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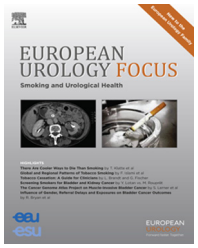

Prostate Cancer

Comparison of Two Prostate Cancer Risk Calculators that Include the Prostate Health Index

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Abstract

Background: Risk prediction models for prostate cancer (PCa) have become important tools in reducing unnecessary prostate biopsies. The Prostate Health Index (PHI) may increase the predictive accuracy of such models.
Objectives: To compare two PCa risk calculators (RCs) that include PHI.
Design, setting, and participants: We evaluated the predictive performance of a previously developed PHI-based nomogram and updated versions of the European Randomized Study of Screening for Prostate Cancer (ERSPC) RCs based on digital rectal examination (DRE): RC3 (no prior biopsy) and RC4 (prior biopsy). For the ERSPC updates, the original RCs were recalibrated and PHI was added as a predictor. The PHI-updated ERSPC RCs were compared with the Lughezzani nomogram in 1185 men from four European sites. Outcomes were biopsy-detectable PC and potentially advanced or aggressive PCa, defined as clinical stage >T2b and/or a Gleason score ≥7 (clinically relevant PCa).
Results and limitations: The PHI-updated ERSPC models had a combined area under the curve for the receiver operating characteristic (AUC) of 0.72 for all PCa and 0.68 for clinically relevant PCa. For the Lughezzani PHI-based nomogram, AUCs were 0.75 for all PCa and 0.69 for clinically relevant PCa. For men without a prior biopsy, PHI-updated RC3 resulted in AUCs of 0.73 for PCa and 0.66 for clinically relevant PCa. Decision curves confirmed these patterns, although the number of clinically relevant cancers was low.
Conclusion: Differences between RCs that include PHI are small. Addition of PHI to an RC leads to further reductions in the rate of unnecessary biopsies when compared to a strategy based on prostate-specific antigen measurement.
Patient summary: Risk prediction models for prostate cancer have become important tools in reducing unnecessary prostate biopsies. We compared two risk prediction models for prostate cancer that include the Prostate Health Index. We found that these models are equivalent to each other, and both perform better than the prostate-specific antigen test alone in predicting cancer.

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1. Introduction

Prostate cancer (PCa) is the most common form of cancer in men in Europe [1]. Prostate-specific antigen (PSA) testing is the mainstay of early PCa detection [2]. However, PSA has limited specificity in predicting the presence of PCa, which leads to unnecessary biopsies and the diagnosis of potentially indolent PCa [3,4]. A prostate biopsy is an invasive procedure, and apart from costs and anxiety, is not without a risk of complications [5].

PSA-based multivariable prediction tools have been developed to improve the prediction of biopsy-detectable PCa. Well-known and externally validated models include the European Randomized Study of Prostate Cancer (ERSPC) risk calculators (RCs) (http://www.prostatecancer-riskcalculator.com/) [6], the Prostate Cancer Prevention Trial calculator (http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp) [7], and the Montreal model [8]. Risk prediction models have become an important tool in reducing unnecessary prostate biopsies [9]. The addition of new biomarkers to an existing prediction tool may increase its accuracy. Novel and promising markers in the field of PCa include the Prostate Health Index (PHI), based on data for total PSA (tPSA), free PSA (fPSA), and [−2]proPSA (p2PSA). PHI has been approved for use by the US Food and Drug Administration (http://www.accessdata.fda.gov/cdrh_docs/pdf9/p090026a.pdf).

Lughezzani et al [10] developed and validated a nomogram that includes PHI. We aimed to compare PCa RCs that include PHI, the Lughezzani PHI-based nomogram, and PHI-updated digital rectal examination (DRE)-based ERSPC models.

2. Patients and methods

2.1. Participants

Our study cohort comprised 1185 men from four sites in Europe (Paris, Rennes, Hamburg, and Münster). Data on tPSA, fPSA, p2PSA, PHI, DRE, prostate volume, and biopsy outcome (PCa detected yes/no) were collected for all men. Participants in the study underwent a biopsy according to the standard clinical practice routinely used at each participating site, which was a ≥10-core biopsy. We calculated PHI using the equation (p2PSA / fPSA) × $\sqrt{}$tPSA [11]. tPSA was between 2.0 and 10.0 ng/ml (Access Hybritech assay [Beckman Coulter, Fullerton, CA, USA], corresponding to 1.6–8.0 ng/ml according to World Health Organization calibration). Outcomes were PCa detectable via sextant biopsy and potentially advanced or aggressive PCa (defined as clinical stage >T2b and/or a biopsy Gleason score ≥7; clinically relevant PCa).

2.2. Nomograms

Lughezzani et al [10] developed a PHI-based nomogram that includes age (yr), DRE (normal/abnormal), prior biopsy (yes/no), transrectal ultrasound (TRUS)-measured prostate volume (ml), and PHI. Two of the eight ERSPC Rotterdam PCa RCs (http://www.prostatecancer-riskcalculator.com/) were used as reference models:

(1) RC3 + DRE: A model that includes tPSA (ng/ml), DRE (normal/abnormal), and DRE-assessed prostate volume (25/40/60 ml) for men without a prior biopsy.
(2) RC4 + DRE: A model that includes tPSA (ng/ml), DRE (normal/abnormal), and DRE-assessed prostate volume (25/40/60 ml) for men with a prior (negative) biopsy.

For the ERSPC models the less invasive DRE-assessed volume (category 25/40/60 ml) was used. For this study, TRUS-assessed volume was therefore categorized into these volume classes with cutoff values of ≤30 ml, 30–50 ml, and >50 ml. Both models predict the chance of a positive sextant biopsy and the degree of PCa aggressiveness. We used logistic regression analyses to estimate the coefficients for p2PSA, p2PSA as a percentage of fPSA (%p2PSA), and PHI, in addition to ERSPC DRE-based RC3 (no prior biopsy) and RC4 (prior biopsy) [12]. These models included the linear predictor of ERSPC RC3 and RC4 as a covariate. We then developed updated versions of RC3 and RC4 using the original model in combination with proPSA, %proPSA, and PHI.

Validation using independent external data is the best way to compare the performance of a model with and without a new marker [13]. We developed updated versions of the RCs that include PHI by recalibrating the original models (re-estimation of the intercept and slope of the linear predictor) [14]. We then added fPSA, p2PSA, and PHI independently of each other in separate logistic regression models [14,15].

2.3. Comparison of the models

We evaluated the predictive performance of the PHI-based nomogram developed by Lughezzani et al [10] and updated versions of ERSPC RC3 and RC4 using the area under the curve for the receiver operating characteristic (AUC). We also evaluated inclusion of PHI instead of PSA in the ERSPC model since PSA is included in PHI and hence involves some collinearity. We also evaluated the added value of age as a covariate by adding age to the PHI-updated ERSPC model.

We used repeated cross-validations of large and smaller validation samples for optimal use of the data available [16]. We split the data into three subsets for men from Hamburg, Münster and France (Rennes/Paris). For the first cross-validation, we removed men from Münster from the population, recalibrated the ERSPC models, and updated these with PHI. These scores were allocated to men from Münster. The same steps were taken for men from France and then men from Hamburg. We then combined the scores for men from Münster, France, and Hamburg to estimate model performance in the total set. Multiple imputation was performed to substitute any missing values for the predictors included in the model (five repetitions).

We performed decision curve analysis (DCA) [13,17] to evaluate the potential clinical usefulness of making decisions based on the Lughezzani and PHI-updated ERSPC models. We estimated the net benefit (NB) for prediction models by summing the benefits (true positive biopsies) and subtracting the harms (false positive biopsies). The harms were weighted by a factor related to the relative harm of a missed cancer versus an unnecessary biopsy. This weighting was derived from the threshold probability (p_t) for PCa at which a patient would opt for a biopsy (range considered 0–40%) [18]. A model with the highest NB at a particular threshold should be chosen over alternative models. The potential reduction in biopsies was calculated according to the following formula: reduction in biopsies per 100 men = $(\Delta NB / [p_t / \{1 - p_t\}]) \times 100$, where p_t is defined as the probability of disease at which an attending physician is indifferent between performing and withholding a biopsy.

Standard statistical software was used (SPSS v 18.0, SPSS, Chicago, IL, USA; R version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Participants

Among the 1185 men studied, 797 (67%, 453 with PCa) had no previous biopsy and 388 (170 with PCa) had a previous negative biopsy (Table 1). Median PSA was 5.0 ng/ml for

Table 1 – Characteristics of the validation data set of 1185 men

Variable [a]	All men (*n* = 1185)	Prior biopsy (*n* = 388, 33%)	No prior biopsy (*n* = 797, 67%)
Age (yr)	64.0 (58.9–70.0)	64.2 (58.6–70.0)	64.0 (59.0–69.9)
Total PSA (ng/ml)	5.2 (4.0–6.7)	5.6 (4.2–7.2)	5.0 (3.9–6.5)
Prostate Health Index	44.8 (32.3–64.4)	41.1 (30.7–58.1)	46.9 (33.3–67.3)
TRUS-assessed volume (ml)	42 (30–58)	46 (33–64)	40 (30–54)
DRE-assessed volume			
<30 ml	256 (22)	73 (19)	183 (23)
30–50 ml	512 (43)	152 (39)	360 (45)
>50 ml	417 (35)	163 (42)	254 (32)
Normal DRE	859 (73)	323 (83)	536 (67)
Biopsy outcome			
Total cancer	623 (53)	170 (44)	453 (57)
Clinically relevant cancer [b]	324 (27)	80 (21)	244 (31)

PSA = prostate-specific antigen; PHI = Prostate Health Index; TRUS = transrectal ultrasound; DRE = digital rectal examination.
[a] Data are presented as median (interquartile range) for continuous variables and *n* (%) for categorical variables.
[b] Clinically relevant prostate cancer is defined as a clinical stage >T2b and/or a biopsy Gleason score ≥7.

men with no prior biopsy and 5.6 ng/ml for men with a prior biopsy, and median PHI values were 47 and 41, respectively. Men without a prior biopsy were more likely to have (clinically relevant) cancer compared to men with a prior biopsy.

3.2. Updating the ERSPC model

For total PCa, PHI improved discrimination (AUC 0.72, 95% confidence interval [CI] 0.69–0.75) compared to PSA testing alone (AUC 0.53, 95% CI 0.50–0.57). For clinically relevant cancer, PSA had AUC of 0.54 (95% CI 0.51–0.58) and PHI addition resulted in a substantial improvement (AUC 0.68, 95% CI 0.64–0.71).

ERSPC RC3 for all men had AUC of 0.65 (95% CI 0.62–0.68) which improved to 0.72 (95% CI 0.69–0.75) on addition of PHI. For men with a prior biopsy, RC4 had AUC of 0.66 (95% CI 0.62–0.69) and addition of PHI improved the predictive ability (AUC 0.72, 95% CI 0.67–0.77; Table 2). Of note, inclusion of p2PSA and %p2PSA in the updated ERSPC model also resulted in further increases in predictive capability, but to a lesser extent than PHI (data not shown).

For total PCa, there was a potential reduction in biopsies without missing additional PCa for risk thresholds ≥25% for the original ERSPC model and for thresholds ≥35% for the PHI-extended ERSPC model when compared to a biopsy-all strategy. For clinically relevant PCa, the original ERSPC model potentially reduced biopsies for risk thresholds ≥20%, whereas the PHI-updated model reduced biopsies for risk thresholds ≥10% (Table 3).

3.3. Comparison of the models

The Lughezzani PHI-based nomogram had similar performance to the PHI-updated ERSPC model, with AUC of 0.75 (95% CI 0.72–0.78) for all PCa and 0.69 (95% CI 0.66–0.72) for clinically relevant PCa. For men without a prior biopsy, PHI-updated RC3 resulted in AUC of 0.73 (95% CI 0.69–0.76) for PCa and 0.66 (95% CI 0.62–0.70) for clinically relevant PCa. For men with a prior biopsy, the corresponding AUC values were 0.72 (95% CI 0.67–0.78) and 0.74 (95% CI 0.68–0.80). Inclusion of TRUS-assessed instead of DRE-assessed volume did not change the AUC for the PHI-updated ERSPC model (Table 4).

The Lughezzani PHI-based nomogram had a significantly higher AUC (0.75, 95% CI 0.72–0.78) than the PHI-updated ERSPC model with DRE-assessed volume (0.72, 95% CI 0.69–0.75; $p < 0.05$) for total cancer, and for total cancer in men

Table 2 – Discriminative ability of PSA, PHI, the original ERSPC model, and the PHI–updated ERSPC model for prediction of total and clinically relevant prostate cancer in 1185 men

	n	Area under the receiver operating curve (95% confidence interval)			
		PSA alone	PHI alone	ERSPC	ERSPC + PHI
Total cancer					
All men	1185	0.53 (0.50–0.57)	0.72 (0.69–0.75)	0.65 (0.62–0.68)	0.72 (0.69–0.75)
Prior biopsy	388	0.50 (0.43–0.56)	0.71 (0.66–0.77)	0.64 (0.58–0.69)	0.72 (0.67–0.78)
No prior biopsy	797	0.56 (0.52–0.60)	0.71 (0.68–0.75)	0.68 (0.64–0.71)	0.73 (0.69–0.76)
Clinically relevant cancer [a]					
All men	1185	0.54 (0.51–0.58)	0.68 (0.64–0.71)	0.62 (0.59–0.66)	0.68 (0.65–0.71)
Prior biopsy	388	0.57 (0.50–0.65)	0.74 (0.69–0.80)	0.67 (0.60–0.73)	0.74 (0.68–0.80)
No prior biopsy	797	0.48 (0.44–0.52)	0.64 (0.60–0.68)	0.63 (0.59–0.67)	0.66 (0.62–0.70)

PSA = prostate-specific antigen; PHI = Prostate Health Index, DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer risk prediction model including total PSA (ng/ml), DRE (normal/abnormal), and DRE-assessed prostate volume (25/40/60 ml).
[a] Clinically relevant prostate cancer is defined as clinical stage >T2b and/or a biopsy Gleason score ≥7.

Table 3 – Reduction in biopsies compared to a biopsy–all strategy per 1000 men for the ERSPC risk calculator and the PHI–updated ERSPC risk calculator for all participants (n = 1185)

	Reduction (n)		
	ERSPC	ERSPC + PHI	Addition of PHI to ERSPC
Total cancer			
Risk threshold			
5%	0	0	0
10%	0	0	0
15%	0	0	0
20%	0	0	0
25%	3	0	0
30%	7	0	0
35%	11	31	20
40%	16	75	59
45%	29	116	87
50%	84	150	67
Clinically relevant cancer [a]			
Risk threshold			
5%	0	0	0
10%	0	6	6
15%	0	27	27
20%	18	122	104
25%	67	149	81
30%	156	194	38

PSA = prostate-specific antigen; PHI = Prostate Health Index, DRE = digital rectal examination; ERSPC = European Randomized Study of Screening for Prostate Cancer risk prediction model including total PSA (ng/ml), DRE (normal/abnormal), and DRE-assessed prostate volume (25/40/60 ml).
[a] Clinically relevant prostate cancer is defined as clinical stage >T2b and/or a biopsy Gleason score ≥7.

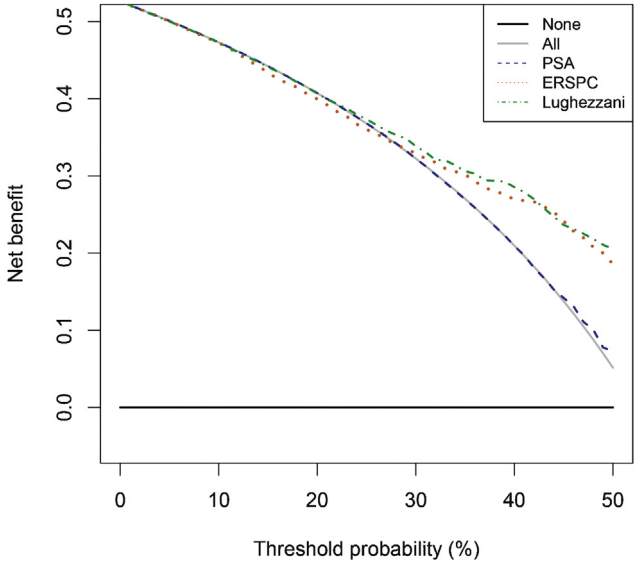

Fig. 1 – Net benefit of the PHI-updated ERSPC model and the Lughezzani PHI-based nomogram for prediction of total prostate cancer. PSA = prostate-specific antigen; PHI = Prostate Health Index; ERSPC = European Randomized Study of Screening for Prostate Cancer risk prediction model.

with a prior biopsy (0.75, 95% CI 0.70–0.80 vs 0.72, 95% CI 0.67–0.78; $p < 0.05$). The PHI-updated ERSPC models had better ability to predict clinically relevant PCa in men with or without a prior biopsy, although the differences were not significant (Table 4).

Inclusion of PHI instead of PSA had no effect on AUC for the PHI-based ERSPC model; in other words, removing PSA from a PHI-based model did not change its performance. Addition of age to the PHI-based ERSPC model led to the greatest increase in AUC compared to the original ERSPC model, with AUC of 0.74 (95% CI 0.71–0.77) for total PCa and 0.69 (95% CI 0.66–0.72) for clinically relevant PCa (Supplementary Table 1).

DCA revealed that any PHI-based model performed much better than PSA alone. A potential net reduction in biopsies was seen at PCa risk thresholds greater than ~30% for total PCa (Fig. 1 for total population, Supplementary Fig. 1A,B for men with and without a prior biopsy) and ~20% for clinically relevant PCa (Fig. 2 for total population, Supplementary Fig. 2A,B for men with and without a prior biopsy). At a risk threshold of 20% for PCa or 10% for clinically relevant PCa, the updated model including PHI did

Table 4 – Discriminative ability of the ERSPC and Lughezzani models including PHI for prediction of total and clinically relevant prostate cancer in 1185 men

	n	Area under the receiver operating curve (95% confidence interval)		
		Lughezzani	ERSPC + PHI	
			DRE volume	TRUS volume
Total cancer				
All men	1185	0.75 (0.72–0.78) *	0.72 (0.69–0.75)	0.72 (0.69–0.75)
Prior biopsy	388	0.75 (0.70–0.80) *	0.72 (0.67–0.78)	0.71 (0.66–0.76)
No prior biopsy	797	0.74 (0.70–0.77)	0.73 (0.69–0.76)	0.73 (0.69–0.76)
Clinically relevant cancer [a]				
All men	1185	0.69 (0.66–0.72)	0.68 (0.65–0.71)	0.68 (0.65–0.71)
Prior biopsy	388	0.73 (0.67–0.79)	0.74 (0.68–0.80)	0.73 (0.67–0.79)
No prior biopsy	797	0.65 (0.61–0.69)	0.66 (0.62–0.70)	0.66 (0.62–0.70)

PSA = prostate-specific antigen; PHI = Prostate Health Index; DRE = digital rectal examination; TRUS = transrectal ultrasound; Lughezzani = risk prediction model including age, DRE (normal/abnormal), TRUS-assessed prostate volume (ml), prior biopsy (yes/no), and PHI; ERSPC = European Randomized Study of Screening for Prostate Cancer risk prediction model including total PSA (ng/ml), DRE (normal/abnormal), PHI, and prostate volume assessed by DRE (category 25/40/60 ml) or TRUS (volume in ml).
[a] Clinically relevant prostate cancer is defined as clinical stage >T2b and/or a biopsy Gleason score ≥7.
* $p < 0.05$ versus ERSPC model with DRE-assessed volume by category.

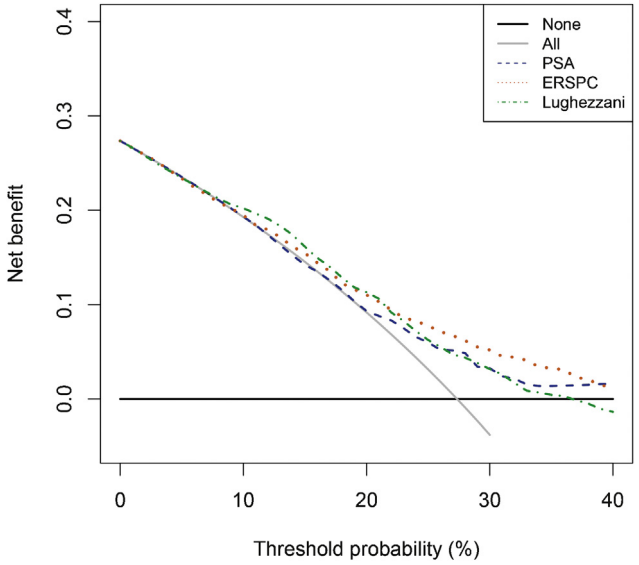

Fig. 2 – Net benefit of the PHI-updated ERSPC model and the Lughezzani PHI-based nomogram for clinically relevant prostate cancer. Clinically relevant prostate cancer is defined as clinical stage >T2b and/or a biopsy Gleason score ≥7. PSA = prostate-specific antigen; PHI = Prostate Health Index; ERSPC = European Randomized Study of Screening for Prostate Cancer risk prediction model.

not result in a net reduction in biopsies compared to a biopsy-all strategy. PHI addition to the RCs would reduce the number of biopsies only at higher values of the risk threshold compared to using PSA alone.

4. Discussion

PHI and its PSA components add important diagnostic information in distinguishing PCa from normal prostate tissue and when considered in addition to existing PCa RC models. However, the net reduction in biopsies was limited and only observed at PCa risk thresholds of approximately 20–30% using the two RCs we investigated. Nevertheless, it must be noted that NB would be higher in a population in which PCa prevalence is closer to the relevant decision threshold (eg, ~30%), as found for some clinic-based series.

The PHI-updated models and the Lughezzani PHI-based nomogram performed similarly in discriminating between men with and without PCa. The Lughezzani nomogram includes TRUS-assessed volume, while the ERSPC models use the less invasive DRE-assessed volume (categories 25/40/60 ml) [19]. No differences were observed between the PHI-updated ERSPC models with TRUS-assessed volume and DRE-assessed volume, and both were equivalent to the Lughezzani PHI-based nomogram (Table 4). We therefore prefer a model without the need for TRUS to assess prostate volume.

We confirmed that PHI performs better in predicting prostate cancer than conventional PSA measurement alone [20,21]. However, the increases in performance between the original and PHI-updated ERSPC models were small. Moreover, the PHI-updated models in this study are highly calibrated for the cohort used, and external validation of the models would be required before clinical use. Further studies on the incremental value of adding PHI to multivariable models are required. Furthermore, magnetic resonance imaging in conjunction with or incorporated in PCa RC models is likely to play a role in PCa diagnosis.

In addition to any gain in discrimination, we considered the NB, but we did not fully consider cost-effectiveness. According to previous analyses, cost-effectiveness depends on the risk threshold used for measuring PHI and on the specific range of PSA values [22,23]. Use of the updated model resulted in a relatively small reduction in prostate biopsies compared to the original RCs for risk thresholds of 0–40%, and no reduction in biopsies at a risk threshold of 20% for PCa or 10% for clinically relevant PCa. A comparative cost-benefit analysis is required to determine how much is gained and at what costs for the additional PHI test compared to the multivariate RC approach as an indication for biopsy. If the costs are similar for PHI and PSA testing, it makes sense to use the approach even if only it reduces unnecessary biopsies by a small amount.

One limitation of our study is the low number of patients with clinically relevant PCa. Thus, no strategy was clearly dominant over the whole range of risk thresholds according to NB. Total PCa was predicted better in men with no prior biopsy compared to men with a prior biopsy, whereas clinically relevant PCa was predicted better in men with a prior biopsy compared to men with no prior biopsy. This could be because patients with high-risk PCa were no longer present in the group with a prior biopsy, and discrimination of total PCa is more difficult once these patients have already been diagnosed.

There is also a potential risk of misclassification because the ERSPC RCs are based on sextant biopsies, while the validation cohorts used ≥10-core biopsies. Previous validation in a clinical setting showed practically no underestimation of cancer risk [24]. We do recognize that the prevalence of cancer in the current validation cohorts was far higher than in the ERSPC setting. PHI may be more clinically useful in a setting with a lower risk of (clinically relevant) PCa. More men can then be spared a biopsy because of low PCa risk.

5. Conclusions

In conclusion, PHI increases the predictive ability of previously developed RCs for detection of cancer. However, only limited reductions in the rates of unnecessary biopsies are possible for both the Lughezzani and the updated ERSPC models.

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, Houlgatte, Vincendeau, Lazzeri, Guazzoni, Stephan, Semjonow, Haese, Graefen.
Analysis and interpretation of data: Vedder, Steyerberg, Roobol, Nieboer.
Drafting of the manuscript: Vedder, Roobol.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Vedder, Steyerberg, Roobol, Nieboer.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.euf.2015.06.004.

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.
[2] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013. Eur Urol 2014;65:124–37.
[3] Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection 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.
[4] Heijnsdijk EA, der Kinderen A, Wever EM, Draisma G, Roobol MJ, de Koning HJ. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer 2009;101:1833–8.
[5] Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876–92.
[6] 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.
[7] 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.
[8] Karakiewicz PI, Benayoun S, Kattan MW, et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. J Urol 2005;173:1930–4.
[9] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124–37.
[10] Lughezzani G, Lazzeri M, Larcher A, et al. Development and internal validation of a Prostate Health Index based nomogram for predicting prostate cancer at extended biopsy. J Urol 2012;188:1144–50.
[11] Jansen FH, van Schaik RH, Kurstjens J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. Eur Urol 2010;57:921–7.
[12] 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.
[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] Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med 2004;23:2567–86.
[15] Steyerberg EW. Clinical prediction models. Berlin: Springer; 2009.
[16] Browne MW. Cross-validation methods. J Math Psychol 2000;44:108–32.
[17] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565–74.
[18] Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. BMC Med Inform Decis Making 2008;8:53.
[19] Roobol MJ, van Vugt HA, Loeb S, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012;61:577–83.
[20] Loeb S, Catalona WJ. The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol 2014;6:74–7.
[21] Filella X, Gimenez N. Evaluation of [–2] proPSA and Prostate Health Index (PHI) for the detection of prostate cancer: a systematic review and meta-analysis. Clin Chem Lab Med 2013;51:729–39.
[22] Nichol MB, Wu J, Huang J, Denham D, Frencher SK, Jacobsen SJ. Cost-effectiveness of Prostate Health Index for prostate cancer detection. BJU Int 2012;110:353–62.
[23] Heijnsdijk EAM, Huang JT, Denham D, De Koning HJ. The cost-effectiveness of prostate cancer detection using Beckman Coulter Prostate Health Index. Eur Urol Suppl 2012;11:E260.
[24] van Vugt HA, Kranse R, Steyerberg EW, et al. Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort. Eur J Cancer 2012;48:1809–15.