Development and Validation of a Nomogram to Estimate the Risk of Prostate Cancer in Brazil

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Abstract. Aim: To develop and validate a nomogram to estimate the probability of prostate cancer (PCa) in men undergoing opportunistic screening. Patients and Methods: This was a cross-sectional observational study on a cohort of men screened for PCa at the Barretos Cancer Hospital (BCH) between January 2004 and December 2007. Patients’ data were collected from their charts and binary logistic regression analyses were performed to assess the power of various factor combinations as predictors of the PCa risk. Results: Out of the 1,313 screened men who underwent prostate biopsy, 553 (42.1%) had histopathological confirmation of PCa. The logistic regression analyses provided an area under the receiver operating characteristics (ROC) curve (AUC) of 0.737 (95% confidence interval (CI)=0.678-0.796) for the best predictor combination. A nomogram was constructed to estimate the individual risk for PCa prior to biopsy. Conclusion: Our nomogram provides an easy and practical method, superior in performance to the traditional criteria, predicting the diagnosis of PCa with a reasonable accuracy.

Prostate cancer (PCa) is a major cause of morbidity and cancer mortality worldwide (1). In the US, 241,740 new cases of PCa were diagnosed resulting in 28,170 deaths in 2012 (2). In Europe, PCa is the most common cancer among males and the second leading cause of cancer-related death. According to the Brazilian National Cancer Institute, there were 60,180 new cases of PCa in 2012 translating to an incidence of 62/100,000 (4).

The global incidence of PCa has increased significantly since 1990, mainly due to the implementation of cancer screening programs, e.g. by prostate-specific antigen (PSA) test and digital rectal examination (DRE) (5). However, the effectiveness of PSA testing and DRE remains controversial. Many experts argue that current data are insufficient to prove that these methods bring more benefits than risks (2). It is undisputed, however, that screening for PCa leads to early diagnosis, possibly resulting in decreased mortality. However, screening may also increase the burden of many patients who do not benefit from the treatment and screening (6).

While the definitive diagnosis of PCa is performed by core needle biopsy, this costly and invasive procedure could be preferably avoided (7). The use of alternative tools with high accuracy in predicting the presence of cancer, such as a nomogram, might help reduce the number of unnecessary biopsies, pain and morbidity in men (8).

A nomogram is a device or model using an algorithm or mathematical formula composed of several variables predicting the probability of an event or outcome (9), such as the occurrence of cancer in prostate biopsy. These models are designed to quantify the combination of several risk factors capable of probabilistic prediction of the outcome of interest. In this context, nomograms can improve the efficiency of PCa detection, exceeding the performance of even the experienced clinical experts (10).

The aim of the present study was to develop and validate nomograms for estimation of the probability of cancer in patients undergoing opportunistic PCa screening in Brazil.
Patients and Methods

This is an observational study of a cross-sectional cohort of men who underwent Mobile Cancer Prevention Unit (MCPU) cancer screenings conducted by the Department of Prevention, Barretos Cancer Hospital (BCH) between January 2004 and December 2007. The details of the MCPU cancer screening program have been previously described (11).

The age range of the men varied between 45 and 80 years with a definitive indication for biopsy: PSA≥4 ng/ml and/or a DRE suspect for PCa and/or PSA≥2.5 ng/ml with a %fPSA ≤15%. All eligible men were referred to the Department of Prevention, HCB, for further evaluation. An ultrasound-guided prostate biopsy using an 18-gauge needle was performed and 6–16 fragments were submitted for histological examination (median of 12 fragments).

The data for constructing the models were collected from the patient charts, including the family history of PCa, education level, age, results of DRE, PSA values and %fPSA. The radiological data available in this study consisted of prostate volume and ultrasound results. Finally, the pathological data comprised of biopsy results. Latent cancer was defined as a tumor with the total tumor volume <0.5 cm³, confined to the prostate, and with Gleason score <7 (12).

Statistical analysis. Potential predictors of PCa explored in this study included age, family history of PCa in first-degree relatives, education, total PSA levels, %fPSA, PSA density, ultrasound results and DRE. Development and validation of the nomogram. Binary logistic regression analyses were used to estimate the power of each variable and their combination as a predictor of the risk of PCa. For these calculations, the study sample was divided into the model construction cases (75% of the study population) and model validation cases (the remaining 25% of the samples). Once the logistic model is adjusted, it needs to be verified for accuracy of fit, which was done using the receiver operating characteristics (ROC) analysis. The area under the ROC curve (AUC) reflects the diagnostic discrimination capacity of the model. According to Hosmer and Lemeshow, AUC>0.7 corresponds to reasonable discrimination, AUC=0.8 excellent and AUC=0.9 an exceptional discrimination (13).

After building the models, the data were sent through a JavaScript program to display the graphics of the estimates of each individual patient (www.hcancerbarretos.com.br/prostate-nomogram). All statistical analyses were performed using the SPSS Statistics 20.0.1 for Windows (IBM Corporation, Somers, NY, USA). The graphic construction of the nomograms was performed using the statistical program R (R Foundation for Statistical Computing, Vienna, Austria) with the aid of the RMS package (Regression Modeling Strategies, address) (14). The level of statistical significance was set at \( p<0.05 \).

Ethical aspects. This study was approved by the Institutional Review Board (IRB) of BCH (protocol number: 280/2009), and the IRB of the Faculty of Medicine, University of São Paulo (protocol number: 286/2011). All patients enrolled in this study by MCPU signed an Informed Consent Form.
Results

During the study period (January 2004- December 2007), altogether 17,571 males were screened by the MCPU program and 1,313 of them, who met the criteria outlined in the guidelines of BCH, underwent prostate biopsy at the Radiology Department.

The mean age of these men was 66.2 years (standard deviation (SD)=8.4, median=67 years) and most of them (87%) had a low level of education (Table I). The majority of patients were from the State of São Paulo and Mato Grosso do Sul. Sixty-three (4.8%) had a history of PCa in his first-degree relative. PSA levels before biopsy varied from 0 to 144 ng/ml (mean=9.1, SD=5.0, median=14.3 ng/ml), %fPSA ranged from 0 to 47% (mean=1.9, SD=7.2, median=15%), average prostate volume was 47.67 cm³ (SD=27.0; median=40 cm³) and PSA density ranged from 0 to 20 ng/ml.cm³ (mean=0.23, SD=0.65, median=0.12 ng/ml.cm³) (Table I). Ultrasound imaging was normal in 594 (45.2%) men, while hypoechoic nodules were found in 710 (54.0%) and hyperechoic nodules in 9 (0.7%).

Out of the 1,313 men included in this study, 553 (42.1%) had histopathological confirmation of prostatic adenocarcinoma with a Gleason score ranging between 5 and 9. Insignificant or latent tumors were found in 66 (5.0%) of the positive cases.

Evaluation of the summons methods. To evaluate the ability of each of the potential predictor variables to correctly identify men with suspected PCa confirmed by biopsy, the AUCs were calculated for each variable individually and combined. AUC=0.544 (95% confidence interval (CI)=0.516-0.572) was obtained for the BCH guideline criteria alone. If only the internationally most frequently used variables (PSA ≥4 ng/ml and/or DRE changes) were included, AUC was 0.521 (IC 95%=0.489-0.552).

To evaluate the ability of serum PSA (free or total), DRE and ultrasound to predict the likelihood of PCa, along with the demographic data, ROC analyses were completed for each variable. The variables with the highest and lowest predictive power of individual subjects of having PCa were PSA density (AU=0.736; 95% CI=0.709-0.764) and DRE (AUC=0.496; 95% CI=0.465-0.528), respectively (Table II).

Logistic models. To build up the model, we used the model construction cases (n=871), whereas the validation cases (n=280) were used to verify the predictive power of the model. In this testing, the best model for estimating the risk of PCa consists of the variables PSA, %fPSA, PSA density, age and ultrasound results (Table III). This adjusted model resulted in AUC=0.766 (95% CI=0.734 to 0.797) in the construction series. When applied to the validation series, this adjusted model gave AUC=0.737 (95% CI=0.678 to 0.796), indicating a reasonable fit (Figure 1).

On the basis of this logistic regression analysis, a graphical representation of a nomogram was constructed for prediction of PCa in patients undergoing ultrasound-guided biopsy as part of the opportunistic screening in BCH (Figure 2).
The nomogram lines have scales marked on them and the relationship between points on each scale is given by placing a straight line across the scales. The nomogram developed here is based upon the simple lines design where the answer (the probability) can be seen summing the scores of each variable.

**Discussion**

Several studies have shown that screening for PCa has improved the survival of PCa patients, including studies from Canada (15), Austria (16) and other European countries (ERSPC) (17). However, other studies, like the PLCO study in North America, failed to show any significant reduction in mortality after a 7-10 year follow-up (18).

It is clear that screening for PCa based on PSA and DRE has still significant limitations, since PSA is highly sensitive but not cancer-specific, and most men with elevated PSA do not have PCa (19). Due to these practical shortcomings, increasing interest has been focused on computer modeling to more accurately predict the risk of PCa, including the use of nomograms.

A cohort of men from different regions of Brazil who underwent opportunistic screening for PCa was used to build such models to elaborate the best combination of variables in the prediction of PCa. All criteria used in the BCH screening program had low accuracy with an AUC of 0.544 (95% CI=0.516-0.572). However, these criteria were slightly more efficient as compared with the criteria recommended by various organizations, such as PSA ≥4 ng/ml and/or DRE changes alone. The combination of these two variables generated an AUC of 0.521 (95% CI=0.489-0.552). In contrast, the nomograms developed in this study showed the greatest accuracy among all combinations tested. With an AUC of 0.766 (95% CI=0.734-0.797) and 0.737 (95% CI=0.678-0.796) in predicting PCa in the model construction series and in the validation series, respectively, this model shows a reasonable fit, comparable with similar approaches previously published (1, 8, 20-25).

Several models for predicting the risk of PCa have been published, with Eastham and colleagues’ being the first to introduce this tool (20). Their original study included 700 men and the variables used in the modeling were PSA, age and ethnicity. Only PSA was an independent predictor of positive prostate biopsy with AUC=0.75. Importantly, most of these studies were performed during the early stages of PSA screening and the traditional standard sextant prostate biopsy was used, which may limit the applicability of the nomogram (21) because this biopsy pattern may not be optimal for detection of PCa (24).

The first nomogram developed in the context of a population-based screening of PCa was published in Finland (22). In that study, %fPSA, PSA, prostate volume and DRE were statistically significant predictors of PCa. However, the authors did not report measures of model validation, accuracy, sensitivity or specificity. Furthermore, the model was not converted to a multivariate risk equation with a graph format, which limits its clinic usefulness (21). Similar values of AUC were reported by Garzotto and colleagues in a study from Portland, OR, United States (8) in which the statistically significant predictors of PCa were DRE, ultrasound results, PSA density and age, with an AUC=0.73.
Karakiewicz and colleagues developed two nomograms with data from three separate cohorts in which men were referred for prostate biopsy based on PSA values, %PSA and DRE changes (1). The data from the first and second cohorts were collected in Montreal, Canada, where 4,193 men were evaluated with ultrasound-guided sextant biopsies after PSA and DRE tests and 514 of whom were subjected to the same procedures plus free PSA measurement. The third cohort consisted of 1,762 men from the University Hospital of Hamburg-Eppendorf, Germany. These men met the criteria for sextant prostate biopsy and data from PSA, free PSA and DRE were collected. The nomogram based on age, DRE, PSA and %fPSA showed a better accuracy than the previous nomogram using only age, DRE and PSA with AUC values of 0.77 (95% CI=0.72-0.81) and 0.69 (95% CI=0.68-0.72), respectively. This study was limited in that it could not evaluate the impact of ethnicity, because all patients were white men. Another limitation of this study was the standard sextant prostate biopsies (21).

The Prostate Cancer Prevention Trial (PCPT) included 5,519 men who underwent prostate biopsy and the collected data were used for testing a nomogram. In multivariate analyses, PSA, family history of PCa, PSA, %fPSA, ethnicity and DRE results were significantly associated with the risk of PCa, with an AUC of 0.70 (17). In another trial, Kranse and colleagues used a logistic regression model based on data from 3,624 men who participated in a screening program in the European Randomized Study of Screening for Prostate Cancer (ERSPC). The AUC for this model was 0.79 (23).

More recently, a nomogram for estimating the risk of PCa and high-grade PCa in the first biopsy was developed in Cleveland, OH, USA based on 1,551 men who had a PSA level of up to 10 ng/ml. The nomogram included age, family history of PCa, PSA, %fPSA, ethnicity and DRE results. The final models showed values of AUC of 0.73 (95% CI=0.71-0.76) and 0.71 (95% CI=0.69-0.74) for the prediction of risk of PCa and high-grade PCa, respectively (25).

The results of the present study are fully comparable to those reported in previous studies (20-25). One limitation of our study is the lack of information on the body mass index as some studies have found a statistically significant association between obesity and the risk of PCa, particularly with a Gleason score >7 (26). Another limitation is the lack of information on previous hormone therapy and use of finasteride. Finasteride is a 5α-reductase inhibitor that has been used as a chemopreventive agent in PCa and may reduce the risk by approximately 25% (27). However, despite the benefits of this drug, its use in preventing PCa is uncommon (28).

Our results indicate that all information necessary for the calculation of the PCa risk can be easily obtained in clinical practice. It is easily accessible to physicians to facilitate their final decision to undertake prostate biopsy for only patients who really need it. This nomogram is a tool that displays an individual patient’s risk of PCa, more accurately than the traditional methods for biopsy indication. It can also avoid unnecessary biopsies and, thereby, decrease the risks and discomforts from the biopsy procedure. Moreover, having been validated for the Brazilian population with representatives from several states, this model is likely to be applicable for urologists nationwide.

### Table III. Results of the logistic regression model to estimate the risk of prostate cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>β-Coefficient</th>
<th>Standard error</th>
<th>Wald</th>
<th>p-Value</th>
<th>Odds-ratio</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA density (ng/ml.cm⁻³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0-0.09</td>
<td>268</td>
<td>0.578</td>
<td>0.223</td>
<td>64.23</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.152 2.758</td>
</tr>
<tr>
<td>0.10-0.149</td>
<td>240</td>
<td>0.705</td>
<td>0.470</td>
<td>34.29</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>0.15-0.199</td>
<td>128</td>
<td>1.548</td>
<td>0.616</td>
<td>52.26</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>≥0.20</td>
<td>235</td>
<td>1.926</td>
<td>0.605</td>
<td>34.29</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td><strong>PSA (ng/ml)</strong></td>
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<td></td>
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<tr>
<td>0-2.49</td>
<td>41</td>
<td>0.570</td>
<td>0.223</td>
<td>9.44</td>
<td>0.024</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>2.50-3.99</td>
<td>166</td>
<td>0.841</td>
<td>0.470</td>
<td>3.20</td>
<td>0.074</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>4.0-9.99</td>
<td>477</td>
<td>0.280</td>
<td>0.469</td>
<td>0.36</td>
<td>0.551</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>≥10.0</td>
<td>187</td>
<td>0.592</td>
<td>0.512</td>
<td>1.33</td>
<td>0.248</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Normal</td>
<td>400</td>
<td>0.705</td>
<td>0.157</td>
<td>20.28</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>Abnormal</td>
<td>471</td>
<td>0.841</td>
<td>0.470</td>
<td>3.20</td>
<td>0.074</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>%fPSA &lt;15</td>
<td>813</td>
<td>-3.064</td>
<td>0.741</td>
<td>17.10</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>≥15</td>
<td>58</td>
<td>0.705</td>
<td>0.157</td>
<td>20.28</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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<tr>
<td>Intercept</td>
<td>871</td>
<td>0.023</td>
<td>0.011</td>
<td>4.48</td>
<td>&lt;0.001</td>
<td>1.78</td>
<td>1.079 2.805</td>
</tr>
</tbody>
</table>

%fPSA, Ratio of the free PSA/total PSA; PSA, prostate-specific antigen.
Conclusion

A nomogram was constructed for predicting the risk of PCAs in men undergoing opportunistic screening. Our model, based on readily-available data, provides an easy and practical method superior in performance to the traditional criteria for biopsy indications. The clinical validation of the model showed that this nomogram has a reasonable accuracy.

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