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Prediction of prostate cancer in unscreened men: External validation of a risk calculator

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ABSTRACT

Background: Prediction models need external validation to assess their value beyond the setting where the model was derived from.

Objective: To assess the external validity of the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator (www.prostatecancer-riskcalculator.com) for the probability of having a positive prostate biopsy (P(posb)).

Design, setting and participants: The ERSPC risk calculator was based on data of the initial screening round of the ERSPC section Rotterdam and validated in 1825 and 531 men biopsied at the initial screening round in the Finnish and Swedish sections of the ERSPC respectively. P(posb) was calculated using serum prostate specific antigen (PSA), outcome of digital rectal examination (DRE), transrectal ultrasound and ultrasound assessed prostate volume.

Measurements: The external validity was assessed for the presence of cancer at biopsy by calibration (agreement between observed and predicted outcomes), discrimination (separation of those with and without cancer), and decision curves (for clinical usefulness).

Results and limitations: Prostate cancer was detected in 469 men (26%) of the Finnish cohort and in 124 men (23%) of the Swedish cohort. Systematic miscalibration was present in both cohorts (mean predicted probability 34% versus 26% observed, and 29% versus 23% observed, both $p < 0.001$). The areas under the curves were 0.76 and 0.78, and substantially lower for the model with PSA only (0.64 and 0.68 respectively). The model proved clinically useful for any decision threshold compared with a model with PSA only, PSA and DRE, or biopsying all men. A limitation is that the model is based on sextant biopsies results.

Conclusions: The ERSPC risk calculator discriminated well between those with and without prostate cancer among initially screened men, but overestimated the risk of a positive biopsy. Further research is necessary to assess the performance and applicability of the ERSPC risk calculator when a clinical setting is considered rather than a screening setting.

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1. Introduction

Prostate cancer (PCa) screening using a prostate specific antigen (PSA) based threshold of 3–4 ng/ml as indication for prostate biopsy lacks specificity. This leads to unnecessary biopsies and missing PCa diagnosis in men with a PSA level below the threshold.[1,2] Risk calculators (or nomograms) for the prediction of a positive prostate biopsy have been developed to support physicians in clinical decision making with respect to the individual patient and reduce the number of unnecessary biopsies with a marginal loss of potentially aggressive PCa's.[2–7] Risk calculators improve the diagnostic value of PSA by increasing its sensitivity and specificity by adding other potential predictive risk factors to the decisional process and provide individual risk estimation of having a biopsy-detectable PCa.[8] Roobol and colleagues reported that 33% fewer biopsies could be done by using a risk calculator based on a lateralised sextant biopsy, applying the PSA cut-off of $\geqslant$3 ng/ml and a calculated probability cut-off of 12.5%, compared with using PSA alone.[2] Another model reduced the number of biopsies with 57% using a probability cut-off of 20% compared to the model including age and PSA.[6] The European Randomized study of Screening for Prostate Cancer (ERSPC) section Rotterdam has developed the ERSPC risk calculator, using multivariable logistic regression analysis. This risk calculator has 6 levels (based on 6 different logistic regression models) and is internet based (www.prostatecancer-riskcalculator.com).[2] In the second level only PSA is included. The third level of this risk calculator estimates the probability of having a positive sextant biopsy in unscreened men. Next to the PSA level the results of digital rectal examination (DRE) and transrectal ultrasound (TRUS), i.e. the presence of hypoechogenic lesions and prostate volume, are included in the risk calculation.[9]

The aim of this study was to externally validate the ERSPC risk calculator (level 3) for assessing the probability of having a positive sextant prostate biopsy in previously unscreened men, using the data of the first screening rounds of the Finnish and Swedish section of the ERSPC. We assessed the performance of the risk calculator not only for calibration and discrimination, but also for its clinical usefulness.[10]

2. Patients and methods

2.1. Study population

The risk calculator has been developed in the Dutch section of the ERSPC and is based on the data of 3624 biopsied men, in the age of 55–75. All men were evaluated between 1993 and 2000. Biopsy indication was a serum PSA $\geqslant$ 4 ng/ml and/or a suspicious DRE or TRUS (1993–1996) and from 1997 only a serum PSA of $\geqslant$ 3 ng/ml.[9]

External validation was performed using the data of the Finnish and Swedish section of the ERSPC. The Finnish cohort consisted of 1922 men, aged 55–67 years, from Helsinki and Tampere screened for the first time in the period 1996–2003. For validation 1825 men with a PSA $\geqslant$ 3 ng/ml were included, excluding 56 (3%) men due to missing values. Biopsy indications were a serum PSA $\geqslant$ 4 ng/ml and a PSA of 3.0–3.9 ng/ml if there is a suspicious DRE (in the period 1996–1998) or if the proportion of free PSA is < 0.16 (since 1999). The Swedish cohort consisted of 661 men from Goteborg screened for the first time in period 1995–1996, 612 men were biopsied for the first time. We excluded 81 men younger than 55 years (n = 78, 13%) and those with missing values (n = 3, <1%), leaving 531 men aged 55–67 years for analysis. Men with serum PSA $\geqslant$ 3 ng/ml underwent a DRE, TRUS and a prostate biopsy.

2.2. Statistics

The differences between the characteristics of the three groups were assessed by using the Chi-square test for categorical variables and the analysis of variance and the Kruskal–Wallis tests for continuous variables. Multivariable logistic regression analysis was used to refit the model combining data of all three cohorts. We compared this model with the original model, and tested for differences in predictive effect by statistical interaction tests of the form 'cohort*predictor'. A significant interaction term means that the relationship between a predictor and outcome varies by cohort. Comparisons were made to models with PSA only and with PSA and DRE. These models were fitted on the data of the Dutch cohort and validated in the Swedish and Finnish cohorts. These comparisons were considered relevant since these models do not require data from an invasive test (TRUS). Statistical analyses were performed using SPSS software (version 17; SPSS, Inc., Chicago, III) and R (version 2.8.1; R foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

2.3. Calibration and discrimination

Calibration, discrimination, and clinical usefulness were assessed in the 3 cohorts for the level 3 of the ERSPC risk calculator.

Calibration refers to the agreement between observed and predicted outcomes. The extent of over- or underestimation relative to the observed and predicted rate was explored graphically using validation plots.[11] We assessed calibration-in-the-large by fitting a logistic regression model with the model predictions as an offset variable. The intercept indicates whether predictions are systematically too low or too high, and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The area under the Receiver Operating Characteristic (ROC) curve was used to assess the ability of the model to discriminate between those with and without PCa. We compared the area under the curve (AUC) of the model in the different cohorts with the AUC of the model using only PSA (level 2 of the ERSPC risk calculator).

2.4. Clinical usefulness

Clinical usefulness was assessed by using decision curve analyses.[12,13] These analyses estimate a 'net benefit' for prediction models by summing the benefits (true positives biopsies) and subtracting the harms (false-positives biopsies). The

latter are weighted by a factor related to the relative harm of a missed cancer versus an unnecessary biopsy. The weighting is derived from the threshold probability of PCa at which a patient would opt for biopsy. This threshold can vary from patient to patient. We concentrated on the net benefit for threshold probabilities between 10% and 40%.[14] This implies

Table 1 – Characteristics of the participants.

	Dutch cohort $n = 3624$	Finnish cohort $n = 1825$	Swedish cohort $n = 531$	p-Value
Age (years) (Average, sd, range)	65.5 (5.4, 55–75)	62.3 (4.3, 55–67)	61.2 (3.1, 55–67)	<0.001
PSA ng/ml median (25–75 percentile)	4.3 (3.1–6.4)	5.6 (4.5–7.8)	4.5 (3.5–6.6)	<0.001
Number suspicious DRE (%)	1284 (35)	389 (21)	99 (19)	<0.001
Number suspicious TRUS (%) (hypoechogenic lesions)	1233 (34)	194 (11)	151 (28)	<0.001
Prostate volume (cc) median (25–75 percentile)	41 (32–55)	37 (28–48)	40 (30–51)	<0.001
Number prostate cancer detected on needle biopsy (%)	893 (25)	469 (26)	124 (23)	0.490

PSA: Prostate Specific Antigen; DRE: Digital Rectal Examination; TRUS: Transrectal Ultrasound Statistical significant: p-value of <0.05.

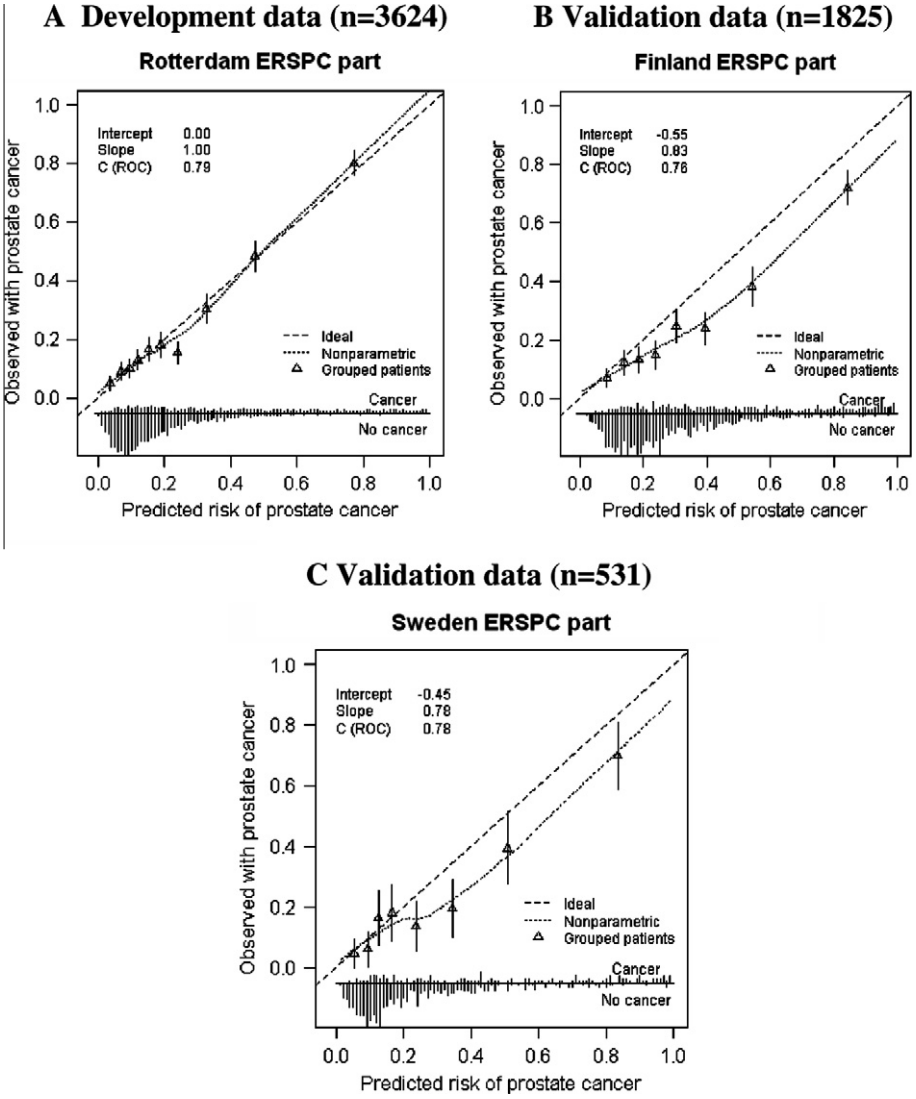


Fig. 1 – Validation plot A for the prediction of the model in the Dutch cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) ($n = 3624$) and the validation plots B and C in the Finnish ($n = 1825$) and Swedish cohort ($n = 531$).

Table 2 – Performance of the risk calculator predicting a positive prostate biopsy in the Dutch cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) and in the two validation cohorts (Finland and Sweden).

	Predicted outcome (%)	Observed outcome (%)	Calibration-in-the-large (95% C.I.)	Calibration slope (95% C.I.)	AUC (95% C.I.)
Risk calculator: PSA, DRE, TRUS and prostate volume.					
Dutch cohort	25	25	0 (–0.09–0.09)	1.0 (0.93–1.09)	0.79 (0.77–0.81)
Finnish cohort	34	26	–0.55 (–0.67–0.42)	0.83 (0.73–0.93)	0.76 (0.74–0.79)
Swedish cohort	29	23	–0.45 (–0.69–0.21)	0.78 (0.61–0.95)	0.78 (0.73–0.83)

PSA: Prostate Specific Antigen; DRE: Digital Rectal Examination; TRUS: Transrectal Ultrasound.

a weight of 9:1 for the 10% threshold, and 3:2 for the 40% threshold for missing cancer versus unnecessary biopsy. The reduction in number of biopsies using different P(posb) in combination with the PSA cut-off value of 3.0 ng/ml was further assessed and related to the number and percentage of insignificant PCa (Gleason $\leqslant$ 6) and significant PCa (Gleason > 6 and/or metastasis). We specifically studied the previously suggested 12.5% threshold[2], so that the risk of missing relevant PCa was limited. The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold probability should be chosen. We compared our level 3 model with the level 2 model, which includes only PSA to predict the presence of cancer at biopsy, and with the model that includes PSA and DRE. Reference strategies were biopsying all men and biopsying no men.

3. Results

3.1. Study population

Except for the number of PCa diagnosis, the men in the three cohorts differed significantly in age, PSA levels, suspicious DRE, suspicious TRUS and prostate volume (Table 1).

3.2. Calibration and discrimination

Calibration was perfect for the Dutch cohort (Fig. 1), but the mean predicted outcome probability was higher than the fraction of observed outcomes for both validated cohorts (Finland: 34% versus 26% and Sweden: 29% versus 23%; both $p < 0.001$) (Table 2). The effects of the predictor variables were somewhat weaker than expected in the validation cohorts, as reflected in calibration slopes of 0.83 and 0.78, respectively (Table 2). The effect of TRUS was smaller in the validation cohorts compared to the Dutch cohort ($p < 0.001$, Table 3)). The predictive effect of PSA was smaller in the Swedish cohort compared with the Dutch cohort ($p < 0.001$, Table 3). An updated version of the risk calculator is presented in the Appendix. For the updated version, the model intercept was such that calibration was on average good in the Finnish and Swedish cohort. For the model with PSA and DRE the predicted outcome was substantially higher than the fraction of observed outcomes for both validated cohorts (Finland: 49% versus 26% and Sweden: 45% versus 23%).

Discrimination was similar among the 3 cohorts (Table 2). The AUC was 0.76 and 0.78 in the validation cohorts and 0.79 in the Dutch cohort, but substantially lower for the model with PSA only (AUC 0.64, 0.68 and 0.69 respectively).

3.3. Clinical usefulness

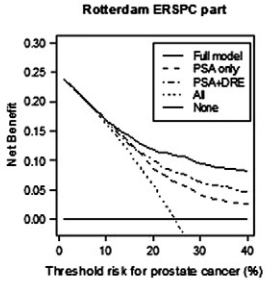
The net benefit, as shown on the y-axis, was highest for the risk calculator over the whole probability ranges in all cohorts, compared with the use of only PSA or biopsying all men or no men (Fig. 2). For the model included PSA and DRE there was no net benefit in the Finnish and Swedish co-

Table 3 – Comparison of results of Logistic Regression analyses on data obtained from Dutch, Finnish, Swedish cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) and the data of all three cohorts.

Variables	Dutch cohort $n = 3624$		Finnish cohort $n = 1825$		Swedish cohort $n = 531$		All three cohorts $n = 5980$		p-Value for interaction*
	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	B	Exp(B) (95% C.I.)	
LogPSA	3.76	42.80 (30.24–60.57)	2.57	13.07 (7.71–22.16)	2.68	14.63 (5.66–37.83)	3.36	28.77 (22.02–37.60)	<0.001
Log volume	–4.21	0.02 (0.01–0.03)	–4.31	0.01 (0.01–0.03)	–4.14	0.02 (0.00–0.07)	–4.18	0.02 (0.01–0.02)	0.349
DRE	0.82	2.27 (1.88–2.73)	1.20	3.31 (2.51–4.37)	0.96	2.61 (1.48–4.59)	0.88	2.41 (2.08–2.78)	0.344
TRUS	0.87	2.38 (1.97–2.87)	0.02	1.02 (0.70–1.50)	0.34	1.40 (0.83–2.37)	0.63	1.87 (1.60–2.19)	<0.001
Finland							–0.40	0.67 (0.52–0.86)	
Sweden							–0.55	0.58 (0.49–0.68)	
Constant	2.55	12.84	3.13	22.85	2.78	16.07	2.84	17.06	

LogPSA: natural log transformation of the serum Prostate Specific Antigen; Logvolume: natural log transformation of the prostate volume; DRE: Digital Rectal Examination; TRUS: Transrectal Ultrasound.
Statistical significant: p-value of <0.05.
* Significant p-value for interaction means that the relationship between the predictor and the outcome varies by cohort.

A: Development data (n=3624)

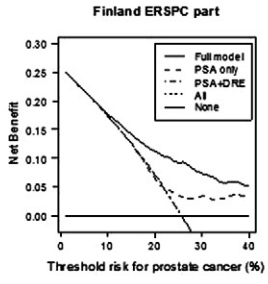


A: Number of biopsies in the Dutch cohort of the ERSPC and cancer at initial screening with various cut-offs of the positive sextant biopsy next to a prostate specific antigen cut-off ≥ 3 ng/ml using the full model.

P(posb) (%)	1: No. men biopsied	2: No. biopsies saved (% of total 1)	3: No. PCa detected	4: No. PCa missed (% of total 3)	5: No. PCa missed Gleason score > 6 (% of total 3)	6: No. PCa missed Gleason score ≤ 6 (% of total 3)	7: No. PCa missed*
	3624		893				
≥10	2670	954 (26)	817	76 (9)	12 (1)	63 (7)	1
≥12.5	2340	1284 (35)	782	111 (12)	18 (2)	92 (10)	1
≥15	2066	1558 (43)	745	148 (17)	21 (2)	126 (14)	1
≥20	1574	2050 (57)	656	237 (27)	35 (4)	201 (23)	1
≥25	1243	2381 (66)	602	291 (33)	46 (5)	243 (27)	2

P(posb): probability of a positive sextant biopsy; PSA: Prostate Specific Antigen; PCa: prostate cancer
*Gleason score and metastasis unknown

B: Validation data (n=1825)*



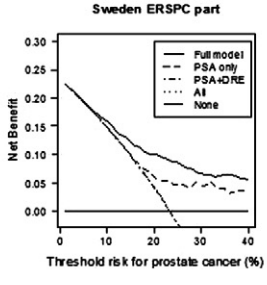
* No clinical usefulness for the model with PSA and DRE

B: Number of biopsies in the Finnish cohort of the ERSPC and cancer at initial screening with various cut-offs of the positive sextant biopsy next to a prostate specific antigen cut-off ≥ 3 ng/ml using the full model.

P(posb) (%)	1: No. men biopsied	2: No. biopsies saved (% of total 1)	3: No. PCa detected	4: No. PCa missed (% of total 3)	5: No. PCa missed Gleason score > 6 (% of total 3)	6: No. PCa missed Gleason score ≤ 6 (% of total 3)	7: No. PCa missed*
	1825		469				
≥10	1675	150 (8)	459	10 (2)	0 (0)	9 (2)	1
≥12.5	1568	257 (14)	452	17 (4)	2 (<1)	13 (3)	2
≥15	1446	379 (21)	437	32 (7)	4 (<1)	26 (6)	2
≥20	1213	612 (34)	402	67 (14)	6 (1)	57 (12)	4
≥25	1002	723 (40)	375	94 (20)	8 (2)	81 (17)	5

P(posb): probability of a positive sextant biopsy; PSA: Prostate Specific Antigen; PCa: prostate cancer
*Gleason score and metastasis unknown

C: Validation data (n=531)*



* No clinical usefulness for the model with PSA and DRE

C: Number of biopsies in the Swedish cohort of the ERSPC and cancer at initial screening with various cut-offs of the positive sextant biopsy next to a prostate specific antigen cut-off ≥ 3 ng/ml using the full model.

P(posb) (%)	1: No. men biopsied	2: No. biopsies saved (% of total 1)	3: No. PCa detected	4: No. PCa missed (% of total 3)	5: No. PCa missed Gleason score > 6 (% of total 3)	6: No. PCa missed Gleason score ≤ 6 (% of total 3)	7: No. PCa missed*
	531		124				
≥10	421	110 (21)	118	6 (5)	1 (<1)	5 (4)	0
≥12.5	374	157 (30)	111	13 (10)	2 (2)	11 (9)	0
≥15	320	211 (40)	105	19 (15)	2 (2)	17 (14)	0
≥20	265	266 (50)	94	30 (24)	3 (2)	27 (22)	0
≥25	225	306 (57)	91	33 (27)	3 (2)	30 (24)	0

P(posb): probability of a positive sextant biopsy; PSA: Prostate Specific Antigen; PCa: prostate cancer
*Gleason score and metastasis unknown

Fig. 2 – Decision curve A for the predicted probabilities in the Dutch cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) and the decision curves B and C in the Finnish and Swedish cohort of the ERSPC (validation cohorts) for the model, model with PSA and DRE and for PSA alone. The table at each decision curve shows the number of biopsies in the different cohorts and cancer at initial screening with various cut-offs of the positive sextant biopsy next to a prostate specific antigen cut-off ⩾3 ng/ml.

horts (Fig. 2). A threshold of a calculated P(posb) ⩾12.5% in addition to requiring PSA ⩾ 3 ng/ml, would result in 35% (n = 1284), 14% (n = 257) and 30% (n = 157) fewer biopsies in the Dutch, Finnish and Swedish cohort respectively (Fig. 2). The price for this reduction would be that we miss 12% (n = 111), 4% (n = 17) and 10% (n = 13) of the PCa respectively, with 2% (n = 18), <1% (n = 2) and 2% (n = 2) with a Gleason score >6, all with no proven metastasis.

4. Discussion

In this study, we externally validated the ERSPC risk calculator to predict the probability of having a positive prostate biopsy in previously unscreened men in two independent screening cohorts. The model discriminated well between men with and without PCa with AUCs over 0.76. The model did overestimate the risk of a positive sextant lateralised P(posb) in the Finnish and Swedish cohorts. This may be caused by interobserver variation of pathologists of small atypical foci in prostate biopsies or adenocarcinoma, which might have led to less PCa diagnoses.[15,16] Furthermore, the effect of TRUS (positive for hypoechogenic lesions) in these cohorts was smaller than in the Dutch cohort. This may be caused by interobserver variation of the TRUS outcome.[17] The performance of TRUS as a screening tool is relatively poor with only 3.5% of a biopsy of hypoechogenic lesions being positive for PCa.[18] Furthermore, the effect of PSA was smaller in the Finnish and Swedish cohort than in the Dutch cohort, which can not readily be explained in the context of the well-controlled and standardised ERSPC study. In the Dutch cohort, the effect of PSA was greater under the 3.0 ng/ml than ⩾3 ng/ml. However, if we refit the model for PSA ⩾ 3 ng/ml, the predictive value of PSA decreased, but was still greater compared with the predictive value of PSA in the Finnish and Swedish cohort. Another reason for this risk overestimation may be caused by the effect of specific characteristics in the Finnish and Swedish cohorts which were not included in the model.[11]

Models predicting the probability of a positive sextant biopsy differ, because of the use of different predictors next to serum PSA, and the specifics of the studied cohorts.[4] External validation is therefore required for models before they can be applied in other settings. There are some other models for the prediction of PCa at initial biopsy using the sextant biopsy technique and developed in a screening setting.[6,19,20] The AUCs of these models were between 0.66 and 0.84.[6,19,20] The AUC of our risk calculator was over 0.76 in the relatively large cohorts considered for external validation. Moreover, the net benefit calculations as shown in decision curves indicated that the risk calculator was useful in taking biopsy decisions in previously unscreened men who wish to undergo PSA driven testing for PCa. Net benefit analysis gives a scientifically better founded judgement of the performance of a prediction model or nomogram than calibration and discrimination alone.[10,13,21] In our study, the net benefit was substantially higher for the risk calculator compared with only PSA in the model. In this net benefit calculation the burden of TRUS was not formally included. It would be difficult to determine the exact weight of the burden in balance to missing prostate cancer and unnecessary biopsy. There was no clinical usefulness with PSA and DRE in the model in the Finnish and Swedish cohort, which is explained by the substantial miscalibration of the model predictions. So, we can conclude that the optimal clinical result will be obtained by determining the indication for biopsy by use of the risk calculator, despite its problems in calibration. Another method for validation of a model is comparison of the performance among models in different cohorts, which may be more straightforward to interpret.[22]

A limitation of the study is that the risk calculator relied on sextant biopsies. This procedure has been replaced by 8 to 18 core biopsies in current practice. Sextant biopsies may lead to missing PCa. Different studies have reported that when more than 6 cores are taken, for example 8 to 12 cores, this might increase the PCa detection rate in a clinical setting.[23–27] A possible drawback of these increased PCa detection is that not only significant PCa is detected, but also more insignificant PCa.[28] Schröder and colleagues[29] concluded that most aggressive PCa which are initially missed, will be detected in a curable state with a lateralised sextant biopsy at rescreening after 4 years. Some may however surface as interval cancers with less favourable outcomes. The question remains whether extended biopsy schemes are needed in a PCa screening setting with repeated screening. Further research is necessary to validate the risk calculator when more than 6 prostate biopsy cores are taken, and when a clinical setting is considered rather than a screening setting.

5. Conclusions

In a screening setting the ERSPC risk calculator is useful to predict the probability of a positive lateralised sextant prostate biopsy and discriminates well between men with and without prostate cancer. The updated version of the ERSPC risk calculator predicts more accurately the probability in the Finnish and Swedish cohort. The risk calculator proved clinically most useful for decision thresholds between 10% and 40% compared with PSA alone or biopsied all men. Use of the risk calculator with thresholds between 10% and 25% substantially reduces doing unnecessary prostate biopsies with missing very few important prostate cancers. The risk calculator can hence support in decision making in a screening setting.

Conflict of interest statement

None declared.

Appendix A. Model updating

We refitted the model with the data of the three cohorts (n = 5980; 4494 men without PCa and 1486 with PCa). The logistic regression formula of the refitted model for the probability of having a positive sextant prostate biopsy was P(posb) = 1/(1 + exp(–L), with L = 2.837 + 3.359 logPSA + –4.181 logvolume + 0.878 DRE + 0.627 TRUS + –0.403 Finland + –0.547 Sweden.

	B	S.E.	Wald	df	*p*-Value	Exp(B)	95% C.I. for Exp(B)	
logPSA	3.359	0.136	605.742	1	<0.001	28.772	22.018	37.597
logVolume	−4.181	0.223	350.126	1	<0.001	0.015	0.010	0.024
DRE	0.878	0.075	138.583	1	<0.001	2.406	2.079	2.784
TRUS	0.627	0.079	62.389	1	<0.001	1.872	1.602	2.187
Cohortgroup			44.938	2	<0.001			
Cohortgroup (1: Finland)	−0.403	0.130	9.575	1	0.002	0.668	0.518	0.863
Cohortgroup (2: Sweden)	−0.547	0.084	42.157	1	<0.001	0.579	0.491	0.683
Constant	2.837	0.342	68.969	1	<0.001	17.059		

LogPSA: natural log transformation of the serum Prostate Specific Antigen; Logvolume: natural log transformation of the prostate volume; DRE: Digital Rectal Examination; TRUS: Transrectal Ultrasound Statistical significant: *p*-value of <0.05.

REFERENCES

1. 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.
2. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;**57**:79–85.
3. Finne P, Finne R, Bangma C, et al. Algorithms based on prostate-specific antigen (PSA), free PSA, digital rectal examination and prostate volume reduce false-positive PSA results in prostate cancer screening. *Int J Cancer* 2004;**111**:310–5.
4. Shariat SF, Karakiewicz PI, Suardi N, et al. Comparison of nomograms with other methods for predicting outcomes in prostate cancer: a critical analysis of the literature. *Clin Cancer Res* 2008;**14**:4400–7.
5. Vickers A, Cronin A, Roobol M, et al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. *J Clin Oncol* 2010;**294**:66–70.
6. Vickers AJ, Cronin AM, Aus G, et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Goteborg, Sweden. *BMC Med* 2008;**6**:19.
7. Vickers AJ, Cronin AM, Aus G, et al. Impact of recent screening on predicting the outcome of prostate cancer biopsy in men with elevated prostate-specific antigen: data from the European Randomized Study of Prostate Cancer Screening in Gothenburg, Sweden. *Cancer* 2010;**116**:2612–20.
8. Schroder F, Kattan MW. The comparability of models for predicting the risk of a positive prostate biopsy with prostate-specific antigen alone: a systematic review. *Eur Urol* 2008;**54**:274–90.
9. Kranse R, Roobol M, Schroder FH. A graphical device to represent the outcomes of a logistic regression analysis. *Prostate* 2008;**68**:1674–80.
10. Vickers A. Prediction models in urology: are they any good, and how would we know anyway? *Eur Urol* 2010;**57**:571–3.
11. Steyerberg EW. *Clinical prediction models. a practical approach to development, validation, and updating*. New York: Springer; 2009.
12. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;**26**:565–74.
13. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128–38.
14. Vickers AJ, Cronin AM, Roobol MJ, et al. A four-kallikrein panel predicts prostate cancer in men with recent screening: data from the European Randomized Study of Screening for Prostate Cancer, Rotterdam. *Clin Cancer Res* 2010;**16**:3232–9.
15. Van der Kwast TH, Evans A, Lockwood G, et al. Variability in diagnostic opinion among pathologists for single small atypical foci in prostate biopsies. *Am J Surg Pathol* 2010;**34**:169–77.
16. Wolters T, van der Kwast TH, Vissers CJ, et al. False-negative prostate needle biopsies: frequency, histopathologic features, and follow-up. *Am J Surg Pathol* 2010;**34**:35–43.
17. Roobol MJ, Kirkels WJ, Schroder FH. Features and preliminary results of the Dutch centre of the ERSPC (Rotterdam, the Netherlands). *BJU Int* 2003;**92**(Suppl 2):48–54.
18. Gosselaar C, Roobol MJ, Roemeling S, et al. The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer. *BJU Int* 2008;**101**:685–90.
19. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2006;**98**:529–34.
20. Porter CR, Gamito EJ, Crawford ED, et al. Model to predict prostate biopsy outcome in large screening population with independent validation in referral setting. *Urology* 2005;**65**:937–41.
21. Vickers AJ, Cronin AM. Traditional statistical methods for evaluating prediction models are uninformative as to clinical value: towards a decision analytic framework. *Semin Oncol* 2010;**37**:31–8.
22. Kattan MW. Validating a prognostic model. *Cancer* 2006;**107**:2523–4.
23. Presti Jr JC, Chang JJ, Bhargava V, et al. The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: results of a prospective clinical trial. *J Urol* 2000;**163**:163–6 (discussion 166-7).
24. Siu W, Dunn RL, Shah RB, et al. Use of extended pattern technique for initial prostate biopsy. *J Urol* 2005;**174**:505–9.
25. Chun FK, Briganti A, Graefen M, et al. Development and external validation of an extended 10-core biopsy nomogram. *Eur Urol* 2007;**52**:436–44.
26. de la Taille A, Antiphon P, Salomon L, et al. Prospective evaluation of a 21-sample needle biopsy procedure designed to improve the prostate cancer detection rate. *Urology* 2003;**61**:1181–6.
27. Eskicorapci SY, Baydar DE, Akbal C, et al. An extended 10-core transrectal ultrasonography guided prostate biopsy protocol improves the detection of prostate cancer. *Eur Urol* 2004;**45**:444–9.
28. Scattoni V, Maccagnano C, Zanni G, et al. Is extended and saturation biopsy necessary? *Int J Urol* 2010;**17**:432–47.
29. Schroder FH, van den Bergh RC, Wolters T, et al. Eleven-year outcome of patients with prostate cancers diagnosed during screening after initial negative sextant biopsies. *Eur Urol* 2010;**57**:256–66.