Published in final edited form as:

Nat Rev Urol. 2010 April ; 7(4): 184–185. doi:10.1038/nrurol.2010.41.

Utility of the Riskindicator model in screening

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Abstract

Use of a multivariable ‘Riskindicator’ model seems to increase the accuracy of screening for clinically significant prostate cancer. Such models, in conjunction with novel biomarkers, hold promise for improving the specificity of screening, and could help to and reduce the number of unnecessary biopsies performed in this setting.

Key issues in prostate cancer screening include the lack of specificity of PSA testing, which leads to unnecessary biopsies, and the detection and treatment of a proportion of tumors that will never present clinically. Thus, much research effort is directed at improving the accuracy of prostate cancer screening. In one such study, Roobol and colleagues¹ describe the use of a multivariable ‘Riskindicator’ model in conjunction with serum PSA level to improve the prediction of prostate cancer risk and reduce the number of unnecessary biopsies in a subset of men from the European Randomized Study of Screening for Prostate Cancer (ERSPC). They conclude that the Riskindicator model might be beneficial in the primary and repeat biopsy settings to increase the specificity of screening for prostate cancer.

The Riskindicator is a predictive tool that was originally developed in a cohort of 6,288 men from the Rotterdam section of the ERSPC. It has been examined in different formats (logistic regression model and graphical device),^{2,3} and is now available online for public use (Figure 1).⁴ The Riskindicator model includes the following variables: serum PSA level, digital rectal examination results, and transrectal ultrasonography (TRUS) findings (prostate volume and presence of hypoechoic lesion).

In the current study, the investigators first evaluated the ability of the Risk indicator model to predict the results of initial prostate biopsy in 1,850 men from the Rotterdam section of the ERSPC. They also tested an expanded model that incorporated prior biopsy history among 1,201 men who underwent repeat screening 4 years later. Finally, they estimated the relative proportion of ‘indolent’ and ‘important’ cancers that would have been missed using these Riskindicator models.

At the initial biopsy, which was triggered by a PSA threshold of 3ng/ml, prostate cancer was detected in 541 men, representing a positive predictive value of 29%. Using the

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Competing interests

W. J. Catalona declares associations with the following companies/organizations: Beckman Coulter, deCODE genetics, GlaxoSmithKline, Nanosphere, Ohmx. See the article online for full details of the relationships. S. Loeb declares no competing interests.

Riskindicator model, the mean predicted probability of prostate cancer was 43% (range 3–99%) in men with a positive biopsy, compared to 20% (range 1–88%) for those with a negative biopsy. On receiver operating characteristic analysis, the area under the curve (AUC) for the model was 0.77.

At the repeat screening, 1,201 men underwent biopsy, of which 568 (47%) had a prior negative biopsy at the first screening. Overall, 225 (19%) cancers were detected. The Riskindicator algorithm gave a mean predicted probability of prostate cancer of 26% (range 4–74%) in men with a positive biopsy, versus 17% (range 2–62%) for those with a negative biopsy. In this group, the Riskindicator had an AUC of 0.71 for the prediction of prostate cancer on repeat biopsy.

The researchers then investigated the effect of different Riskindicator cut-off points on prostate cancer detection. If a Risk indicator-predicted probability of $\geq 12.5\%$ was taken as the indication for biopsy, the model would have missed 73 (14%) and 37 (16%) cancers at the initial and repeat screenings, respectively. However, the authors estimated that 70% and 81% of these tumors met their criteria for ‘potentially indolent’ features.

Limitations of this study include the use of a limited sextant biopsy scheme, the overlapping wide ranges of predicted probabilities of prostate cancer using the Riskindicator, and the criteria used to define indolent disease. The Riskindicator defines indolent cancers as clinical stage $\leq T2$, PSA $\leq 20\text{ng/ml}$, primary and secondary Gleason grade ≤ 3 , $\leq 50\%$ positive cores, $< 20\text{mm}$ total cancer in biopsy cores, and benign tissue in all cores $\geq 40\text{mm}$. Thus, a patient with a serum PSA level of 19ng/ml and clinical stage T2b lesion with a positive core in each lobe containing 9mm cancer (D’Amico intermediate risk disease⁵) could potentially be considered to have indolent prostate cancer by the authors’ criteria. The Riskindicator might miss a greater proportion of potentially important tumors if more-stringent criteria for indolent cancer were used.

Another important issue with the Riskindicator is the inclusion of multiple parameters from TRUS, which is typically performed after the decision has been made to proceed with prostate biopsy, and the fact that virtually all patients have hypoechogenic regions on TRUS. Thus, this algorithm might not be pragmatic in the initial screening setting. Owing to the lack of consensus over the indications and timing of repeat biopsy, the Riskindicator might be a more helpful predictive tool at this stage, using TRUS findings from the original biopsy.

Finally, the Riskindicator models used in this study did not incorporate other important variables such as PSA velocity. Not only has this parameter been shown to enhance the specificity of screening for clinically significant prostate cancer,⁶ but a PSA velocity greater than 0.35ng/ml/year predicts an increased risk of fatal prostate cancer more than a decade before diagnosis.⁷

Despite these limitations, this study will be an important contribution in the ongoing effort to improve prostate cancer screening protocols, if validated in independent, external datasets. As predictive tools can perform differently in populations with different underlying features,⁸ it will be critical to test the Riskindicator in more-diverse patient populations. Once further validated, the benefits of the Riskindicator are that it uses straightforward predictors, and that it is available online, which makes it readily applicable in the clinic.

Prostate biopsy is an invasive procedure with the potential for serious infectious and noninfectious complications. Moreover, the identification through conventional screening of tumors that will remain indolent leads to unnecessary over treatment for many patients. As suggested by Roobol and colleagues,¹ the incorporation of multiple predictors into a risk-

assessment tool, such as the Riskindicator, along with the identification of new biomarkers, might help to improve the specificity of prostate cancer screening programs and reduce the incidence of unnecessary biopsies in the future.

Acknowledgments

W. J. Catalona is supported in part by the Urological Research Foundation, Beckman Coulter, Prostate SPORC grant (P50 CA90386-05S2) and the Robert H. Lurie Comprehensive Cancer Center grant (P30 CA60553).

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Figure 1.

The Riskindicator. This model predicts the risk of prostate cancer in a previously screened patient with a negative prior biopsy (positive TRUS, negative DRE, prostate volume 30ml, PSA 3.5ng/ml). The chance of the patient having a positive biopsy is 21%. Image courtesy of SWOP Prostate Cancer Research Foundation (www.prostatecancer-riskcalculator.com). Abbreviations: DRE, digital rectal examination; TRUS, transrectal ultrasonography.