# *Nomogram prediction for prostate cancer and aggressive prostate cancer at time of biopsy: utilizing all risk factors and tumor markers for prostate cancer*

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NAM RK, TOI A, KLOTZ LH, TRACHTENBERG J, JEWETT MAS, LOBLAW A, POND GR, EMAMI M, SUGAR L, SWEET J, NAROD SA. Nomogram prediction for prostate cancer and aggressive prostate cancer at time of biopsy: utilizing all risk factors and tumor markers for prostate cancer. The Canadian Journal of Urology. 2006;13(Supplement 2):2-10.

***Background:*** *There is a large amount of confusion in interpreting prostate specific antigen (PSA) values for prostate cancer. More precise risk assessments for prostate cancer detection are needed for men faced with an abnormal PSA.*

***Methods:*** *We studied a sample of 2637 men who underwent a prostate biopsy for an abnormal digital rectal exam (DRE) or PSA. Using factors including age, ethnicity, family history of prostate cancer, previous negative biopsy, presence of voiding symptoms, prostate volume, DRE and PSA, we constructed nomograms to predict the probability of prostate cancer at biopsy.*

***Results:*** *Of the 2637 men, 1282 men (48.6%) had prostate cancer detected. Age, ethnicity, family history of prostate cancer, a previous negative biopsy, prostate volume, DRE and PSA were all significant predictors of prostate cancer. Nomograms were constructed based on these factors to predict the risk of prostate cancer and of aggressive prostate cancer (defined as a Gleason Score 7 or more). The positive predictive value varied from 5% to 95% based on the nomograms. The nomograms were validated using bootstrapping methods and the expected and observed proportions were found to be highly concordant.*

***Conclusions:*** *For men with an abnormal PSA or DRE, the risk for prostate cancer can be accurately estimated using a nomogram based on age, ethnicity, family history of prostate cancer, previous negative biopsy, presence of voiding symptoms, prostate volume, DRE and PSA. This tool will aid physicians and patients in determining the need for prostate biopsy.*

**Key Words:** prostate cancer, prostate specific antigen, biopsy, nomogram

Acknowledgement
This study was funded by the National Cancer Institute of Canada Grants #010284 and #015164. Dr. Nam was supported by the Canadian Urological Association Young Investigators Award.

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## Introduction

Prostate cancer is the most common male malignancy in North America and is a large public health burden.[1] It is difficult to assess individual risk for prostate cancer and to determine who is at risk for developing an aggressive form of prostate cancer. This is due, in part, to the high prevalence of prostate cancer among

older men,[2] the absence of clear susceptibility genes for prostate cancer, and the lack of tumor markers with high specificity.

To date, the measurement of serum prostate specific antigen (PSA) and the digital rectal examination (DRE) are used for the early detection of prostate cancer.[3] We and others have evaluated additional biomarkers, but none have been able to replace PSA to detect prostate cancer.[4-6] Recently, Stamey et al argued that PSA levels less than 20.0 ng/mL cannot be used to distinguish between patients with prostate cancer and benign prostatic hyperplasia.[7]

Further, all patients with prostate cancer may not require treatment; large, population-based studies have shown that many patients with low grade prostate cancer have a higher chance of dying from other conditions rather than from prostate cancer itself.[8,9]

Nevertheless, the PSA test continues to be widely used. Patients and physicians are often faced with an abnormal PSA value and must decide whether or not a biopsy is warranted. We have shown that incorporating established risk factors for prostate cancer in a multivariate model can significantly improve the positive predictive value of the PSA test.[10,11] By combining a panel of predictive variables including age, ethnicity, family history of prostate cancer and prostate volume, the positive predictive value of PSA to detect prostate cancer varied from 10% to 90% among 2637 patients who underwent a prostate biopsy for an abnormal PSA or DRE.[10] These risk factors were also associated with histologic grade at diagnosis.

Using the same cohort, we generated nomograms for predicting both prostate cancer and aggressive forms of prostate cancer incorporating PSA, DRE status and other variables associated with prostate cancer that can be used as a clinical tool to help guide biopsy management strategies. For patients and clinicians faced with an abnormal PSA or DRE, this clinical tool could aid in understanding an individual risk for having prostate cancer and also aggressive forms prostate cancer.

## Methods

### *Study subjects*

Patients were drawn from a sample of 2838 eligible men who were referred to the Prostate Centers of the University of Toronto (Sunnybrook & Women's College Health Sciences Centre and University Health Network), between June 1999 and June 2004.[10] Patients were included in the study if their PSA value was greater than 2.5 ng/mL[12] or if they had an abnormal DRE. All patients underwent transrectal ultrasonography (TRUS) and one or more prostate biopsies. Patients eligible for this study were unselected and were accrued consecutively. No patient had a past history of prostate cancer. Of the 2839 men, 46 patients were not capable of giving consent to participate in a research study. Of the remaining 2793 men, 2637 (94%) agreed to participate. All research was conducted with informed consent and with the approval of the hospital research ethics board.

### *Baseline data information and primary endpoint*

A urological voiding history (American Urological Association Symptom Score,[13]) DRE results, serum PSA level, family history of prostate cancer information, and ethnic background were obtained by research personnel through questionnaire administration and medical record review. All data were stored within a centralized database. Prostate volume was measured by TRUS. Volume was determined by two physicians with extensive experience performing TRUS and prostate biopsy (R.K.N., A.T.) and was estimated using the formula found to have the best accuracy for prostate volume: length (mm) x width (mm) x sagittal height (mm) x 0.0005236 = volume (c.c.),[14] *(length and height measured on midsagittal view, width on transverse axial view).*

Six to 15 ultrasound-guided needle core biopsies were performed (median=8), using an 18-gauge spring loaded biopsy device. Samples were obtained using a systematic pattern and additional targeted samples were obtained from suspicious areas. The primary endpoint was the histologic presence of adenocarcinoma of the prostate in the biopsy specimen. All grading was based on the Gleason scoring system.[15] All histologic interpretations were interpreted by two experienced genitourinary pathologists (L.S. and J.S.).

We and others have reported that after an initial negative biopsy, approximately 15% to 30% of patients have cancer found at repeat prostate biopsy.[11,16] Therefore, patients who had an initial negative biopsy were offered repeat prostate biopsies. Of the 2637 patients, 1166 (44.2%) had cancer on initial biopsy. Of the remaining 1471 men who did not have cancer, 408 men had one or more repeat prostate biopsies and 116 (28.4%) of them had cancer detected. In total, of the 2637 patients, 1282 (48.6%) had cancer (cases) and 1355 (51.4%) had no evidence of cancer (controls).

### *Data analysis*

Cases were defined as patients with adenocarcinoma of the prostate (from any biopsy) and controls were defined as having no evidence of cancer. Potential

factors associated with increased prostate cancer risk were compared between cases and controls, including age, ethnicity, family history of prostate cancer, prostate volume, the presence of lower urinary tract symptoms (LUTS), PSA levels and DRE. We also considered having had a previous negative biopsy as a dichotomous variable. We have previously shown that the risk of cancer is lower among men with a previous negative biopsy.[10,11] We did not include the total number of needle cores taken at the time of biopsy because we have previously showed that it was not a significant predictor for cancer.[11]

Unconditional logistic regression analysis was used to estimate the odds ratio for prostate cancer detection, for each of these factors, alone and in combination. Age, prostate volume, and PSA level, were handled as continuous variables with linear transformations. Ethnicity was divided into three categories: 1) Asian/Other; 2) Caucasian; and 3) Black. Family history of prostate cancer was considered positive if one or more first or second degree relatives had a family history of prostate cancer. DRE and the presence of LUTS were categorized dichotomously.

### *Creation of nomograms*

A regression model was constructed including all potential predictors to optimize model fit. All variables were considered for nomogram construction. Only first-order terms were included in the model for simplicity in interpretation (i.e. no interactions). Two nomograms were constructed based on the regression model using a logit link function in the Program-R, V 2.0.1 (http://www.r-project.org) , using the nomogram function in the Design package by Harrell et al.[17] The first nomogram was constructed to determine the probability for having cancer at the time of biopsy. The second was to determine the probability of having aggressive cancer (histologic grade of

TABLE 1. **Comparison of factors associated with prostate cancer between cases and controls**

| **Factor** | **Cancer n=1282 (48.6%)** | **No cancer n=1355 (51.4%)** | **p-value** |
|---|---|---|---|
| Median age (years) | 66.3 (mean: 66.0) (range: 41.3 – 93.8) | 64.0 (mean: 63.6) (range: 39.9 – 90.8) | <0.0001 |
| Family history of PC | | | |
| Absent | 1083 (47.5%) | 1199 (52.5%) | 0.003 |
| Present | 199 (56.1%) | 156 (43.9%) | |
| Ethnicity | | | |
| Asian | 39 (29.3%) | 94 (70.6%) | <0.0001 |
| Caucasian | 1072 (49.2%) | 1109 (50.8%) | |
| Black | 144 (56.9%) | 109 (43.1%) | |
| Other | 27 (38.6%) | 43 (61.4%) | |
| LUTS | | | |
| Absent | 774 (51.3%) | 734 (48.7%) | 0.001 |
| Present | 508 (45.0%) | 621 (55.0%) | |
| Median prostate volume (cc) | 47.0 (mean: 52.9) (range: 15 – 295) | 61.0 (mean: 71.0) (range: 15 – 295) | <0.0001 |
| DRE | | | |
| No nodule | 943 (45.3%) | 1138 (54.7%) | <0.0001 |
| Nodule | 339 (61.0%) | 217 (39.0%) | |
| Median PSA (ng/mL) | 7.85 (mean: 13.6) (range: 0.6 – 498.8) | 6.76 (mean: 8.3) (range: 0.05 – 132.4) | <0.0001 |
| Previous negative biopsy | | | |
| No | 1166 (52.3%) | 1063 (47.7%) | <0.0001 |
| Yes | 116 (28.4%) | 292 (71.6%) | |

Gleason Score 7 or more) at biopsy.

To evaluate the accuracy of the nomogram in predicting risk for prostate cancer, patients were categorized into ten ordinal risk groups based on the number of points scored using the nomogram. The proportion of patients with prostate cancer in each risk group was then calculated to obtain the observed sample proportion. Estimates of the population proportion were based on 2000 bootstrap samples.[18] The mean and median proportions across bootstrap samples were calculated in each risk group as well as 95% empirical and bias-corrected and accelerated (BCa) confidence intervals[18] for the true proportion. Both asymptotic and BCa confidence intervals were constructed for the AUC to internally validate the nomogram, with nearly identical results. For simplicity, only the asymptotic confidence intervals are provided.

A separate nomogram and bootstrap process were performed for predicting high-grade (Gleason Score 7 or more) prostate cancer. Patients with grade Gleason Score 6 or less prostate cancer were excluded from this analysis.

## Results

The mean age at biopsy of the 2637 men was 64.8 years (range 39.9 – 93.8 years). The mean PSA level was 10.8 ng/mL (median 7.28 ng/mL; range 0.05 – 498.8 ng/mL), and 38.4% had an abnormal DRE. The majority of the patients were Caucasian (82.7%). In addition, 253 (9.6%) were black and 133 (5.0%) were Asian. Thirteen percent of patients reported at least one relative with prostate cancer.

Of the 2637 men, 1282 men (48.6%) were found to have adenocarcinoma of the prostate at biopsy from one or more biopsies (cases), and 1355 patients (51.4%) had no evidence of cancer (controls). Of the patients with cancer, more than half had a Gleason Score of 7 or more; 24 (1.9%) had Gleason Score 4 to 5, 496 (38.7%) had Gleason Score 6, 600 (46.8%) had Gleason Score 7, and 162 (12.6%) had Gleason Score 8 to 10 cancer.

All studied risk factors were found to be significantly associated with prostate cancer detection, Table 1. Age at biopsy, family history of prostate cancer, DRE and PSA were positively associated with prostate risk, whereas

TABLE 2. **Multivariate analysis of factors associated with prostate cancer**

| **Factor** | **Adjusted odds ratio for prostate cancer*(95% C.I.)** | **p-value** |
|---|---|---|
| Age | 1.05** (1.03 – 1.05) | <0.0001 |
| Family History of PC | | |
| Absent | 1.00 | |
| Present | 1.41 (1.1 – 1.8) | 0.007 |
| Ethnicity | | |
| Caucasian | 1.00† | |
| Asian | 0.40 (0.3 – 0.6) | <0.0001 |
| Black | 1.51 (1.1 – 2.0) | 0.006 |
| LUTS | | |
| Absent | 1.00 | |
| Present | 0.86 (0.7 – 1.0) | 0.09 |
| Prostate volume | 0.98** (0.97 – 0.99) | <0.0001 |
| DRE | | |
| No nodule | 1.00 | |
| Nodule | 1.48 (1.2 – 1.8) | 0.0003 |
| PSA | 1.07** (1.05 – 1.08) | <0.0001 |
| Previous negative biopsy | | |
| No | 1.00 | <0.0001 |
| Yes | 0.45 (0.4 – 0.6) | |

*Multivariate model includes age at biopsy, family history of prostate cancer, ethnicity, presence of lower urinary tract symptoms (LUTS), prostate volume, DRE, PSA and previous negative biopsy.
**Age at biopsy (per year), prostate volume (per cc) and PSA (per ng/mL) considered as continuous variables within the multivariate model.
†Baseline group for ethnic background defined as Caucasian and Other

the presence of LUTS, prostate volume and a previous negative biopsy were negatively associated with prostate risk. Asians had the lowest risk for prostate cancer. In multivariate analysis, all factors other than the presence of LUTS were significantly associated with prostate cancer risk, Table 2.

To determine which, if any, of these factors were associated with predicting the presence of aggressive prostate cancer at diagnosis (those with histologic grade Gleason Score 7 or more), we also conducted a multivariate analysis of the same variables using the presence of grade Gleason 7 or more prostate cancer as the primary outcome. Patients with grade Gleason Score 6 or less were excluded. Of all the predictor variables, only family history of prostate cancer and the presence of LUTS were not significant predictors for Gleason Score 7 or more prostate cancer, Table 3. All other variables were highly associated with aggressive prostate cancer.

To avoid potential bias of excluding patients with Gleason Score 6 or less prostate cancer, in a separate multivariate analysis, we grouped patients with Gleason Score 6 or less prostate cancer with the non-cancer control group and compared them with patients with Gleason Score 7 or more. This yielded similar results compared to the analysis that excluded patients with Gleason Score 6 or less, Table 3.

### *Nomograms to estimate risk for prostate cancer*

To provide a practical tool for clinicians to estimate prostate cancer risk when faced with an abnormal PSA or DRE, we constructed nomograms to predict both the presence of prostate cancer, Figure 1a, and aggressive forms of prostate cancer (patients with Gleason Score 7 or more cancers) Figure 2a. Although some variables were not statistically significant from multivariate analysis, they were retained in the nomogram to maximize accuracy. The nomogram is

TABLE 3. **Multivariate analysis for the presence of aggressive prostate cancer (Gleason Score 7 or more)**

| **Factor** | **Adjusted odds ratio (95% C.I.) GS ≥7 versus non cancer controls only** | **p-value** | **Adjusted odds ratio (95% C.I.) GS ≥7 versus GS ≤6 and non cancer controls** | **p-value** |
|---|---|---|---|---|
| Median age (years) | 1.06** (1.05 – 1.08) | <0.0001 | 1.05** (1.04 – 1.07) | <0.0001 |
| Family history of PC | | | | |
| Absent | 1.00 | | 1.00 | |
| Present | 1.16 (0.8 – 1.6) | 0.35 | 0.98 (0.7 – 1.3) | 0.90 |
| Ethnicity | | | | |
| Caucasian | 1.00† | | 1.00† | |
| Asian | 0.40 (0.3 – 0.6) | <0.0001 | 0.51 (0.3 – 0.8) | 0.0004 |
| Black | 1.48 (1.0 – 2.1) | 0.04 | 1.25 (0.9 – 2.7) | 0.18 |
| LUTS | | | | |
| Absent | 1.00 | | 1.00 | |
| Present | 0.82 (0.7 – 1.0) | 0.10 | 0.89 (0.7 – 1.1) | 0.27 |
| Median prostate volume (cc) | 0.97** (0.97 – 0.99) | <0.0001 | 0.98** (0.97 – 0.99) | <0.0001 |
| DRE | | | | |
| No nodule | 1.00 | | 1.00 | |
| Nodule | 2.11 (1.7 – 2.7) | <0.0001 | 2.22 (1.8 – 2.8) | <0.0001 |
| Median PSA (ng/mL) | 1.08** (1.07 – 1.1) | <0.0001 | 1.08** (1.06 – 1.09) | <0.0001 |
| Previous negative biopsy | | | | |
| No | 1.00 | <0.0001 | 1.00 | <0.0001 |
| Yes | 0.26 (0.18 – 0.38) | | 0.28 (0.19 – 0.41) | |

**Age at biopsy (per year), prostate volume (per cc) and PSA (per ng/mL) considered as continuous variables within the multivariate model.

†Basel ine group for ethnic background defined as Caucasian and Other.

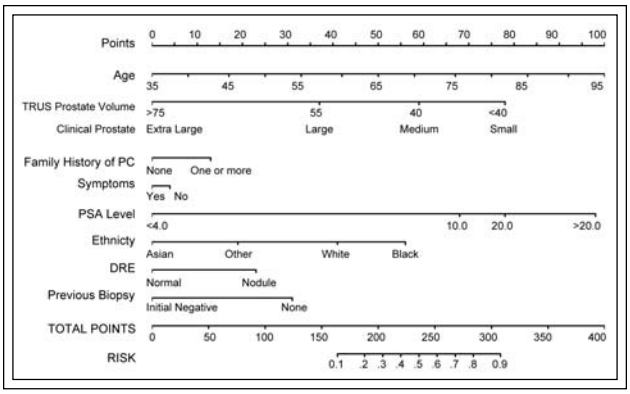


**Figure 1a.** Nomogram for predicting prostate cancer at biopsy for 2637 patients who underwent one or more prostate biopsies because of a PSA level of >2.5 ng/mL or an abnormal DRE. Each scale position has a corresponding point value (top axis). Point values for each scale are summed to arrive at a total point score. The risk for prostate cancer at biopsy can be determined by corresponding the Total Points scale to the Risk scale (bottom axis). Alternatively, the corresponding probability curve can be used to determine risk for prostate cancer based on the total point value in Figure 1b.

used by first locating a patient's position for each predictor variable on its horizontal scale and then a point value is assigned according to the Points scale (top axis). Point values are summed for each variable and the total points is located on the Total Points scale (bottom axis). This corresponds to a probability value

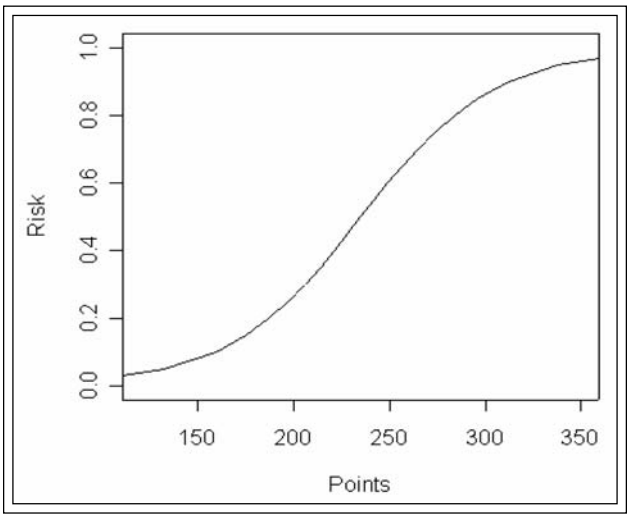


**Figure 1b.** Probability curve for the presence of prostate cancer at biopsy based on the total points derived from the nomogram in Figure 1a.

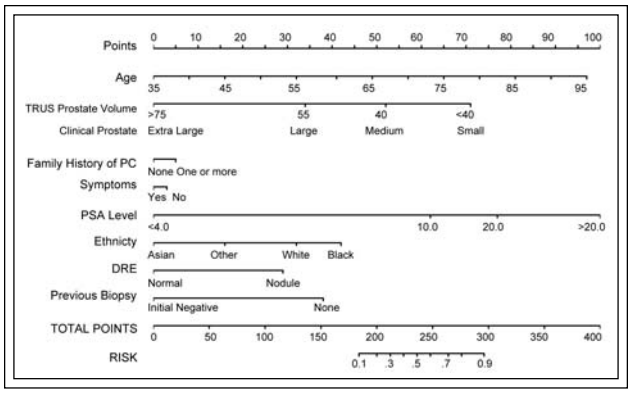


**Figure 2a.** Nomogram for predicting aggressive prostate cancer defined as patients with histologic grade of Gleason Score 7 or more. Patients with Gleason Score 6 or less cancer were excluded.

for having prostate cancer or aggressive prostate cancer.

For the nomogram predicting the probability of prostate cancer, the range of total points in the sample population ranged from 132 points (5% probability for prostate cancer) to 338 points (95% probability for prostate cancer) Figure 1b. For the nomogram predicting aggressive prostate cancer, the range of total points to predict prostate cancer ranged from 166 points (5%) to 316 points (95%) Figure 2b.

We evaluated the nomograms' accuracy in predicting the presence of prostate cancer and aggressive prostate cancer by determining the median, mean and 95% BCa and empirical confidence intervals across 2000 bootstrap samples. Plots of the

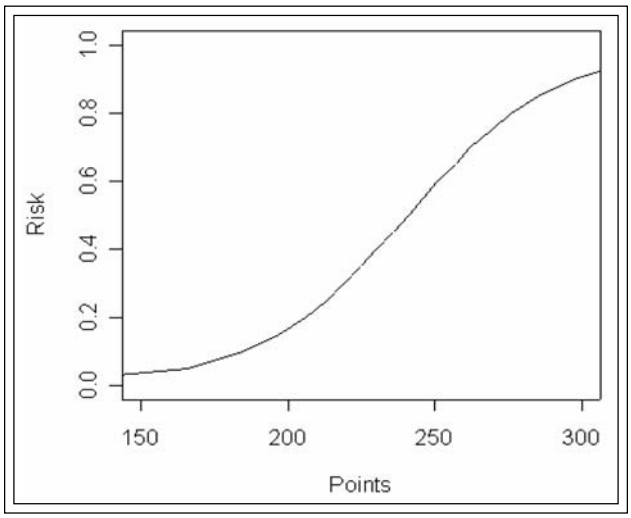


**Figure 2b.** Probability curve for the presence of aggressive prostate cancer at biopsy based on the total points derived from the nomogram in Figure 2a.

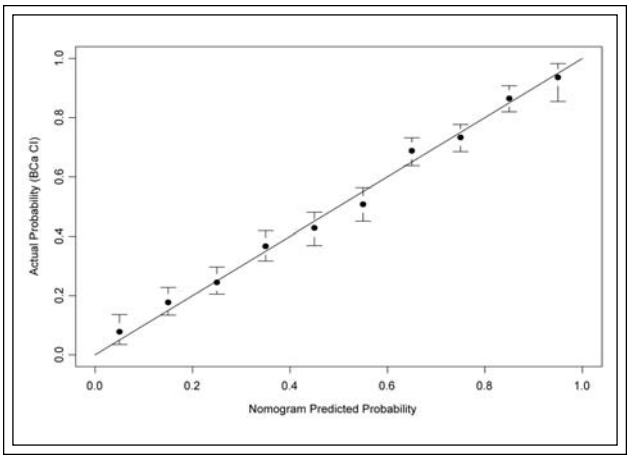


**Figure 3a.** Nomogram probability plot comparing predicted and actual probabilities for prostate cancer detection at biopsy showing nomogram calibration. Ideal nomograms would have predicted probabilities that match actual probabilities (i.e. a 45 degree solid line).

actual observed probability for prostate cancer and the predicted probability for prostate cancer by the nomograms across the ten ordinal risk groups of the total point scores demonstrated a high degree of concordance for the nomogram predicting prostate cancer Figure 3a. The area under the curve (AUC) for the nomogram was 0.77 (95% C.I.: 0.76 – 0.79). For the nomogram predicting aggressive prostate cancer, there was some loss in accuracy in groups 2, 6 and 7 among the 10 ordinal risk groups of total points Figure 3b, but maintained a high level of concordance. The AUC for this nomogram was 0.74 (95% C.I.: 0.72 – 0.76).

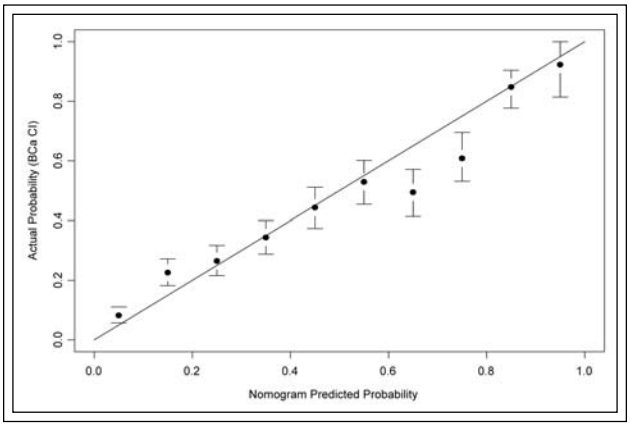


**Figure 3b.** Nomogram probability plot comparing predicted and actual probabilities for aggressive (Gleason Score 7 or more) prostate cancer at biopsy showing nomogram calibration.

## Discussion

For men with an abnormal PSA or DRE who present for consideration of a prostate biopsy, we have constructed nomograms to predict the presence of prostate cancer and aggressive prostate cancer using standard risk factors and tumor markers for prostate cancer. With a high degree of accuracy, the nomograms were able to change the positive predictive value for prostate cancer and for aggressive prostate cancer, either upwards (to 95%) or downwards (to 5%) based on the total points accumulated. We believe these nomograms provide important information for physicians and patients who undergo PSA testing for prostate cancer and who face an abnormal result. It is important to note that these nomograms only apply to men with an abnormal PSA value (>2.6 ng/mL) or an abnormal DRE and not to the general screening population. It will be of interest to construct a nomogram for patients for the general population based on any PSA value.

This is the first study that combines all established risk factors and tumor markers for prostate cancer into a simple method to determine the risk for prostate cancer. Although many physicians intuitively use these factors to estimate a patient's risk for prostate cancer and to determine the need for prostate biopsy, we provide precise estimates of risk for prostate cancer in a simple format. Others have examined some of these factors for initial[19,20] and repeat[21] biopsy, but none have been as comprehensive as the current study. Finne et al studied 758 men with an abnormal PSA from a Finnish Prostate Cancer Screening Study and developed a nomogram for prostate cancer risk, but this model did not include information on family history of prostate cancer, ethnicity or previous biopsy.[19] Also, the AUC for their nomogram was not reported and comparisons could not be made with our current model. Karakiewicz et al also developed a nomogram to evaluate prostate cancer risk, but only included age, PSA and DRE in the model.[20] In that analysis, the AUC of the nomogram to predict prostate cancer was from 0.69 to 0.70. To improve this, they added the free:total PSA ratio which improved the AUC to 0.77, but this was done only to a subgroup of patients. We did not examine how free:total PSA ratio affected the risk for prostate cancer, as its use is only applicable to a subgroup of men (usually with a PSA between 4 ng/mL and 10 ng/mL[22]) and the purpose of our nomogram was to evaluate all patients presenting for a prostate biopsy. Lopez-Corona et al constructed a nomogram for patients undergoing a repeat biopsy after an initial negative biopsy and their

AUC for their nomogram was 0.70.[21] In contrast, our nomogram applies to both initial and repeat biopsy.

Stamey et al examined 1317 patients who underwent surgery and compared PSA levels with respect to the volume of prostate cancer and benign prostatic hyperplasia tissue.[7] He concluded that the level of PSA (<20 ng/mL) was only related to the amount of benign prostate tissue present. However, they did not compare these patients to normal controls and did not consider how other risk factors for prostate cancer might have affected their analysis.

Another novel aspect of this study is the construction of a nomogram that can predict the presence of aggressive forms of prostate cancer (Gleason Score 7 or more). We have previously shown that a combination of host factors including age, ethnicity, family history of prostate cancer, and prostate volume was significantly associated with grade at diagnosis from prostate biopsy.[10] Also, association and linkage studies have demonstrated genetic susceptibility for aggressive prostate cancer.[23,24] Many experts have argued that patients with low grade prostate cancer may not require treatment.[25-27] Albertsen et al from a large population-based survey showed that patients with low grade cancer (Gleason Score 6 or less) have significantly fewer life years lost from prostate cancer, compared to patients with high grade cancers.[26] Further, patients with low grade cancer often had a higher chance of dying from other co-existing disease rather than from prostate cancer.[8] On the other hand, many experts would agree that patients with prostate cancer of Gleason Score 7 or more require aggressive treatment, given the high potential for these patients of developing metastatic disease.[26,28] This nomogram would be particularly clinically useful for older patients with an abnormal PSA. If the nomogram predicts a low chance for having aggressive prostate cancer, then it would be reasonable for the patient to forego a biopsy. Further, an elevated PSA level may be less significant after factoring a large prostate volume for a younger man and therefore the need for a prostate biopsy could be unnecessary (particularly if he was Asian with no family history of prostate cancer). In contrast, the same PSA level for a smaller prostate in an older patient would make it important to perform a biopsy, particularly if there is a large chance for having aggressive prostate cancer. The exact probability cut-off for undergoing a biopsy is the decision of the treating physician and patient and should be individualized after considering the patient's comorbidities.

Another consideration is that prostate volume assessment will be required prior to biopsy in order to estimate the risk for prostate cancer. Although transrectal ultrasound alone has not been used as a sole diagnostic test, it would be required to obtain an accurate prostate volume measurement. However, other less invasive imaging techniques could be employed to estimate prostate volume. Nevertheless, it would be reasonable to perform transrectal ultrasound prior to prostate biopsy in order to obtain a patient's prostate volume for the nomogram. Other surrogate markers for prostate volume such as the presence of urinary symptoms or size estimations by DRE could be substituted for volume, but none have been very accurate in estimating prostate size.[29] We and others[11,19] have shown that prostate volume alone is a powerful predictor for prostate cancer and it would be inappropriate to exclude it from the model. For those patients where prostate ultrasound is not available, we have provided qualitative cut-points of prostate size based on DRE.

One limitation of the nomogram is that not all patients underwent a repeat biopsy among those with an initial negative biopsy (27%). It is important to consider whether patients had an initial negative biopsy within the model, given the 15% to 30% prevalence of prostate cancer at repeat biopsy.[11,16] Cancer lesions may be missed in the initial biopsy due to sampling error. Thus, the prediction model had to consider whether a patient had a previous negative biopsy given that it could affect the risk for having prostate cancer. Although not all patients underwent a repeat biopsy after an initial negative biopsy, the majority of repeat biopsies were because of a persistent abnormal PSA level or the presence of high grade prostatic intraepithelial neoplasia (HGPIN).[11]

In summary, we have developed nomograms to be used as clinical instruments for men faced with an abnormal PSA (>2.6 ng/mL) or DRE to estimate their risk for prostate cancer. These estimates incorporate the influence of age, ethnicity, family history of prostate cancer, prostate volume, urinary symptoms, previous biopsy, PSA and DRE. Further studies examining screening populations will be required to estimate risk for the general population based on these factors. However, for men who have an abnormal PSA and DRE, these nomograms will provide important information for clinicians to recommend forgoing a potential unnecessary biopsy or more strongly recommending a biopsy. Also, it will provide more information to identify patients at high risk for prostate cancer where repeat biopsy is necessary after previous negative biopsies. □

References


1. von Eschenbach A, Ho R, Murphy GP, Cunningham M, Lins N. American Cancer Society guidelines for the early detection of prostate cancer. *Cancer* 1997;80(9):1805-1807.
2. Sakr WA, Grignon DJ, Haas GP, Heilbrun LK, Pontes JE, Crissman JD. Age and racial distribution of prosatic intraepithelial neoplasia. *European Urology* 1996;30:138.
3. Stamey TA, Yang N, Hay R, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *New Engl J Med* 1987;317(15):909-915.
4. Nam RK, Toi A, Vesprini D et al. The V89L polymorphism of the SRD5A2 gene predicts prostate cancer presence and progression. *Urology* 2000;57:199-204.
5. Catalona WJ, Bartsch G, Rittenhouse HG et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. *J Urol* 2004;171(6 Pt 1):2239-2244.
6. Partin AW, Brawer MK, Bartsch G et al. Complexed prostate specific antigen improves specificity for prostate cancer detection: results of a prospective multicenter clinical trial. *J Urol* 2003;170(5):1787-1791.
7. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? *J Urol* 2004;172(4 Pt 1):1297-1301.
8. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280(11):975-980.
9. Barry MJ, Albertsen PC, Bagshaw MA et al. Outcomes for men with clinically nonmetastatic prostate carcinoma managed with radical prostatectomy, external beam radiotherapy, or expectant management. *Cancer* 2001;91(12):2302-2314.
10. Nam RK, Toi A, Trachtenberg J et al. Making Sense of PSA: Improving its Predictive Value Among Patients Undergoing Prostate Biopsy. *J Urol* 2006;175:489-494.
11. Nam RK, Toi A, Trachtenberg J et al. Variation in patterns of practice in diagnosing screen-detected prostate cancer. *BJU Int* 2004;94(9):1239-1244.
12. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. *JAMA* 1997;277(18):1452-1455.
13. Barry MJ, Fowler FJJ, O'Leary MP et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148:1549-1557.
14. Terris MK. Ultrasonography and biopsy of the prostate. Vol 4. 8 ed. Philadelphia: Saunders;2002.
15. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol* 1974;111(1):58-64.
16. Djavan B, Ravery V, Zlotta A et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: When should we stop? *J Urol* 2001;166:1679-1683.
17. Harrell F. *http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/Design*. 2005.
18. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York: Chapman & Hall;1993.
19. Finne P, Auvinen A, Aro J et al. Estimation of prostate cancer risk on the basis of total and free prostate-specific antigen, prostate volume and digital rectal examination. *Eur Urol* 2002;41(6):619-626;discussion 626-617.
20. 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(6):1930-1934.
21. Lopez-Corona E, Ohori M, Scardino PT, Reuter VE, Gonen M, Kattan MW. A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session. *J Urol* 2003;170(4 Pt 1):1184-1188;discussion 1188.
22. Catalona WJ, Partin AW, Slawin KM et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA* 1998;279(19):1542-1547.
23. Giovannucci E, Stampfer MJ, Krithivas K et al. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc Natl Acad Sci USA* 1997;94(7):3320-3323.
24. Wang L, McDonnell SK, Elkins DA et al. Analysis of the RNASEL gene in familial and sporadic prostate cancer. *Am J Hum Genet* 2002;71(2):449.
25. Johansson JE, Andren O, Andersson SO et al. Natural history of early, localized prostate cancer. *JAMA* 2004;291(22):2713-2719.
26. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 1995;274(8):626-631.
27. Chodak GW, Thisted RA, Gerber GS et al. Results of conservative management of clinically localized prostate cancer. *New Engl J Med* 1994;330(4):242-248.
28. Catalona WJ. Management of cancer of the prostate. *New Engl J Med* 1994;331:996-1004.
29. Bosch JL, Bohnen AM, Groeneveld FP. Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. *Eur Urol* 2004;46(6):753-759.