



## Prostate Cancer

# A Risk-Based Strategy Improves Prostate-Specific Antigen–Driven Detection of Prostate Cancer

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### Abstract

**Background:** Screening for prostate cancer (PC) is controversial due to uncertainties about its efficiency.

**Objective:** We aimed to develop strategies to reduce the number of unnecessary biopsies while still detecting most clinically important PC cases.

**Design, setting, and participants:** In 1850 men initially screened and biopsied (prostate-specific antigen [PSA] value  $\geq 3.0$  ng/ml) in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer, we calculated both the probability of having a positive lateralized sextant biopsy [P(biop+)] and the probability of having an indolent cancer [P(ind)] if PC was detected at biopsy ( $n = 541$ ). Analyses of repeat screening included 225 cancers in 1201 men.

**Interventions:** The P(biop+) was based on applying a logistic regression model that included ultrasound volume, digital rectal exam, and transrectal ultrasound in addition to the PSA value. The P(ind) was based on a recently validated nomogram.

**Measurements and limitations:** At initial screening the fraction of positive biopsies was 29% (541 of 1850). Applying an additional P(biop+) cut-off of 12.5% implied that 613 of the 1850 men (33%) would not have been biopsied. This would result in an increase in the positive predictive value (PPV) to 38% (468 of 1237). At repeat screening a similar P(biop+) cut-off would result in an increase in the PPV from 19% (225 of 1201) to 25% (188 of 760). Thirteen percent of PC cases would not have been diagnosed, of which 70% (initial screening) and 81% (repeat screening) could be considered as potentially indolent. None of the deadly PC cases would have been missed. A PSA cut-off of  $\geq 4.0$  ng/ml resulted in similar numbers of biopsied cases saved but considerably higher numbers of missed diagnoses.

**Conclusions:** An individualized screening algorithm using other available pre-biopsy information in addition to PSA level can result in a considerable reduction of unnecessary biopsies. Very few important PC cases, for which diagnosis at a subsequent screening visit might be too late for treatment with curative intent, would be missed.

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## 1. Introduction

Despite recent results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) that show relative mortality reduction up to 30% in favor of screening [1,2], controversy still exists due to the absence of a risk–benefit analysis providing convincing evidence regarding its net effectiveness.

Prostate cancer (PC) screening using a serum prostate-specific antigen (PSA)–based threshold as a the sole indication for prostate biopsy lacks specificity, resulting in large numbers of unnecessary biopsies and, at the same time, in missing cancer diagnoses in men with PSA levels below the chosen PSA cut-off value.

Data coming from the Prostate Cancer Prevention Trial (PCPT) showed that the quantitative relation of PC prevalence and PSA is continuous [3]. This has opened the discussion of whether the PSA threshold indicating a prostate biopsy should be lowered to values of approximately 2.0 ng/ml or 2.5 ng/ml [4]. Lowering the PSA threshold would result in the detection of more PC but would also increase the number of unnecessary biopsies dramatically [5–7].

In order to reduce the number of unnecessary biopsies, many probability-based algorithms have been developed that use, besides the PSA level, additional relevant prebiopsy information such as age, results of digital rectal examination (DRE) and transrectal ultrasound (TRUS), and prostate volume [8–13].

Another concern with respect to screening for PC are characteristics of the cancers that are detected through active screening. A considerable percentage of the screening-detected PCs are indolent and most probably do not need to be detected at all or can still be detected later in a curable stage [14–17].

In the recently developed Riskindicator [18,19], both issues—the reduction of biopsies and the identification of potentially indolent PC—are combined. In the current study, we assessed the reduction in number of potentially unnecessary biopsies using risk profile-based cut-off values as indicators for biopsy in men with a serum PSA  $\geq 3.0$  ng/ml and, at the same time, assessed the number of indolent PCs, important PCs, and related progression rates and PC deaths diagnosed or missed at an initial and repeat screening visit (4-yr interval).

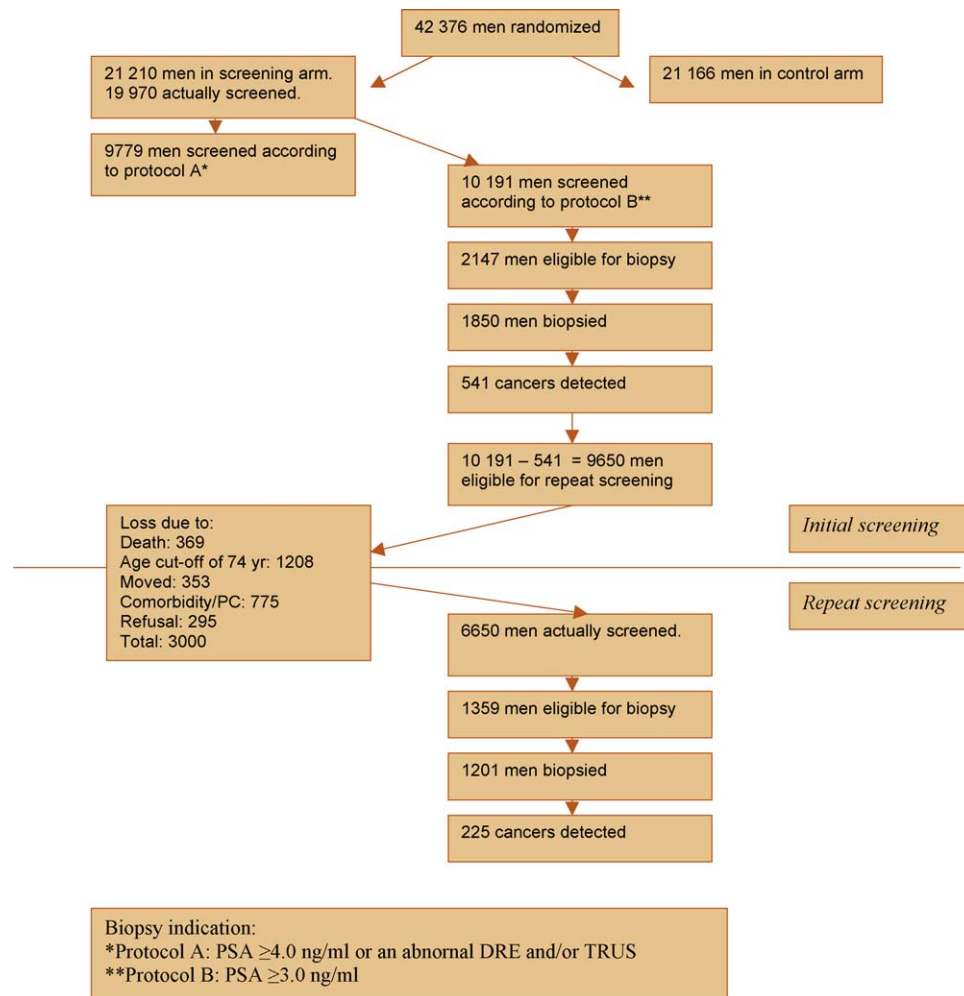


Fig. 1 – Trial flow diagram.

DRE = digital rectal examination; PC = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

## 2. Patients and methods

### 2.1. Initial screening

During the period from May 1997 to December 1999, 10 191 men were screened using a serum PSA level of  $\geq 3.0$  ng/ml as the only indication for biopsy (Beckman Hybritech assay; Beckman Coulter, Inc., Fullerton, CA, USA). This cohort represents the second segment of the total cohort randomized to the screen arm of the Dutch part of the ERSPC ( $n = 19\ 970$ ). The biopsy procedure consisted of a lateralized sextant biopsy and an additional seventh biopsy in case of a hypoechoic lesion.

### 2.2. Repeat screening

The second study group consisted of 6650 men from the initial cohort of 10 191 men who were screened for the second time (from May 2001 to March 2004; screening interval, 4 yr; PSA-based biopsy indication  $\geq 3.0$  ng/ml). Details are indicated in the trial flow diagram (Fig. 1).

### 2.3. Probability of a positive biopsy or of an indolent prostate cancer

We developed a multistep graphic device called the Riskindicator [18,19] ([www.prostate-riskcalculator.com](http://www.prostate-riskcalculator.com)) for estimating the risk of having a biopsy-detectable PC (steps 1–5) and of having a potentially indolent PC (step 6) using multivariable logistic regression analysis.

The six different logistic regression models and the source population are displayed in Table 1. For the Riskindicator the contributions of the different predictors were graphically translated via rotation (Fig. 2).

In this study, step 3 of the Riskindicator was used to estimate the probability of having a sextant biopsy-detectable PC [P(biop+)] in men screened for the first time. The P(biop+) of men biopsied at repeat screening was calculated using step 4 or step 5, depending on the previous screening result. Missing values in our two data sets were negligible (0.2%). The predictive capability of the calculated probabilities was assessed by receiver operating characteristic analysis.

The probability of having indolent PC [P(ind)] for all cancers detected at initial and repeat screening was calculated by using step 6 of the Riskindicator. Step 6 is based on a recently validated nomogram [19] and predicts the chance of having an indolent PC in men presenting with the following features: (1) clinical stage T1c or T2 disease, (2) PSA  $\leq 20$  ng/ml, (3) primary and secondary Gleason grade  $\leq 3$ , (4) positive

cores  $\leq 50\%$ , (5) total cancer in biopsy cores  $\leq 20$  mm, and (6) benign tissue in all cores  $\geq 40$  mm. Cancers that do not meet these criteria are not considered indolent.

We assessed the reduction in number of biopsies using different cut-offs of the calculated P(biop+) at initial and repeat screening in combination with the PSA cut-off value of 3.0 g/ml. This was related to the number and percentage of potentially clinically important and indolent PC cases missed and the number of PC cases that showed either clinical or PSA progression (defined as a confirmed rise of the PSA level of  $\geq 0.5$  ng/ml) or led to death. Avoidable biopsies that showed characteristics of indolent PC were considered “potentially unnecessary.”

## 3. Results

### 3.1. Cancer detection at initial screening

At initial screening, 2147 men (21.0%) had a PSA  $\geq 3.0$  ng/ml, 1850 were actually biopsied (90%), and 541 PCs were detected (Table 2). The positive predictive value (PPV; number of cancers found per number of biopsies done) was 29% (541 of 1850). The cancer detection rate (CDR; number of cancers found among the total number of men eligible) in this study setting was 5% (541 of 10 191). After a mean follow-up of 11 yr, 139 PC cases (26%) showed progression and 18 men died of their disease (1.7%) (Table 3).

Applying step 3 of the Riskindicator resulted in a mean P(biop+) of 27% (range: 1–99%). Mean predicted probabilities were 20% (1–88%) for the noncancer cases and 43% (3–99%) for the cancer cases, corresponding to an area under the curve (AUC) of the predicted probabilities of 0.77 (0.74–0.79).

We note that within the Riskindicator, the positive predictive properties of a high PSA level combined with the negative predictive properties of a high prostate volume equate to a high PPV of PSA density [18].

Among the 541 PC cases, 240 (44%) cases were classified as likely indolent. Applying step 6 of the Riskindicator for the prediction of indolent disease in those 240 PC cases resulted in a mean P(ind) of 52% (range: 5–96%); 58 (24.2%) had a P(ind) score  $\geq 70\%$ .

**Table 1 – Description of the logistic regression models and their source population used in the Riskindicator**

Step of Riskindicator	Source population	Outcome	Variables used in the model
1	6288 men screened at initial screening	Chance of positive biopsy in men never screened	Age, family history of prostate cancer, AUA seven-symptom score
2	6288 men screened at initial screening	Chance of positive biopsy in men never screened	Serum PSA value
3	3624 men screened at initial screening	Chance of positive biopsy in men never screened	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hypoechoic lesion, 1/0)
4	247 PC patients (stage: T1c, T2) treated with radical prostatectomy	Chance of having a potentially indolent prostate cancer	Serum PSA value, ultrasound-assessed prostate volume, biopsy Gleason score, cancerous tissue length of total of prostate biopsies, noncancerous tissue length of total of biopsies
5	2896 men screened at repeat screening	Chance of positive biopsy in men previously screened	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hypoechoic lesion, 1/0)
6	2896 men screened at repeat screening	Chance of positive biopsy in men previously screened and biopsied	Serum PSA value, ultrasound-assessed prostate volume, outcome of DRE (1/0), outcome of TRUS (ie, a hypoechoic lesion, 1/0), having had a previous negative biopsy (1/0)

AUA = American Urological Association; PSA = prostate-specific antigen; PC = prostate cancer; DRE = digital rectal examination; TRUS = transrectal ultrasound.

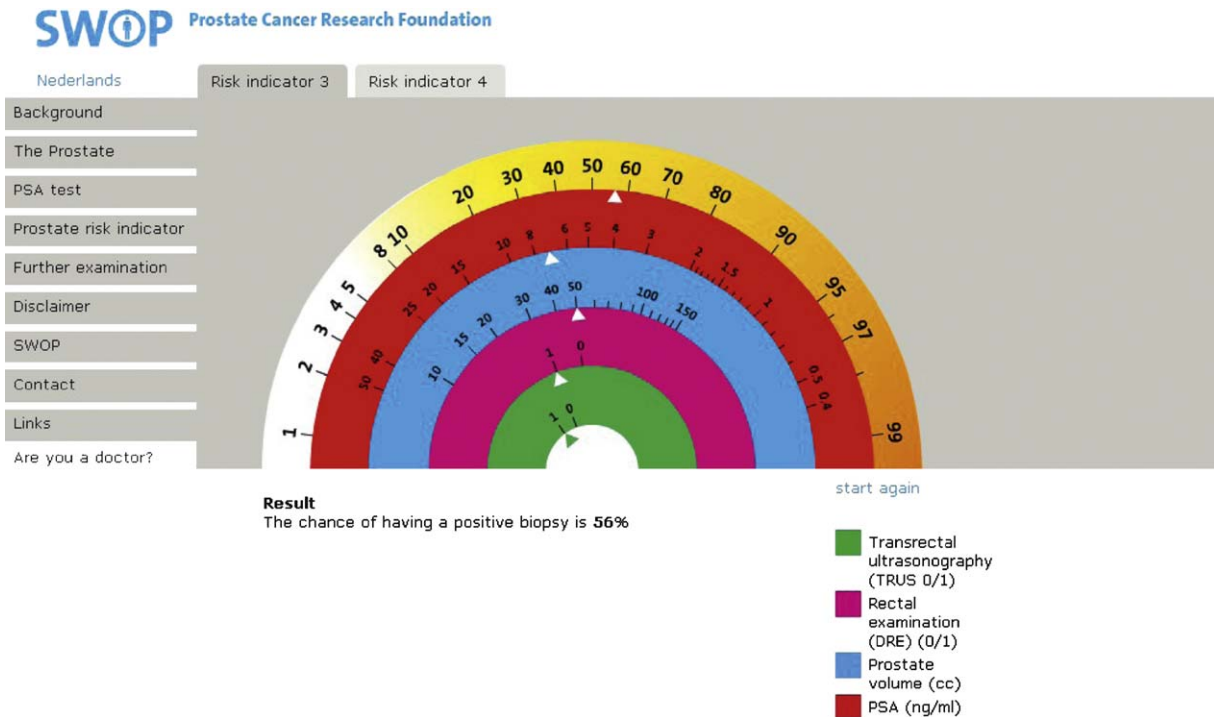


Fig. 2 – Step 3 of the Riskindicator (<http://www.prostatecancer-riskcalculator.com/via.html>).

### 3.2. Cancer detection at repeat screening

At repeat screening 1359 men had a PSA  $\geq 3.0$  ng/ml (20%) and 1201 men were actually biopsied (88%). Of these 1201 men, 568 were previously biopsied (47%) at initial screening. A total of 225 PC cases were detected (PPV: 18%; CDR: 3.4%), including 60 PC cases in men previously biopsied. After a mean follow-up of 7 yr, 26 PC cases (12%) showed progression and 1 man died of his disease (0.4%, Table 4).

The mean P(biop+) as calculated with step 4 (previous PSA test) and step 5 (previous negative biopsy) was 19% (range: 2–74%). Mean predicted probabilities were 17% (2–62%) for the noncancer cases and 26% (4–74%) for the cancer cases, corresponding to an AUC of the predicted probabilities of 0.71 (0.68–0.75).

Of the 225 PC cases detected at repeat screening, 146 (65%) were classified as likely indolent. Applying step 6 for the prediction of indolent disease on those 146 PC cases

resulted in a mean P(ind) of 63% (range: 8–95%); 63 (43%) had a P(ind) score  $>70\%$ .

### 3.3. Cut-offs for the probability for biopsy outcome

The result of different P(biop+) cut-off values at initial screening with respect to decrease in number of biopsies and number and characteristics of PC detected or missed are shown in Table 3. At initial screening a threshold combination of PSA  $\geq 3.0$  ng/ml and a calculated probability of having a positive biopsy  $\geq 12.5\%$  would result in 33% fewer biopsies ( $n = 613$ ) and a rise in the PPV from 29% (541 of 1850) to 38% (468 of 1237). Almost 14% of all PC would be missed ( $n = 73$ ). Of these PC cases, 51 (70%) were classified as potentially indolent. Twenty-two important cases (all organ confined at time of diagnosis) would have been missed with the proposed algorithm (4%, 22 of 541).

Ninety percent of the cases that showed progression during follow-up and 17 of the 18 deadly PC cases (94%) would have been detected at initial screening when applying this individualized biopsy indication. Applying a higher PSA threshold for biopsy (eg,  $\geq 4.0$  ng/ml) would result in a similar number of biopsied cases saved; however, the number of PC cases missed would be considerably higher (135 PC cases missed vs 73 with the individualized approach).

At repeat screening a threshold combination of PSA  $\geq 3.0$  ng/ml and a calculated probability of having a positive biopsy  $\geq 12.5\%$  would result in 37% fewer biopsies ( $n = 441$ ) and an increase in the PPV from 19% (225 of 1201) to 25% (188 of 760) (Table 4).

Table 2 – Results of initial and repeat screening (4 yr later)

		Initial screening	Repeat screening
A	Eligible men (n)	10 191	6650
B	Men with PSA $\geq 3.0$ (n, % of A)	2147 (21.0)	1359 (20.4)
C	Men biopsied (n, % of B)	1850 (90.3)	1201 (88.4)
D	Cancers detected (n)	541	225
E	PPV of PSA $\geq 3.0$ ng/ml (D/C)	29.2	18.7
H	Potentially indolent PC (n, % of D)	240 (44.4)	146 (64.9)

PSA = prostate-specific antigen; PPV = positive predictive value; PC = prostate cancer.

**Table 3 – Number of biopsies and (potentially indolent) cancers at initial screening with various cut-offs of the positive lateralized sextant biopsy next to a prostate-specific antigen cut-off  $\geq 3.0$  ng/ml**

P(biop+) (%)	A: No. men biopsied	B: No. biopsies saved (% of total A)	C: No. PC detected	D: PPV (% C/A)	E: No. PC lost (% of total C)	F: No. important PC lost (false-negative rate = F/301)	G: No. indolent PC lost (true-negative rate = G/240)	No. cases progressed	No. PC deaths
–	1850	–	541	29.2	0	0 (0)	0 (0)	139	18
$\geq 10$	1405	445 (24)	492	35.0	49 (9)	14 (5)	35 (15)	133	18
$\geq 12.5$	1237	613 (33)	468	37.8	73 (14)	22 (7)	51 (21)	125	17
$\geq 15$	1097	753 (41)	443	40.4	98 (18)	30 (10)	68 (28)	123	17
$\geq 20$	861	989 (54)	383	44.5	158 (29)	54 (18)	104 (43)	115	13
$\geq 25$	689	1161 (63)	344	49.9	197 (36)	69 (23)	128 (53)	105	–
PSA cut-off $\geq 4.0$	1231	619 (34)	406	33.0	135 (25)	50 (17)	85 (35)	122	16

P(biop+) = positive lateralized sextant biopsy; PSA = prostate-specific antigen; PPV = positive predictive value; PC = prostate cancer.

**Table 4 – Number of biopsies and (potentially indolent) cancers at repeat screening with various cut-offs of the positive lateralized sextant biopsy next to a prostate-specific antigen cut-off  $\geq 3.0$  ng/ml**

P(biop+) (%)	A: No. men biopsied	B: No. biopsies saved (% of total A)	C: No. PC detected	D: PPV (% C/A)	E: No. PC lost (% of total C)	F: No. important PC lost (false-negative rate = F/79)	G: No. indolent PC lost (true-negative rate = G/146)	No. cases progressed	No. PC deaths
–	1201	–	225	18.7	0	0 (0%)	0 (0%)	26	1
$\geq 10$	896	305 (25)	201	22.4	24 (11)	5 (6)	19 (13)	23	1
$\geq 12.5$	760	441 (37)	188	24.7	37 (16)	7 (9)	30 (21)	22	1
$\geq 15$	641	560 (47)	172	26.8	53 (24)	8 (10)	45 (31)	19	1
$\geq 20$	417	784 (65)	136	32.6	89 (40)	20 (25)	69 (47)	14	1
$\geq 25$	264	937 (78)	98	37.1	127 (56)	30 (38)	97 (66)	12	1
PSA cut-off $\geq 4.0$	731	470 (39)	129	17.6	96 (43)	33 (42)	63 (43)	13	–

P(biop+) = positive lateralized sextant biopsy; PSA = prostate-specific antigen; PPV = positive predictive value; PC = prostate cancer.

Sixteen percent of all PC would be missed ( $n = 37$ ). Of these PC cases, 30 (81%) were classified as likely indolent. Only seven important cases (all organ confined at time of diagnosis) would have been missed with the proposed algorithm (3%, 7 of 225). Eighty-five percent of the cases that showed progression during follow-up (22 of 26) and the deadly PC case would have been detected when applying an individualized biopsy indication. Applying a higher PSA threshold for biopsy (eg,  $\geq 4.0$  ng/ml) is comparable to a P(biop+) cut-off of  $\geq 12.5\%$  with respect to the number of biopsies saved; however, again, the number of PC cases missed was considerably higher (96 PC cases missed vs 37 with the individualized approach).

#### 4. Discussion

We found that a PSA cut-off of 3.0 ng/ml as an indication for a prostate biopsy-based screening algorithm resulted in a predictive value for a positive biopsy of 29% at initial screening and 19% at repeat screening 4 yr later. This implies that respectively 71% and 81% of the biopsies may have been unnecessary if the cut-off value of  $\geq 3.0$  ng/ml is considered valid. Additional information available at the time of biopsy could be used to provide individualized predictions of the biopsy outcome. Incorporation of a probability cut-off next to the PSA level of 3.0 ng/ml to trigger a biopsy would considerably improve the PPV

depending on the specific cut-off value and the screening round. As shown, a P(biop+) cut-off of 12.5% resulted in a substantial rise in the PPV both at initial and repeat screening. This multivariate probability cut-off was calculated using the Riskindicator [18], a nomogram recently validated [20,21] and compared with a similar tool based on data from the PCPT trial [22,23]. A similar rise in the PPV can also be reached by raising the PSA cut-off level (ie,  $\geq 4.0$  ng/ml). As shown here, however, this approach coincides with a considerably higher number of missed important PC diagnoses, confirming that biopsy indications purely based on the PSA level lack specificity. This is especially true in the diagnostic grey zone of PSA (3.0–10.0 ng/ml); above-normal levels often occur in men with benign prostatic hyperplasia.

Additional subjective prebiopsy information incorporated within a model can limit its applicability. DRE, TRUS, and prostate volume are, to a large extent, subjective measures. Despite this, we must note that at the level of the group as a whole, ignoring these factors leads to a significantly inferior model. Ignoring these sources of information is therefore unjustified if they are available (even at the level of the individual). This is confirmed by a validation of Riskindicator step 3, using the screening results of the Finnish ERSPC screening cohort (1881 men). The predictive value of PSA alone on this cohort resulted in an AUC of 0.64, while the Riskindicator step 3 model reached an AUC of 0.77, despite the fact that DRE, TRUS, and

prostate volumes were assessed by different physicians [20].

Avoiding biopsies by applying an additional indication for biopsy next to a serum PSA cut-off level necessarily coincides with missing cancer diagnoses, but the number of potentially important cancers missed with this multivariate approach was small. The large majority of missed cases were potentially indolent PC cases and their proportion increased with repeat screening. The ratio of indolent cases to important cases in those missed was in the range of 1:2.5 and 1:5.6 at initial and repeat screening, respectively.

A key question is whether all biopsy-detectable PCs should be detected, knowing the numerous studies of overdiagnosis and overtreatment caused by the detection of non-life-threatening or indolent PCs inherent to early detection [5,24–27]. Instead of trying to detect as many PC cases as possible by means of lowering biopsy thresholds or repeat biopsy procedures or screening visits, it seems necessary to find ways to detect only those cancers that need to be treated before they become life threatening. Avoiding potentially unnecessary biopsies is a first step toward achieving individualized screening. Hopefully, in the future, marker substances and improved nomograms will become available that will improve the value of PSA and lead to a more selective detection of aggressive PC. Given the very long lead time for PC [14] and the fact that men are screened repeatedly, it is likely that a missed cancer diagnosis at the initial screening visit still results in the detection of a still-curable PC several years later. With this in mind, the missing of PC diagnoses could be given different weight in the context of fewer biopsies and missed cancer diagnoses.

The majority of the PC cases that will not be detected using a combined biopsy indication are potentially indolent cases for which one can question the need for detection at all or possibly detection at a later stage while still curable.

The first nomogram for the identification of indolent PCs was developed by Kattan et al using data from clinically detected PCs [28]. Steyerberg et al [19] updated this nomogram toward a screening setting and incorporated it into the Riskindicator. Nomograms to predict biopsy outcome developed on a certain patient population may not be valid when applied on different patient populations. Additionally, it must be noted that all steps of the Riskindicator are based on screening results obtained with lateralized sextant prostate biopsies, a method that has become obsolete in contemporary practice and is replaced by biopsy schemes consisting of at least 8, but often 10 to 12, biopsy cores. The most important reason for this change was the awareness of missed diagnoses and the risk of undergrading [29,30]. However, after an initial period of optimism caused by the stage and grade reduction at time of diagnosis as a result of the introduction and application of the PSA test as a screening tool, doubts have arisen about whether all these low-stage and low-grade PCs should be detected. This makes an algorithm that emphasizes the detection of potentially life-threatening disease without unnecessarily testing men and diagnosing indolent PC cases a definite need.

## 5. Conclusions

A screening algorithm that uses, in addition to a PSA level of 3.0 ng/ml, other available prebiopsy information (ultrasound volume, outcomes of DRE and TRUS) and that also considers previous screening visits can result in a considerable reduction of unnecessary biopsies. Perhaps even more important, this strategy results in missing very few PC cases for which diagnosis at a subsequent screening visit might be too late for treatment with curative intent.

The proposed strategy, therefore, might reduce two of the most important negative side effects of an early detection program for PC: unnecessary invasive testing (prostate biopsy) and overdiagnosis with the related overtreatment. This study can be considered a plea for a more individualized screening algorithm.

**Author contributions:** Monique J. Roobol 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:* Roobol.

*Acquisition of data:* Roobol, Wolters, van den Bergh.

*Analysis and interpretation of data:* Roobol, Steyerberg, Kranse.

*Drafting of the manuscript:* Roobol.

*Critical revision of the manuscript for important intellectual content:* Roobol, Steyerberg, Kranse, Wolters, van den Bergh, Bangma, Schröder.

*Statistical analysis:* Roobol, Steyerberg.

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*Supervision:* Schröder, Bangma.

*Other (specify):* None.

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