% higher chance of diagnosing prostate cancer, but most of them have low-grade cancers [21].

Racial Differences on Prostate Cancer

The lifetime risk of a prostate cancer diagnosis varies in different ethnic groups. In a study in the United Kingdom (UK), the risk ranged from 13.3% in Caucasian, 29.3% in Black, to 7.9% in Asian men. The risk of dying from prostate cancer also varied from 4.2% in Caucasian, 8.7% in Black, to 2.3% in Asian men [22]. Therefore, different races had a similar diagnosis-to-death ratio of around 3:1, and Black men did not have a higher risk of dying from prostate cancer once diagnosed [22]. An earlier meta-analysis, however, showed that Black men diagnosed with prostate cancer had a 13% higher risk of prostate cancer death, which was not fully explained by comorbidity, PSA screening, or access to health care [23].

Genetic Mutations Associating with Higher Risk of Prostate Cancer

Twin studies suggested that the inherited component of prostate cancer risk is more than 40% [24]. Genome-wide association studies (GWAS) evaluated the entire genome for commonly inherited variants (>1–5% population frequency), and more than 40 prostate cancer susceptibility loci explaining approximately 25% risk were found [25]. A more recent meta-analysis of 43,303 prostate cancer men and 43,737 controls from Europe, Africa, Japan, and Latin countries has identified 23 new susceptibility loci for prostate cancer, explaining 33% of familial risks [26]. In terms of screening or early detection, it is not cost-effective to screen for all susceptible loci, and unknown whether this would provide a better harm-to-benefit ratio.

Is the Presence of a Risk Factor a License to Screen?

A study using estimates from the literature reported that screening men with a PSA level at the highest tenth percentile at 45 years old provided a better harm-to-benefit ratio compared with those with positive family history and Black race. A higher PSA at 45 years old accounted for 44% of prostate cancer deaths, while family history and Black race only accounted for 14% and 28% cancer deaths, respectively [27]. Hence, it is important to weigh both harm and benefit as equally important; in a high-risk population, there might be a larger benefit, but applying a screening approach that is not selective for potentially lethal disease, the harm may be equally increased [28].

When to Screen?

When to screen for prostate cancer is another controversial topic. It includes the starting and ending age for screening, including the so-called baseline PSA measurement at relatively young age, and the screening interval.

Starting Screening, Baseline PSA at Younger Age

A large case-control study in the Swedish population showed that a higher baseline PSA at younger age groups of 45–49 and 51–55 years was associated with higher risk of metastasis and prostate cancer deaths after a follow-up of 25 years. More than 40% of metastasis and deaths from prostate cancer occurred in men with PSA with the highest tenth percentile (>1.6 ng/ml at ages 45–49 and >2.4 ng/ml at ages 51–55) [27].

In a study investigating the PSA level of again Swedish men at the age of 60, a PSA level of <1 ng/mL was associated with only 0.5% risk of metastasis and 0.2% risk of prostate cancer death at the age of 85 [29]. In a Danish study, men with a PSA concentration of 4–10 ug/L had a seven-fold risk of prostate cancer death compared with

men with PSA <1 ug/L [30]. These data were confirmed in analyses based on the ERSPC where it is repeatedly shown that men aged 55–69 with baseline PSA levels below 1.0 ng/ml have a very low risk of prostate cancer detection, let alone dying from the disease [31, 32].

In a comparison of prostate cancer incidence and mortality between the Dutch, Swedish, and Finnish parts of ERSPC and a cohort without PSA screening (Northern Ireland), results showed that the yield of prostate cancer screening increased with the increasing baseline serum PSA level at study entry. The benefits of early detection may be small for men with a baseline serum PSA of 0–3.9 ng/mL at study entry. The number needed to investigate (NNI) to save one prostate cancer death was 24,642 in men with initial PSA <2 ng/mL, compared to NNI of 133 in men with PSA 10–20 ng/mL [33].

However, starting PSA testing at mid-age might also result in yet more testing, biopsies, and subsequent overdiagnosis. The retrospective analyses presented above, recommending, e.g., retesting intervals up to 10 years if the baseline PSA is considered low, cannot assess the effect in contemporary daily clinical practice. In an editorial by Carter et al., this lack of knowledge is clearly described. The authors question whether it is realistic to assume that a clinician will advise not to return for a PSA test within the next 10 years when the data actually show that more than half of the prostate cancer deaths in men aged 45–49 occur with a PSA of less than 1.6 ng/ml (90% of the population) [34]. So while the concept of a baseline PSA test at midlife definitely sounds appealing in retrospective analyses, the question remains whether this advice will be followed in contemporary practice.

Screening Interval

As mentioned above, in the Rotterdam section of ERSPC, men of ages 55–65 years with a baseline PSA of less than 1 ng/mL were associated with very low cancer detection after 8 years. Only 3.3% men had PSA >3 ng/mL and

0.49% cancer detection rate. As a result, an 8-year interval for screening in men with baseline PSA less than 1 ng/mL was recommended [32].

A similar conclusion was drawn on the basis of a multiethnic study in the United States. Gelfond et al. reported a 10-year prostate cancer risk of 3.4% for men (median age 58) with PSA <1 ng/mL, and among the diagnosed cancer men, 90% were of low-risk cancers. In contrast, those with PSA 3.1–10 ng/mL had a 39.0% 10-year risk of prostate cancer diagnosis. A recommendation of screening interval of 10 years or more was suggested for men with baseline PSA <1 ng/mL [35].

In comparing 2-year (Goteborg section) and 4-year (Rotterdam section) PSA-based screening in the ERSPC trial in men with ages 55–64, a 2-year screening interval reduced the incidence of advanced prostate cancer by 43% but increased the detection of low-risk prostate cancer by 46% [36]. This direct relationship between benefit and the intensity of a PSA-based screening algorithm was recently confirmed by another ERSPC analysis by Auvinen et al., where it was shown that the extent of overdiagnosis and the mortality reduction were closely associated [37]. Efforts to maximize the mortality effect by applying a PSA-based screening algorithm in all men are bound to increase overdiagnosis. The authors correctly note that this harm-to-benefit ratio might be improved by focusing on men considered to be at high risk, but how we actually can achieve that remains unclear [37].

Ending Age of Screening

In a simulation study by Ross et al., the number needed to treat (NNT) in order to prevent one cancer death increased with age. Compared with screening until age 65 (NNT 7.7), screening to 75 (NNT 12.5) and 80 (NNT 17.5) years was 2–3 times higher [38]. Zhang et al. described the optimal stopping age of PSA testing from both patients' and societal perspectives from a decision process model. Patients'

perspective was to maximize expected QALYs, while societal perspective was to maximize cost-effectiveness for QALYs. From the patients' perspective, the optimal policy was stopping PSA testing and biopsy at 76, while the estimated age was 71 from societal perspective [39].

With increasing age, the benefits of early detection reduce when deaths from other causes increase. The optimal age to stop screening is difficult to be determined. As mentioned before in the natural history studies and in the RCTs comparing surgery and watchful waiting (SPCG4 [7] and PIVOT [8]), men with life expectancy less than 10–15 years are not recommended to have any prostate cancer screening in the American and European Urological Association guidelines [40, 41].

However, due to the continuous increase in life expectancy of men, the difficulty in estimating the remaining lifetime of older men, and the availability of better treatment with fewer complications, we are now facing a changing scenario. Therefore, it would be difficult to set a rigid age to stop screening. An individual assessment with proper counseling and shared decision-making should be offered instead.

How to Screen?

Nowadays, there are better tools than PSA in screening for prostate cancer which might improve the harm-to-benefit ratio in screening. As the newer tools have better sensitivity or specificity in detecting prostate cancer, a proportion of unnecessary biopsies based solely on elevated PSA might be avoided. This could reduce both unnecessary biopsies and overdiagnosis. The most obvious way to move forward, while the 100% sensitivity and specificity lethal prostate cancer test is lacking, is to combine relevant information into prediction tools. In addition, novel imaging techniques can certainly be of aid in identifying those men that can benefit from early detection and treatment.

PSA-Based Prostate Cancer Risk Calculators

There are many risk calculators available, all having their advantages (widely externally validated, easy to use) and disadvantages (only suitable in particular settings, requiring complicated data and calculations). A meta-analysis of 6 risk calculators (out of 127 unique prediction models) included Prostateclass, Finne, Karakiewicz, Prostate Cancer Prevention Trial (PCPT), Chun, and the European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (ERSPC RC3) [42].

It showed that PCPT risk calculator did not differ from PSA testing in terms of AUC (0.66), while Prostateclass and ERSPC RC3 had the highest AUC of 0.79. The latter models doubled the sensitivity of PSA testing (44% vs 21%) while maintaining the same specificity [42].

Calibration of the models, which is important in assessing the actual predicted risk, was however poorly reported. In assessing the performance of prediction models, it was reported that both discrimination (AUC) and calibration are important [42]. Decision-analytic measures (decision curve analysis) should be reported if a model relates to clinical decisions [43].

Novel Biomarkers for Prostate Cancer Prediction

Urine PCA3

The prostate cancer antigen 3 (PCA3) is a non-coding messenger RNA found to be elevated in urine of most men with prostate cancer. A post-prostatic massage urine sample is needed for analysis. A higher PCA3 score was associated with a greater risk of prostate cancer. The discriminative ability of PCA3 was significantly better than PSA (AUC 0.76 vs 0.58) [44, 45]. However, when combined to an existing risk calculator (ERSPC RC3), there was hardly any additional predictive capability [46]. PCA3 is currently approved by US Food and Drug

Administration (FDA) in 2012 as a prostate cancer diagnostic test in men with previous negative prostate biopsy.

Urine TMPRSS2-ERG

The gene fusion TMPRSS2-ERG between transmembrane protease serine 2 (TMPRSS2) gene and the v-ets erythroblastosis virus E26 oncogene homolog (ERG) gene exists in up to 80% of prostate cancers. Urine levels of TMPRSS2-ERG correlate with clinically significant prostate cancer [47]. Adding post-DRE urine PCA3 to urine TMPRSS2-ERG further improved the prediction of prostate cancer and clinically significant prostate cancer on repeated prostate biopsies. The AUC for prostate cancer detection was 0.72, 0.65, 0.77, and 0.88 for PSA, PCA3, TMPRSS2-ERG, and combination of PCA3 and TMPRSS2-ERG, respectively [48]. This is confirmed by a larger prospective multicenter study ($n = 443$), in which TMPRSS2-ERG had independent additional predictive values to PCA3 and ERSPC risk calculator in predicting prostate cancer [49].

Prostate Health Index (PHI)

PSA isoform [-2]proPSA (p2PSA) was shown to be more accurate than PSA or %free PSA in predicting prostate cancer [50]. Prostate health index (PHI) was created by combining PSA, free PSA, and p2PSA in the formula $(p2PSA/free\ PSA) \times \sqrt{\text{total PSA}}$. PHI and p2PSA had specificity 3 times of that of PSA, with best performance in the range of PSA 2–10. This could reduce unnecessary biopsies while maintain a high cancer detection rate [51]. In 2012, the FDA has approved the use of PHI and p2PSA in men older than 50 years old with a total PSA 4–10 ng/mL and normal DRE to reduce unnecessary prostate biopsies. PHI was also associated with more aggressive or clinically significant prostate cancers [52, 53]. Using a simulation model, PHI was shown to be more cost-effective than PSA-only screening [54].

Four-Kallikrein Panel (4K)

The 4-kallikrein panel consisting of PSA, free PSA, intact PSA, and human kallikrein 2 (hK2) was shown to differentiate pathologically indolent and aggressive disease. It was shown that more than 50% of biopsies could be reduced by applying the 4K panel while missing 12% high-grade cancer and avoiding overdiagnosis of one-third of low-grade cancers [55–57].

These findings were confirmed in a large cohort of 6129 men in the Prostate Testing for Cancer and Treatment (ProtecT) study, with better AUC compared with PSA (0.82 vs 0.74). Using 6% risk of high-grade cancer as cutoff, more than 40% biopsies could be reduced while delaying diagnosis of only 10% of high-grade cancers [58].

A 4K score was created by combining the 4-kallikrein panel with age, DRE findings, and history of prior prostate biopsy and was validated to accurately identify men with high-grade prostate cancer [59]. Using the 4K score can reduce 30–58% biopsies while delaying diagnosis in less than 5% high-grade cancers. However, when combined in a multivariate prediction model, the added value is limited [46].

STHLM3

The population-based Stockholm 3 (STHLM3) study reported that the so-called STHLM3 model, which included plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, MIC1), genetic polymorphisms (232 single nucleotide polymorphisms), and clinical variables (age, family history, previous prostate biopsy, DRE), predicted Gleason 7 or above prostate cancer in a large development ($n = 11130$) and validation ($n = 47688$) cohort in Sweden. The STHLM3 model performed significantly better than PSA (AUC 0.74 vs 0.56) for Gleason 7 or above prostate cancers and could reduce 32% biopsies [60]. The issue of overdiagnosis was however not fully addressed as most prostate cancers diagnosed were still low grade, and the cost-effectiveness of such an extensive model is questionable [61].

Which Novel Biomarker for Prostate Cancer Diagnosis Should We Choose?

All of the aforementioned novel biomarkers and imaging techniques like MRI have proved to be more specific and more discriminative (in terms of AUC) than PSA and could potentially reduce a significant proportion (up to 50%) biopsies while delaying diagnosis in only a handful of clinically aggressive prostate cancers. However, there are very few head-to-head comparisons of different novel tools in terms of performance and cost-effectiveness, and the ever-increasing cost of novel tests would make screening for prostate cancer unaffordable. This creates a difficult scenario for both physicians and patients in choosing the optimal test before biopsy decisions [62]. One conclusion can be drawn from these data: combining relevant pre-biopsy information as compared to decision-making on the basis of a single PSA measurement will always help to reduce unnecessary testing and overdiagnosis.

Prostate Imaging: Multiparametric MRI of the Prostate

Conventional TRUS prostate has a poor sensitivity and specificity in identification of prostate cancers, and therefore, the main use of it is to guide prostate biopsy but not for diagnosis [63]. Recently the multiparametric MRI entered the urological diagnostic practice and is considered a promising imaging modality for the detection of prostate cancer [64]. A systematic review showed that targeted biopsy (with MRI information) had a higher detection rate of significant prostate cancer (sensitivity 0.91 vs 0.76) and a lower detection rate of insignificant cancer (sensitivity 0.44 vs 0.83) [65].

Conclusions

On the basis of natural history and screening studies, we can conclude that the risk of overdiagnosis of prostate cancer is present and consid-

erable when applying systematic PSA-based screening in combination with random TRUS-based prostate biopsy. This should not prevent us from screening for prostate cancer, as none of us want to return to the era when many prostate cancers presented at an advanced or metastatic stage. We should aim to screen the right men (at particular high risk of aggressive prostate cancer and/or with a long life expectancy), at the right time, with the right tools. With all available knowledge, we are able to reduce the current rate of unnecessary biopsies and overdiagnosis of low-grade/low-risk prostate cancer. Adapting recommendations and guidelines is difficult but should be the way forward.

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