A Novel Nomogram to Predict the Probability of Prostate Cancer on Repeat Biopsy

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Purpose: We developed a predictive model that incorporates clinical data and prostate specific antigen kinetic from general practice to detect prostate cancer in patients with a previously negative prostate biopsy.

Materials and Methods: From January 2001 to January 2007 data on 419 men who underwent repeat prostate biopsy with 12 or more cores were used to develop the nomogram. From February 2007 to June 2007 data on 63 men with the same criteria were used to validate the nomogram. The factors that we evaluated for the risk of a positive repeat prostate biopsy were patient age, digital rectal examination findings, total prostate specific antigen, the free-to-total prostate specific antigen ratio, prostate specific antigen density and slope, and previous high grade prostatic intraepithelial neoplasia.

Results: On multivariate logistic regression all factors except age and prostate specific antigen showed significant ability to predict the outcome of 12-core repeat prostate biopsy. In the validation group the AUC of the predicted results from the model was 0.856 (95% CI 0.744–0.931), better than that of prostate specific antigen, the free-to-total prostate specific antigen ratio, and prostate specific antigen density and slope ($p < 0.05$).

Conclusions: We successfully developed an accurate model to predict the outcome of repeat prostate biopsy. Adding the free-to-total prostate specific antigen ratio, digital rectal examination, prostate specific antigen and slope, and history of high grade prostatic intraepithelial neoplasia sharply improves the accuracy of our model.

Key Words: prostate, prostatic neoplasms, prostate-specific antigen, nomograms, biopsy

Prostate cancer will become a social emergency in the near future in Western countries because it is one of the leading causes of cancer death and it tends to increase with age more rapidly than many other malignancies. However, the conventional strategy for PSA screening, which calls for biopsies in all men with total PSA greater than 4 ng/ml, leads to many false-positive results and, thus, is associated with a high cost in terms of unnecessary biopsies.[1]

The cost is not only economic, but also psychological and emotional since anxiety on the part of the patient and family can be of considerable detriment to patient well-being. Considerable efforts are currently under way to improve prostate biopsy performance and emphasis has been directed primarily at enhancing specificity by decreasing false-positive results.[2] Also, after 1 or more negative biopsies patients with increased PSA insistently ask about the reason for their abnormal findings and most often the physician has no definitive answer.[3]

Several methods have been used to enhance the specificity of prostate cancer detection, including PSA velocity, PSA density, PSA transition zone density, age specific PSA, the ratio of free-to-total PSA, the level of α1-antichymotrypsin complexed PSA,[3] nomograms[4,5] and artificial neural networks.[6]

We developed a predictive model that incorporates clinical data and PSA kinetics from general practice to detect prostate cancer in patients with a previous negative prostate biopsy. The significant independent covariates for detecting carcinoma in the current study are patient age, DRE findings, total PSA, the free-to-total PSA ratio, PSA density, PSA slope and previous HGPIN. This predictive model might aid physicians in choosing patients for repeat prostate biopsy.

MATERIALS AND METHODS

From January 2001 to January 2007 data on 419 men who underwent repeat prostate biopsy with 12 or more cores were used to develop the nomogram. From February 2007 to June 2007 data on 63 men with the same criteria were used to validate the nomogram. Men with PSA interference, such as 5α-reductase therapy with finasteride or dutasteride, were excluded. All patients were scheduled for transrectal sonography with 12 or more cores because of abnormal DRE findings and/or abnormal PSA. All patients provided written informed consent.

Patients were examined in the left lateral decubitus position. Grayscale ultrasonography was performed with a 7.5 MHz Type 8551 endosonic multiplane transducer (B-K Medical, Herlev, Denmark). Prostate biopsies were performed by 4 of us who are urologists. Prostate specimens were evaluated by the referred pathologist.

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Serum was obtained before any diagnostic procedure. Total immunoreactive and free PSA were assayed using the chemiluminescent Immulite® immunoassay in accordance with manufacturer instructions. The assays are solid phase, 2-site sequential chemiluminescent immunometric tests that are automatically performed on an automated analyzer with detection limits of 0.02 and 0.03 μg/l for free and total PSA. For PSA kinetic evaluation we included PSA measurements done before repeat prostate biopsy if they were assayed at our central laboratory with the Immulite technique.

The percent free PSA was calculated as the ratio of free-to-total PSA multiplied by 100. PSA density was calculated as the PSA value divided by transrectal ultrasound estimated prostate volume. PSA velocity was calculated according to Khan et al as the running average of the rate of change during 3 or more consecutive assays with an elapsed time of more than 3 months.[7]

PSA slope was determined by fitting the line of least squares (PSA vs time) in patients with 3 or more PSA assays in 18 months or more before the last biopsy. Specifically we fit the equation, $y = a + bx$, to data on each patient, where y represents PSA, a represents the intercept and b represents the slope. The latter parameter reflects the PSA increase in 1 year and it uses the same unit as PSA velocity (ng/ml per year).[8]

The factors that we evaluated for the risk of positive repeat prostate biopsy were patient age, DRE findings, total PSA, the free-to-total PSA ratio, PSA density, PSA slope and previous high grade PIN. Multivariate logistic regression analysis, specifically stepwise logistic regression analysis, determined which factors were independent predictors of prostate carcinoma in the model building set. The relative risk and 95% CI were also derived. The nomogram was constructed using the Design library of S-Plus®. Calibration was assessed graphically. The same software was used to calculate statistical power. All tests were 2-sided with significance considered at 0.05.

RESULTS

Median PSA before the last biopsy was 8.8 μg/l (range 0.4 to 93.4). Median PSA was 8.45 μg/l in controls and 9.37 μg/l in patients with prostate cancer. All men underwent repeat prostate biopsy with 12 or more cores (range 12 to 24). The median number of previous negative biopsy session was 1 (range 1 to 5). The table shows the clinical characteristics of the 419 men. Briefly, median age was 69.4 years (range 49 to 90), median percent free PSA was 16.1%, median PSA density was 0.16 (range 0.01 to 2.2) and 35.7% of the men presented with suspicious DRE findings.

Median PSA slope was 0.5 ng/ml per year (range −7 to 15). A total of 33 men (7.8%) presented with HGPIN, of whom 13 (39%) showed prostate cancer. A total of 130 cancers (31%) were found on ultrasound guided prostate biopsy.

Of the 419 men in the develop group 173 had not undergone 3 PSA assays in 18 months or more. A total of 246 men had all clinical data available for multivariate logistic regression and constructing the nomogram. All 63 patients in the validation group had all data available.

Stepwise multivariate logistic regression analysis revealed that all factors except age and PSA showed significant ability to predict the outcome of 12-core repeat prostate biopsy. Independent analysis using forward and backward stepwise procedures yielded identical results.

The figure shows the resulting repeated prostate biopsy nomogram. The mathematical formula for easily calculating the prostate cancer risk on repeat biopsy is $\text{risk} = 1/(1 + e^{-Z})$, where $Z = 0.1727 + 0.671 \times (\text{DRE}) - 0.1426 \times (\text{free-to-total PSA ratio}) + 1.7452 \times (\text{PSA density}) + 0.222 \times (\text{PSA slope}) + 0.6292 \times (\text{HGPIN})$.

Data on the cohort of 63 men were used to validate the model. The AUC of predicted results of the model of this validation cohort was 0.856 (95% CI 0.744 to 0.931), which was better than PSA, the free-to-total PSA ratio, PSA density and PSA slope ($p < 0.05$).

We suggest a cutoff value of 0.2 (range 0 to 1) for the prostate cancer risk calculated with our nomogram, corresponding to 87.5% sensitivity (95% CI 67.6–97.2) and 76.9% specificity (95% CI 60.7–88.8) in our validation group. The 39 controls in the validation group were at a mean prostate cancer risk of 0.16 and the 24 patients were at a prostate cancer risk of 0.47. Statistical power was greater than 0.9. With a prostate cancer risk of less than 0.2 it is better to repeat total PSA, free PSA and DRE after 6 to 12 months, and so recalculate the prostate cancer risk. For a value of 0.2 or more it is better to repeat prostate biopsy.

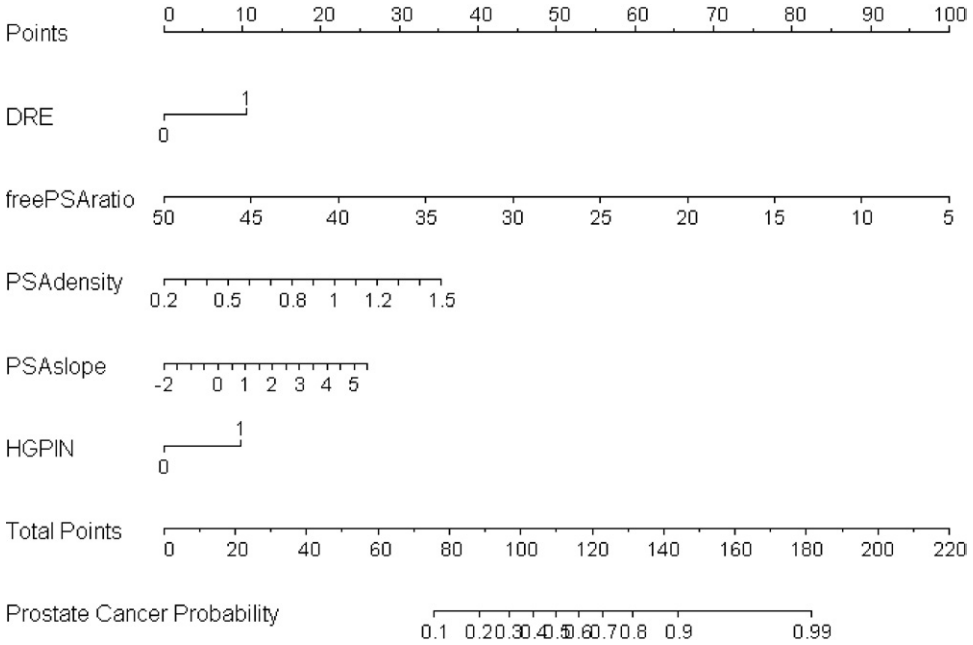
DISCUSSION

In the repeat biopsy setting the prostate cancer detection rate is as high as 30% and it continues to remain increased at subsequent biopsy sessions, as evidenced by positive biopsy rates of 13% to 35% at saturation biopsy.[9–12]

In 2003 Lopez-Corona et al presented their nomogram that predicts positive biopsy after a previous negative biopsy session.[10] Their nomogram includes 8 predictors, that is age,

Descriptive statistics

	Training Group	Validation Group	p Value (Mann-Whitney U test)
No. pts	419	63	
Median % age (range)	69.4 (49–90)	66.75 (51–85)	0.22
Suspicious DRE	35.7	39.6	0.72
Median ng/ml PSA (range)	8.8 (0.4–93.4)	7.81 (3.9–32.6)	0.21
Median % free PSA (range)	16.1 (2.2–65)	16.1 (3.6–50)	0.90
Median ng/ml/yr PSA velocity (range)	0.61 (−12.5–15)	0.71 (−4–11)	0.18
Median ng/ml/yr PSA slope (range)	0.55 (−7.4–15)	0.7 (−8.7–7.43)	0.56
Median cc prostate vol (range)	51 (10–330)	54 (12–330)	0.70
Median PSA density (range)	0.16 (0.01–2.2)	0.136 (0.044–0.82)	0.48
Median transition zone (range):			
Vol (cc)	33 (4–200)	33 (7–200)	0.80
PSA density	0.26 (0.01–2.5)	0.22 (0.09–1.18)	0.26
% Previous HGPIN	7.87	12.69	0.53



Nomogram predicting biopsy outcome in men undergoing repeat biopsy. To determine nomogram predicted probability of repeat prostate biopsy locate patient variable values at each axis. Draw vertical line to Points axis to determine how many points are attributable for each variable value. Sum points for all variables.

the presence or absence of a family history of prostate cancer, PSA, PSA slope, PSA density, DRE findings, the cumulative number of negative cores previously obtained, and the history of HGPIN and ASAP. In this nomogram PSA has a negative coefficient and it is difficult to calculate the corresponding value for PSA slope.

In a second study from the same group considering 10 predictors the PSA slope range seems too wide at between −40 and 145 for practical use.[11] Again, patient age is a parameter, so that the diagnosis is easier in older than in younger patients.

In 2006 Walz et al reported 2 nomograms, including a full model with all 9 predictors and a decreased model with significant predictors only.[12] It is easy to use but it misses PSA kinetics such as PSA velocity or slope.

The main advantage of our model is that it concentrates the most important factors for prostate cancer, such as DRE findings, the free-to-total PSA ratio, PSA density and slope, and previous HGPIN. Several interesting observations may be derived from close examination of the axes defining the nomogram risk variables. The PSA derivatives (free-to-total PSA ratio, PSA density and PSA slope) are more important factors than simple PSA for repeat prostate biopsy. We think that PSA kinetics are more decisive than a single PSA measurement and at the moment PSA slope is the best descriptor of PSA kinetics before biopsy.[8] We did not include age in our nomogram because it was not significant. This fact is in contrast with all other nomograms for repeat prostate biopsy.[11,12] The fact that age was not a predictive factor avoids a common risk of the nomograms, that is that prediction is easier in old men but almost impossible in younger men.

Validation was performed using internal data. We found an interesting accuracy with an AUC of 0.856, which is one of the best results for a diagnostic tool for prostate cancer.

A limitation of our nomogram is that it needs 3 or more PSA measurements in 18 months or more. In the absence of at least 3 PSA values in 18 months we recommend waiting and repeating the PSA test to calculate the prostate cancer risk. PSA slope calculation needs the availability of 3 or more PSA values made with the same laboratory technique.[8] The least squares fit used to elaborate PSA slope decreased intra-individual fluctuation. The least squares fit can easily be calculated with an electronic sheet.[13] Too much confusion is related to PSA velocity, first for its variable mathematical description in every study and then for its semantic ambiguity. Velocity and rate are analogous mathematical terms. Rate relates to the distance that an object travels in time using the equation, distance = rate × time. Urologists use the terminology of PSA velocity to denote a change in PSA with respect to time. Therefore, using the mentioned equation one should be able to multiply PSA velocity by time to achieve the distance that PSA traveled. However, PSA distance traveled is clinically irrelevant.[14] We recommend not using PSA velocity in our nomogram instead of PSA slope.

Puppo reported that after a previous biopsy patients come to urological examination with a high number of PSA measurements.[3] The patient expects that the urologist will evaluate the PSA list for an answer. Our nomogram with PSA slope is the answer. PSA slope cannot be evaluated in patients with PSA interference, such as 5α-reductase therapy with finasteride or dutasteride, or acute prostatitis.[8]

We did not include the presence of ASAP in our nomogram because, when there has been previous ASAP, there is no doubt that repeat prostate biopsy should be performed. Another important point is interobserver reproducibility. Epstein and Herawi studied cases diagnosed elsewhere as ASAP and concluded that such cases have the highest likelihood of being changed upon review.[15]

Our nomogram is an evolution of the previously published nomograms for repeat biopsy[9,12] because this model considers PSA kinetics and the previous diagnosis of HGPIN in men who underwent 12-core repeat biopsy. Moreover, we first suggest a cutoff value for a rapid decision to repeat

prostate biopsy. The cutoff value of 0.2 correspond to high sensitivity and to the interesting specificity of 76%, which means 3 positive repeat biopsies for every 4 that are done. We hope that our nomogram will be considered for external validation at other institutions.

CONCLUSIONS

We have successfully developed an accurate model to predict the outcome of repeat prostate biopsy. Adding the free-to-total PSA ratio, DRE, PSA density, PSA slope and history of HGPIN sharply improves the accuracy of our model.

Abbreviations and Acronyms

ASAP	=	atypical small acinar proliferation
DRE	=	digital rectal examination
HGPIN	=	high grade prostatic intraepithelial neoplasia
PSA	=	prostate specific antigen

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