



Review – Prostate Cancer

Early Detection of Prostate Cancer in 2007

Part 1: PSA and PSA Kinetics

Fritz H. Schröder^{a,*}, H. Ballentine Carter^b, Tineke Wolters^a, Roderick C.N. van den Bergh^a, Claartje Gosselaar^a, Chris H. Bangma^a, Monique J. Roobol^a

^a Department of Urology, Erasmus MC, Rotterdam, The Netherlands

^b The James Buchanan Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA

Article info

Article history:

Accepted October 24, 2007

Published online ahead of print on November 5, 2007

Keywords:

Prostate cancer
PSA
PSA velocity
Screening
Risk stratification

Abstract

Objective: This is the first of two review papers attempting to clarify the best way to detect prostate cancer (PCa) in 2007. Screening for PCa has not yet been shown to lower PCa mortality. Still, opportunistic screening is wide spread in Europe and in most other parts of the world.

Methods: Current literature and data from screening studies are reviewed and discussed. Prostate-specific antigen (PSA) has been and remains one of the corner stones of early detection of PCa. Traditionally used cut-off values cannot be applied in an uncritical fashion after it was shown that a significant amount of overdiagnosis and that large proportions of cancers and poorly differentiated cancers are present in the low PSA ranges. The paper addresses the continued relevance of PSA cut-off values. The diagnostic value of PSA velocity is reviewed in conjunction with PSA cut-off values and as a possible replacement of total PSA. A need for more selective screening in the low PSA ranges is pointed out.

Results and conclusions: The data show that men presenting initially with PSA values below 1 do not have to be rescreened for a period of 8 yr. In the PSA range 1–2.9 ng/ml, new parameters are needed that improve specificity and are selective for screening for aggressive lesions. PSA velocity so far has not been shown to be useful in the early detection of PCa but may be useful in detecting aggressive PCa selectively. For the time being, it seems sensible to continue using PSA cut-off values such as 3.0 or 4.0 ng/ml provided overtreatment is decreased by using available nomograms.

© 2007 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Erasmus MC, University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, United States. Tel. +31 10 463 4328; Fax: +31 10 463 5315.
E-mail address: e.vandenberg@erasmusmc.nl (F.H. Schröder).

1. Introduction

The value of screening for prostate cancer (PCa) in terms of lowering PCa mortality is at present unproven. Two large studies [1,2] address the issue and results are expected within the next few years. Indirect evidence coming from observational and case control studies is contradictory but may indicate that at least part of the decrease in PCa mortality in the United States is due to the highly prevalent opportunistic screening in this country [3].

The purpose of this review is to advise about the best way to detect PCa early in those men who wish to undergo testing. Methods for early detection of PCa are available. In a situation of uncertainty about the value of screening in reducing PCa mortality, application of these methods cannot be denied to well-informed men. Information should include potential downsides and benefits, and should preferably be balanced and validated. The rate of opportunistic screening involves up to 75% of men at risk at least in some parts of the United States [4] and is also increasing in European countries. In the Netherlands 20–40% of men in the relevant age groups have undergone at least one prostate-specific antigen (PSA) test [5]. Health care providers will request clear, evidence-based information on how to screen best for PCa if the introduction of population-based screening is considered after a hopefully positive outcome of the ongoing randomized studies.

For the purpose of this review, data resulting from the European Randomized Study of Screening for Prostate Cancer (ERSPC) were used and put into perspective with relevant information on the same issues from current literature. Uncertainties include the appropriate use of the available screening tests, specifically of PSA, biopsy techniques, age limits at which to start and to discontinue monitoring, the interscreening interval, the issue of overdiagnosis, and the identification and management of potentially indolent PCa. This report is the first part of a series of reviews and concentrates on the aspects related to PSA.

2. PSA and early detection of PCa

Despite its low specificity for PCa and other uncertainties, PSA remains the corner stone of PCa detection.

2.1. PSA distribution in men aged 55–74

Data resulting from the first and second rounds of screening of ERSPC Rotterdam are shown in Table 1.

During the first round, 1014 cancers were diagnosed (detection rate, 5.1%); men who turned 75 yr, refused to participate, or died were not eligible for the second screen. Only very minor differences in PSA distribution between the two screens are seen, which are due to the changes in the populations. This information is relevant for future consideration of PSA cut-off values. It is important to realize that with any cut-off values used, a majority of men can be given the reassuring message that no biopsy was necessary. Many similar studies of PSA distribution in clinical settings are available. Table 1 is different; it relates to the general population of men aged 55–75 yr. In particular, the large proportion of men with PSA >10.0 ng/ml is missing.

2.2. Using PSA cut-off values

Most guidelines for early detection of PCa of professional organizations use cut-off values of PSA to indicate a biopsy. Recommendations vary between PSA values of 2.0 and 4.0 ng/ml. Recent data from the control group of the Prostate Cancer Prevention Trial (PCPT) suggest however that the relationship between a positive biopsy and PSA is a continuous one [6]. In the control group setting in which 5587 men were screened and biopsied upon indication or at the end of the study, it was shown that conventional cut-off values, including the lowest ones in use, will miss substantial numbers of cancers and also many of those with aggressive characteristics by Gleason score. The resulting data were used to calculate sensitivity and specificity derived from biopsying all men participating in the control group of PCPT. The data are shown in Table 2. No cut-off points of similarly acceptable sensitivities and specificities can be identified [7]. The classical cut-off value of 4.0 ng/ml misses more than 75% and a PSA cut-off of 2.0 ng/ml would miss more than 45% of biopsy detectable

Table 1 – PSA distribution at first and second screen after 4 yr (men aged 55–74 yr at first screen, ERSPC Rotterdam)

| PSA (ng/ml) | Initial screen | | Second screen (4 yr later) | |
|-------------|----------------|------|----------------------------|------|
| | N | % | N | % |
| 0–0.9 | 7139 | 35.7 | 4547 | 34.3 |
| 1–1.9 | 6205 | 31.1 | 4071 | 30.8 |
| 2–2.9 | 2508 | 12.6 | 1949 | 14.7 |
| 3–3.9 | 1426 | 7.1 | 1011 | 7.6 |
| 4–9.9 | 2235 | 11.2 | 1456 | 11 |
| >10 | 457 | 2.3 | 194 | 1.5 |
| Total | 19,970 | | 13,228 | |

PSA, prostate-specific antigen; ERSPC, European Randomized Study of Screening for Prostate Cancer.

Table 2 – Performance characteristics of PSA from the PCPT (adapted from [7])

| PSA (ng/ml) | Any PCa sens (%) | No PCa spec (%) | Any Gl <7 sens (%) | Any Gl >7 spec (%) |
|-------------|------------------|-----------------|--------------------|--------------------|
| 1.1 | 82.0 | 40.6 | 92.8 | 37.0 |
| 1.6 | 67.4 | 58.8 | 84.4 | 54.8 |
| 2.1 | 54.4 | 70.8 | 75.6 | 67.3 |
| 2.6 | 43.6 | 79.6 | 67.2 | 76.5 |
| 3.1 | 35.8 | 85.1 | 57.6 | 82.3 |
| 4.1 | 24.5 | 92.3 | 40.4 | 90.0 |
| 6.1 | 5.4 | 98.0 | 13.2 | 97.8 |
| 8.1 | 2.0 | 99.1 | 4.8 | 99.0 |
| 10.1 | 1.0 | 99.5 | 2.4 | 99.5 |

PSA, prostate-specific antigen; PCPT, Prostate Cancer Prevention Trial; PCa, prostate cancer; Gl, Gleason score; sens, sensitivity; spec, specificity.

cancers. As will be shown, in the PSA ranges below 3.0 ng/ml, this entails a very high risk of over-diagnosis and overtreatment as well as unnecessary biopsies. It is therefore likely that cut-off values of PSA will continue to be used until a better alternative has been found. The authors recommend not to use a PSA cut-off but to allow men to determine their own risk by using a risk calculator based on the data and to decide whether or not to undergo a biopsy (see www.uroweb.org).

Within ERSPC Rotterdam a biopsy was initially recommended if a man presented with a PSA value ≥ 4.0 ng/ml and/or an abnormal rectal examination (DRE) or a hypoechoic lesion on transrectal ultrasound (TRUS). The resulting distribution of men within given PSA ranges, numbers and proportions of biopsies, cancer detection, positive predictive value (PPV), and numbers of biopsies to detect one cancer are given in Table 3. The reader should keep in mind, however, that the information given is based on one PSA determination. Biological and test variations are not taken into account.

2.2.1. PSA range 0–0.9 ng/ml

Of the men screened in the first round, 36.4% fell into this PSA range. The PPV of carrying out DRE and

TRUS in these men was 2.2%; 46 needed to be biopsied to find one cancer. Subsequently, data on the second and third screens after 4 and 8 yr, respectively, on these men became available. These screens are according to the ERSPC protocol. Of 2344 PSA-based screens during an 8-yr period, 8 resulted in cancers, a detection rate of 0.47% [8]. No additional cancers could be identified in the total cohort by linkage to the cancer registry. With this data in hand it seems justified to recommend rescreening to men with PSA values <1.0 ng/ml not earlier than 8 yr after an initial screen. This recommendation in a modified form has become part of the narrative of the guidelines of the American Cancer Society (ACS) [9]. However, this recommendation applies only to men aged ≥ 55 yr. Lower values (0.6–0.7 ng/ml) were found to be associated with an increased risk of PCa (relative risk [RR], 3.75) years later [10] in men aged 40–50 yr.

2.2.2. PCa detection in the PSA range 1–3.9 ng/ml

These low PSA ranges are the domain of DRE and TRUS. However, in confirmation of other studies, the PPV of DRE is low in the range 8–10% [11,12]. In addition, it was shown that most of the cancers detected by DRE in the low PSA ranges have

Table 3 – Distribution of PSA and prostate cancers in 9779 men aged 55–74 yr biopsied for PSA ≥ 4.0 , DRE, and TRUS (ERSPC Rotterdam)

| PSA | Men (n) | % of total | Biopsies (n) | % of total biopsies | Cancer (n) | % of total cancers | PPV | Biopsies (n) per cancer |
|-------------|---------|------------|--------------|---------------------|------------|--------------------|------|-------------------------|
| 0.0–0.9 | 3559 | 36.4 | 183 | 8.1 | 4 | 0.8 | 2.2 | 45.8 |
| 1.0–1.9 | 3051 | 31.2 | 511 | 22.5 | 45 | 9.5 | 8.8 | 11.4 |
| 2.0–2.9 | 1198 | 12.3 | 221 | 9.7 | 30 | 6.3 | 13.6 | 7.4 |
| 3.0–3.9 | 702 | 7.2 | 174 | 7.7 | 44 | 9.3 | 25.3 | 3.9 |
| 4.0–9.9 | 1063 | 10.9 | 985 | 43.4 | 241 | 51.0 | 24.5 | 4.1 |
| ≥ 10.0 | 206 | 2.1 | 193 | 8.5 | 109 | 23.0 | 56.5 | 1.8 |
| Total | 9779 | 100.0 | 2267 | 100.0 | 473 | 100.0 | 20.9 | 4.8 |

PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound; ERSPC, European Randomized Study of Screening for Prostate Cancer; PPV, positive predictive value.

favorable prognostic factors [13]. The ERSPC study group decided in 1997 to discontinue the use of DRE and TRUS as screening tests. Instead, the PSA cut-off for recommending biopsy was lowered from 4.0 to 3.0 ng/ml. This change resulted in an overall 10% decrease in the rate of biopsies, owing to omitting DRE as a test in men with PSA <3.0 ng/ml, and in a very similar detection rate of 4.7% using the PSA 3.0 ng/ml cut-off instead of the 5.0% rate using PSA \geq 4.0 ng/ml and DRE/TRUS [11]. Also, omitting DRE and TRUS did not result in an increased detection of PCa or interval PCa after 4 yr [14].

The PPV in the PSA range 3.0–3.9 ng/ml increased from 6.4% (DRE, TRUS) to 18.0% by biopsying all men with a PSA of 3 ng/ml or higher [15]. Early on during the study it was shown that the use of the ratio of free to total PSA and several other derived parameters can decrease the number of biopsies at the price of losing otherwise detectable cancer [16]. Follow-up data and final outcome data of ERSPC and PLCO (Prostate, Lung, Colon, and Ovary screening trial) will allow establishment of the risk of cancers that may have been present but were not diagnosed in the PSA ranges below the currently used cut-off values. Obviously, PCa mortality should be the final outcome measure.

3. Is it necessary to detect all PCas in the low PSA ranges?

The data from the control group of the PCPT, in which very large proportions of the study population were biopsied either for cause or at the end of the 7-yr study period, had a strong impact on the clinical use of PSA in detecting PCa. The data show that the use of a PSA cut-off value will always lead to missing large proportions of the biopsy detectable PCas and a substantial number of those that can be found to have unfavorable prognostic parameters by means of Gleason scores of \geq 7 [7]. A summary of the PCPT control arm data is given in Table 3 [7]. As stated before, PSA cut-off of 4.0 ng/ml will miss 75.5% and an experimental cut-off of 2 ng/ml would still miss 45.6% of all detectable cancers. The same cut-off values would miss 59.6% and 24.4% of those cancers diagnosed with a Gleason score of 7 or higher. The information shown has led many clinicians to adopt more aggressive biopsy policies with the extreme of biopsying men with PSA values below 2.0 ng/ml in fear of missing aggressive PCa.

In this section an attempt will be made to show that it is not necessary to identify all PCas in the PSA ranges below 4.0 or 3.0 ng/ml.

3.1. Identification of indolent PCa

Indolent PCa has been defined by Kattan et al [17] as a subgroup of those men who can be identified prior to making treatment decisions as having clinically insignificant PCa according to well-established but arbitrary criteria [18]. In applying these criteria to 1022 radical prostatectomy specimens from two major centers, 20% of men could be retrospectively identified as having “insignificant disease.” These cancers were clinically detected. When the same selection criteria were applied to 247 screen-detected cases classified as having T1c or T2a cancers from the ERSPC Rotterdam who were all treated by radical prostatectomy, a percentage of insignificant cases of 49% resulted [19]. This data set was used to validate the nomogram designed by Kattan et al. No additional significant variables were identified, the model was confirmed, and the discriminative ability was almost identical with an area under the curve in receiver operator characteristic analysis of 0.76. If the resulting probabilities for indolence are applied to all screen-detected PCas, depending on the cut-off value of the probability of indolence, 20–45% of all detected cancers can be safely classified as potentially indolent. These men may be offered active surveillance with probabilities of only 6–15% of including potentially aggressive cancers in this selection [19,20].

3.2. Preliminary evidence around overdiagnosis

Overdiagnosis is defined as the diagnosis of a disease entity, which in the absence of screening would not be diagnosed during the lifetime of its carrier [21]. If overdiagnosis leads to treatment of this disease, the term “overtreatment” is applied. Overdiagnosis is determined by disease and host factors, specifically life expectancy. Within ERSPC, with regard to the age group of 55–74 yr and a 4-yr screening interval, mean lead time has been estimated to amount to 10.3 yr and overdiagnosis to 54% [21]. Overdiagnosis, in addition to the parameters mentioned, depends on age and the screening methodology. If screening reduces PCa mortality, a certain amount of overdiagnosis may be acceptable. The degree is up for ethical considerations. For the time being, however, it still remains uncertain which screen-detected PCas can be earmarked as “overdetected” and, in case treatment is omitted, what the outcome in terms of metastatic progression and PCa mortality in this group of men might be. Data of ERSPC Rotterdam do offer opportunity to shed more light on this issue.

3.3. Characteristics and outcome of cancers found in low PSA ranges

There is evidence from the PCPT control group and from ERSPC that the proportion of aggressive cancers increases with increasing PSA values at the time of diagnosis and that, on the other hand, the proportion of indolent cancers is inversely related to PSA levels. ERSPC offered the opportunity to study the prevalence of potentially insignificant (minimal) tumors according to [22] in 550 radical prostatectomy specimens of cancers detected during the first and second rounds of screening (Table 4). The authors realize that these definitions are arbitrary to a large degree because their untreated natural history is poorly defined. Also, it must be noted that a substantial proportion (30–40%) of patients in [22] have the characteristics of aggressive disease. In four specimens the biopsy-proven PCa could not be retrieved. In both rounds the proportion of minimal disease was strongly dependent on PSA values, amounting to 67% and 56% for PSA below 3 ng/ml in round 1 and round 2, respectively, and overall to 33% versus 43% if all cancers were considered [22]. This finding is much in line with the findings obtained in [19]. The nomogram presented in this study is available for the identification of potentially indolent cancers, which are best treated by active surveillance (www.uroweb.org).

ERSPC Rotterdam offers an opportunity to evaluate with an 8-yr follow-up period the outcome of those 15,853 men who participated in the screening arm and initially presented with PSA values <3.0 ng/ml. All cancers detected by screening or interval cancers are included. The total number of men biopsied in the second round because of progression to PSA \geq 3.0 ng/ml was 1090. Of the total of 462 cancers, 11 were diagnosed with potentially advanced disease, and 5 died of PCa; all 11 were in the group of 66 interval cancers (Schröder et al, submitted 2007).

The resulting overall detection rate of 2.9% in 15,853 men over an 8-yr period in ERSPC is in sharp contrast with the 21.9% detection rate in 5587 men in PCPT who were all biopsied during an 8-yr period. If PCPT procedures had been used in the ERSPC cohort, 21.9% of men would have been found to have PCa, a total number of 3472 cases. In fact 462 were found. From the available data it can be concluded that 3010 PCa cases were missed and did not show up as screen detected or interval cancers during the 8-yr interval. Although the follow-up period of 8 yr may be too short, the data are reassuring for those men who present with PSA values below 3.0 ng/ml and who do not undergo a biopsy. There seems to be no need to identify all biopsy detectable cancers at a first screen in the PSA range below 3.0 ng/ml (Schröder et al, submitted 2007).

4. Diagnostic value (not the prognostic value) of PSA kinetics

PSA velocity (PSAV) and PSA doubling time (PSADT) as diagnostic tools are subject to intense debate at present. In the framework of this review, the discussion of PSAV and PSADT as diagnostic tools will be limited to two situations:

- (1) The use of PSAV in conjunction with a cut-off value (eg, PSA <4.0 ng/ml)
- (2) The possible replacement of total PSA by PSAV

4.1. Verification bias

The application of a new test to a cohort of men with PCa diagnosed by the use of different tests is subject to verification bias (attribution bias, assignment bias). Verification bias arises because biopsies are generally indicated only with elevated PSA values or other abnormal clinical tests such as rectal examina-

Table 4 – Tumor volumes in 550 radical prostatectomy specimens per PSA range detected in rounds 1 and 2 (ERSPC Rotterdam) [22]

| PSA range (ng/ml) [*] | Median, mean tumour volume (ml [range]) | % minimal tumor | Median, mean tumor volume in ml (range) | % minimal tumor |
|--------------------------------|---|-----------------|---|-----------------|
| | Round 1 (n = 386) | | Round 2 (n = 164) | |
| <3.0 | 0.28, 0.32 (0.00–1.09) | 67 | 0.28, 0.38 (0.00–1.80) | 56 |
| 3.0–3.9 | 0.58, 0.72 (0.00–3.10) | 45 | 0.43, 0.63 (0.00–2.17) | 31 |
| 4.0–9.9 | 0.77, 1.08 (0.00–13.48) | 27 | 0.63, 1.06 (0.01–7.93) | 46 |
| >10 | 1.82, 2.16 (0.00–7.99) | 13 | 1.33, 2.04 (0.00–8.94) | 36 |
| Total | 0.65, 1.06 (0.00–13.48) [*] | 33 | 0.45, 0.86 (0.00–8.94) [*] | 43 |

^{*} Significant, $p = 0.001$.
^{**} Correlation tumor volume/PSA level. round 1: $R^2 = 0.15$, Round 2: $R^2 = 0.12$ ($p = 0.0001$).

| | | Condition as determined by “Gold standard” | |
|--------------|----------|---|----------------|
| | | Cancer present | Cancer absent |
| Test outcome | Positive | True Positive | False Positive |
| | Negative | False Negative* | True negative |
| | | ↓ | ↓ |
| | | Sensitivity | Specificity |

Sensitivity: true positives (N) / (true positives + false negatives) (N)
(or: those who test positive divided by all those who have cancer)

Specificity: true negatives (N) / (true negatives + false positives) (N)
(or: all those who test negative divided by all those who do not have cancer)

Fig. 1 – Definitions of test accuracy.

tions and not by the new test under study. If not all test negatives undergo a biopsy, the numbers of true positives and true negatives are wrongly estimated, and the accuracy of the test cannot be determined. Sensitivity is calculated by dividing the number of true positives by the sum of the true positives and false negatives (Fig. 1). Determining sensitivity seems easy. However, since we know that there are many biopsy detectable cancers present in the low PSA ranges, the number of men who would test positive and have cancer and the true number of men who test negative and do not have cancer remain unknown. This means that sensitivity and specificity cannot be properly calculated. In light of these limitations, it has been suggested to use the terms “relative sensitivity” and “relative specificity” [23].

Establishing the true sensitivity of PSAV in diagnosing PCa needs to be done prospectively in a cohort of men who were all biopsied and underwent sequential PSA determinations following a predetermined schedule. The test characteristics of any desired cut-off value can then be determined. If a preset PSAV cut-off value is selected as a biopsy indicator again, “relative” sensitivity and specificity will result because the denominator in both equations remain unknown because the test characteristics of PSA below the chosen cut-off level still remain unknown.

4.2. PSA velocity below total PSA cut-off values

This section refers to commonly used PSA cut-off values of 2.5, 3.0, and 4.0 ng/ml. There is a need to identify aggressive cancers below this cut-off. Do PSA kinetics, specifically PSAV, help in this respect as originally suggested by Carter et al [24].

Smith and Catalona [25] studied 982 serially screened men whose initial screening was negative

for cancer. All men had at least one PSA value >4.0 ng/ml and all underwent biopsy. For those men who entered the study with PSA levels <4.0 ng/ml, the PSAV cut-off point of 0.75 ng/ml/yr or more maximized sensitivity and specificity for predicting cancer with an odds ratio of 7.2 (95% confidence interval [95%CI], 4.52–11.47). The authors concluded that PSA slope is useful for serial PCa screening. These data could not be reproduced in a very similar setting [26]. Of the 588 consecutive participants of ERSPC Rotterdam studied, all presented with PSA values <4.0 ng/ml at their first screen and progressed 4 yr later to PSA values >4.0 ng/ml. None were biopsied in round 1; all were biopsied in round 2. The results are shown in Table 5. PSAV was calculated as the rise of PSA in 4 yr divided by 4. With rising PSAV the number of cancers diagnosed and the relative sensitivity decreases dramatically, and cancers detected by the PSA cut-off are missed. This result is associated with an increase of relative specificity in direct relation to increasing PSAV. Because biopsy indication is driven by PSA values ≥4.0 ng/ml, which function as the “gold standard” in this setting, it is obvious that PSAV cannot improve sensitivity (ie, exceed the number of cases found by the “gold standard biopsy indication”). Men who have a rapidly rising PSA but do not reach 4.0 ng/ml are not biopsied, which obviously introduces attribution bias. Perrin [27] pointed out this bias without identifying it by name. He correctly stated that “none of the available (retrospective) studies proves the diagnostic value of PSAV.” Even in a prospective setting, it is unlikely that PSA kinetics will be useful because of the very low proportion of men who have rapidly rising PSA values [25,28,29]. However a strategy that uses PSA (but not biopsy) to identify men with rapid increasing PSA may be useful [10,30,31].

It remains unknown how many PCAs would have been detected if PSAV instead or in addition to the PSA cut-off had been used as a biopsy indication.

Other data from ERSPC show, in an easily understandable fashion, that a high PSAV is a relatively rare event in screening for PCa [28]. Table 6 gives the rate of PSA progression to values of ≥3.0 ng/ml 4 yr after an initial normal screen in which all 5771 men presented with a PSA <3.0 ng/ml and did not undergo biopsy. It is evident that those who had the highest PSAV are those men who presented with PSA values <2.0 ng/ml in the first round. The data confirm the findings in PLCO (Schröder et al, submitted 2007) that these men are a relatively small fraction of 4.8% of the 4880 men in this range in round 1. Most cancers are detected in those men who progress from the PSA range 2.0–2.9 to ≥3.0 ng/ml. Data in the original paper

Table 5 – Comparison of the predictive value of PSAV cut-offs (0.25, 0.5, 0.75, 1.00) in rescreeing after 4 yr (adapted from [25])

| PSA/PSAV (ng/ml) | Men (n) | PCa (n) | Rel sens (%) | Rel spec (%) | Odds ratio univariate (95%CI) |
|------------------|---------|---------|--------------|--------------|-------------------------------|
| PSA \geq 4.0 | 588 | 167 | 100.0 | 0.0 | |
| PSAV >0.25 | 550 | 158 | 94.6 | 6.9 | 1.30 (0.60–2.81) |
| PSAV >0.50 | 387 | 109 | 65.3 | 33.9 | 0.97 (0.66–1.41) |
| PSAV >0.75 | 203 | 49 | 29.3 | 63.4 | 0.72 (0.49–1.06) |
| PSAV >1.00 | 110 | 34 | 20.4 | 81.9 | 1.16 (0.74–1.82) |

PSA, prostate-specific antigen; PSAV, prostate-specific antigen velocity; PCa, prostate cancer; rel sens, relative sensitivity; rel spec, relative specificity; CI, confidence interval.

PSA rose in all men from <4.0 to \geq 4.0 ng/ml; all men were biopsied (n = 588, 167 cancers).

Table 6 – PSA progression 4 yr after screening (N = 5771; age, 55–74 yr; PSA round 1 <3.0 ng/ml) (adapted from reference [26])

| PSA Round 1 (ng/ml) | N | PSA \geq 3.0 Round 2 (ng/ml [%]) | Biopsies N (%) | PCa N | PPV % | CDR % |
|---------------------|------|------------------------------------|----------------|-------|-------|-------|
| <1.0 | 2622 | 23 (0.9) | 21 (91.3) | 4 | 19.0 | 0.15 |
| 1.0–1.9 | 2268 | 211 (9.3) | 181 (85.8) | 43 | 23.8 | 1.9 |
| 2.0–2.9 | 881 | 428 (48.6) | 376 (87.9) | 105 | 27.9 | 11.9 |
| Total | 5771 | 662 (11.5) | 578 (87.3) | 152 | 26.3 | 2.6 |

PSA, prostate-specific antigen; PCa, prostate cancer; PPV, positive predictive value; CDR, cancer detection rate.

Differences in PPVs are not significant (Fisher exact test).

show that prognostic factors do not differ between those cancers diagnosed in men who progressed from very low PSA values as opposed to those who progressed from PSA range 2.0–2.9 ng/ml [28].

Other evaluations of PSAV in low PSA ranges include Fang et al [31] who showed in a comparison of 21 men with clinically detected cancer and 68 from the Baltimore Longitudinal Study of Ageing (BLSA) that a PSAV of 0.1 ng/ml or more was associated with a relative risk of being diagnosed with PCa of 6.53. Yu et al [32] examined the relationship between total PSA and PSAV in 1851 men who were biopsied and 894 men who were diagnosed with PCa. They showed that, in the PSA ranges <2.5 or 2.6–4.0 ng/ml, the proportion of men with PSA velocities >2.0 ng/ml/yr was 1% and 14%, respectively. They found that PSAV varies directly with total PSA levels. No multivariate comparison of total PSA and PSAV was carried out.

PSA velocity was also assessed in ERSPC [33] and the PCPT [7]. In these trials sufficient information was collected to allow a multivariate analysis determining the relative value of each of the parameters under investigation. Roobol et al [33] evaluated PSAV in a multivariate setting on data derived from the second round screening of ERSPC Rotterdam in 774 men who all underwent biopsy. Parameters studied included PSA, DRE, suspicious TRUS, PSAV, PSADT, prostate volume, and age. PSAV

turned out to be insignificant with an odds ratio of 0.73 (95%CI, 0.21–2.67) [34].

Also, in a complete evaluation of the predictors of PCas in round 1 and round 2 screening in ERSPC Rotterdam in multivariate analysis of round 2 parameters, only PSA increase was significant (odds ratio, 6.9) for those men who had not been previously biopsied. A previous negative biopsy and a large prostate were significant negative predictors. Details are given in reference [34]. The database of PCPT, specifically the data related to the 5519 men biopsied in the placebo control group, also allowed a multivariate analysis of predictors of a positive biopsy [35]. PSAV was a significant predictor in a monivariate analysis but was no longer statistically significant as soon as the single predictor PSA was added to the risk equation.

4.3. Replacing PSA with PSAV

The concept of using PSAV as the biopsy indication independent of PSA cut-off values is based on the observation that PSAV (and PSADT) may selectively diagnose aggressive cancers. If proven, this concept would fulfil one of the major needs of early detection of PCa and potentially decrease the proportion of diagnosis and treatment of cases that might never come to the surface clinically during the lifetime of a patient (overdiagnosis, overtreatment). The value of

PSA kinetics in diagnosing aggressive PCa has been studied. Relevant data from observational studies [10,30,31] and from the only available randomized study of surgical treatment versus observation of clinically diagnosed locally confined PCa [36] have been used. As suggested by Carter et al [37], a PSA history of at least three PSA values separated by at least 3 mo should be obtained and collected over a period of 18–24 mo [37]. Then a cut-off of PSAV can be applied as a biopsy indication; 0.35 ng/ml/yr is suggested by Carter et al [10]. Limiting the biopsy indication to those men with a high PSAV in this concept would selectively identify potentially deadly PCa. A number of open questions need to be answered before this concept is applicable: How reliable are three PSA determinations separated by 3 mo and collected over 18–24 mo in estimating PSA kinetics? Does PSAV have added value once the last value is known? Is PCa still curable once this evaluation has been concluded? “Aggressive” disease must be further defined (morbidity also counts). The concept is based on small numbers of observations of clinical cases in whom PSAV was determined at 3-yr intervals. Is it applicable to the screening situation? Appropriate prospective studies will have to answer these questions.

Another still experimental concept is application of the PSA test early in life starting at age 40 yr. Fang et al [38] found on the basis of data from the BLSA that, for men aged 40–49.9 yr, the relative risk was 3.75 (range, 1.6–8.6) with a PSA >0.6 ng/ml to develop PCa 25 yr later. In men aged 50–59 yr using a PSA cut-off level of 0.71 ng/ml, a relative risk of similar magnitude was seen. Lilja et al [30] presented confirmatory findings based on data of the Malmö health care study. These studies relate to clinical cases. The value of serial early PSA determinations for early detection is still to be shown.

5. Conclusions on PSA in early detection of PCa

On the basis of presentation of recent findings and their discussion in the previous section, the following conclusions can be drawn.

- Men presenting initially with PSA <1.0 ng/ml may not have to be rescreened for a period of 8 yr.
- PSA 1.0–2.9 ng/ml: If everyone in this PSA range is biopsied, many cancers can be found, with a proportion of 20–30% showing aggressive patterns by Gleason score. In this PSA range there is an urgent need to improve specificity (avoid unnecessary biopsies). The question of whether all

cancers in this low PSA range need to be diagnosed will be subject to discussion later in this report. Goal of future research should be to improve specificity and selectivity for the identification of aggressive cancers.

- PSA velocity: PSAV was not shown to be useful in the early detection of PCa at a population level. This finding does not preclude that men found to show a high PSAV through accidental individual observations should be biopsied, especially if PSAV is >0.35 ng/ml. This could have led to earlier biopsies and would have applied to about 11% of the total ERSPC population in the second screening round.
- For the time being it seems sensible to continue the use of cut-off values of PSA provided measures are taken to avoid overtreatment of indolent cases. Previously screened and previously biopsied men require different strategies [33].

There is a need to find effective parameters that allow identification of aggressive cases in lower PSA ranges, specifically in the PSA range 2.0–3.0 ng/ml. The value of molecular subforms, which are still under evaluation at this time, has not been covered in this paper; much progress can be expected from their use [39]. PSA cut-off values may become obsolete in the future if indeed PSA testing early in life allows selective prediction of the presence of aggressive PCas. For the time being it seems legitimate to use PSA cut-off values in conjunction with identification of indolent cases.

Conflicts of interest

None of the authors has a direct financial relationship to companies producing or marketing the PSA test. The first author is consultant to Ferring Ltd Copenhagen. The ERSPC study Europe wide is cofunded by Beckman Coulter Ltd.

Acknowledgement

This study is funded by grants of the Dutch Cancer Society (KWF 94-869, 98-1657, 2002-277, 2006-3518); The Netherlands Organisation for Health Research and Development (002822820, 22000106, 50-50110-98-311); the 6th Framework Program of the EU: P-Mark: LSHC-CT-2004-503011; and Beckman Coulter Hybritech Inc.

The authors are grateful to Mrs Ellen van den Berg for typing and handling this manuscript.

References

- [1] Roobol MJ, Schröder FH, guest editors; Fitzpatrick J, editor. The European Randomised Study of Screening for Prostate Cancer (ERSPC): rationale, structure, and preliminary results 1994–2003. *BJU Int* 2003;92(Suppl 2):1–123.
- [2] Gohagan JK, Prorok PC, Hayes RB, Kramer BS. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials* 2000;21(6 Suppl):251S–72S.
- [3] Loeb S, Catalona WJ. Prostate-specific antigen in clinical practice. *Cancer Lett* 2007;249:30–9.
- [4] Enger SM, Van den Eeden SK, Sternfeld B, et al. California Men's Health Study (CMHS): a multiethnic cohort in a managed care setting. *BMC Public Health* 2006;306:172.
- [5] Meer mannen doen test op prostaatanker. CBS 2006.
- [6] Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215–24.
- [7] Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA* 2005;294:66–70.
- [8] Roobol MJ, Roobol DW, Schroder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). *Urology* 2005;65:343–6.
- [9] Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection. *CA Cancer J Clin* 2001;51:38–75; quiz 77–80. Erratum in: *CA Cancer J Clin* 2001;51:150.
- [10] Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006;98:1521–7.
- [11] Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994;151:1283–90.
- [12] Schroder FH, van der Crujisen-Koeter I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. *J Urol* 2000;163:806–12.
- [13] Schroder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 1998;90:1817–23.
- [14] Gosselaar C, Roobol MJ, Roemeling S, et al. Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Prostate* 2006;66:625–31.
- [15] Schroder FH, Roobol-Bouts M, Vis AN, van der Kwast T, Kranse R. Prostate-specific antigen-based early detection of prostate cancer—validation of screening without rectal examination. *Urology* 2001;57:83–90.
- [16] Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part I: Results of a retrospective evaluation of 1726 men. *Urology* 1995;46:773–8.
- [17] Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumours. *J Urol* 2003;170:1792–7.
- [18] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994;271:368–74.
- [19] Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, de Koning HJ, Schroder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. *J Urol* 2007;177:107–12, discussion 112.
- [20] Roemeling S, Roobol MJ, Kattan MW, et al. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. *Cancer* 2007;110:2218–21.
- [21] Draisma G, Boer R, Otto SJ, et al. Lead times and over-detection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95:868–78.
- [22] Postma R, Schroder FH, van Leenders GJ, et al. Cancer detection and cancer characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC) - Section Rotterdam. A comparison of two rounds of screening. *Eur Urol* 2007;52:89–97.
- [23] Schroder FH, Alexander FE, Bangma CH, Hugosson J, Smith DS. Screening and early detection of prostate cancer. *Prostate* 2000;44:255–63.
- [24] Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215–20.
- [25] Smith DS, Catalona WJ. Rate of change in serum prostate-specific antigen levels as a method for prostate cancer detection. *J Urol* 1994;152:1163–7.
- [26] Schroder FH, Roobol MJ, van der Kwast TH, Kranse R, Bangma CH. Does PSA velocity predict prostate cancer in pre-screened populations? *Eur Urol* 2006;49:460–5, discussion 465.
- [27] Perrin P. PSA velocity and prostate cancer detection: the absence of evidence is not the evidence of absence. *Eur Urol* 2006;49:418–9.
- [28] Schroder FH, Raaijmakers R, Postma R, van der Kwast TH, Roobol MJ. 4-year prostate specific antigen progression and diagnosis of prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. *J Urol* 2005;174:489–94, discussion 494.
- [29] Crawford ED, Pinsky PF, Chia D, et al. Prostate-specific antigen changes as related to the initial prostate-specific antigen: data from the prostate, lung, colorectal, and ovarian cancer screening trial. *J Urol* 2006;175:1286–90.

- [30] Lilja H, Ulmert D, Bjork T, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *J Clin Oncol* 2007;25:431–6.
- [31] Fang J, Metter EJ, Landis P, Carter HB. PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/ml. *Urology* 2002;59:889–93.
- [32] Yu X, Loeb S, Roehl KA, Han M, Catalona WJ. The association between total prostate-specific antigen concentration and prostate specific antigen velocity. *J Urol* 2007;177:1298–302.
- [33] Roobol MJ, Kranse R, De Koning HJ, Schröder FH. Prostate-specific antigen velocity at low PSA levels as screening tool for prostate cancer: results of second screening round of ERSPC (Rotterdam). *Urology* 2004;63:309–13.
- [34] Roobol MJ, Schroder FH, Kranse R, ERSPC, Rotterdam. A comparison of first and repeat (four years later) prostate cancer screening in a randomized cohort of a symptomatic men aged 55–75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC, Rotterdam). *Prostate* 2006;66:604–12.
- [35] Ankerst DP, Thompson IM. Merging digital rectal exam, family history, age and prostate-specific antigen to create a decision-making tool. *Arch Ital Urol Androl* 2006;78:143–6.
- [36] Fall K, Garmo H, Andrén O, Bill-Axelsson A, et al. Prostate-specific antigen levels as a predictor of lethal prostate cancer. *J Natl Cancer Inst* 2007;99:526–32.
- [37] Carter HB, Pearson JD, Waclawiw Z, et al. Prostate-specific antigen variability in men without prostate cancer: effect of sampling interval on prostate-specific antigen velocity. *Urology* 1995;45:591–6.
- [38] Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Ageing. *Urology* 2001;58:411–6.
- [39] Schroder FH. Biomarkers and screening for prostate cancer. *Ann Oncol* 2006;17(Suppl 10):x201–6.