Original Article

Selective Detection of Histologically Aggressive Prostate Cancer

An Early Detection Research Network Prediction Model to Reduce Unnecessary Prostate Biopsies With Validation in the Prostate Cancer Prevention Trial

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BACKGROUND: Limited survival benefit and excess treatment because of prostate-specific antigen (PSA) screening in randomized trials suggests a need for more restricted selection of prostate biopsy candidates by discerning risk of histologically aggressive versus indolent cancer before biopsy. **METHODS:** Subjects undergoing first prostate biopsy enrolled in a multicenter, prospective cohort of the National Cancer Institute Early Detection Research Network (N = 635) were analyzed to develop a model for predicting histologically aggressive prostate cancers. The control arm of the Prostate Cancer Prevention Trial (N = 3833) was used to validate the generalization of the predictive model. **RESULTS:** The Early Detection Research Network cohort was comprised of men among whom 57% had no cancer, 14% had indolent cancer, and 29% had aggressive cancer. Age, body mass index, family history of prostate cancer, abnormal digital rectal examination (DRE), and PSA density (PSAD) were associated with aggressive cancer (all $P <$ .001). The Early Detection Research Network model outperformed PSA alone in predicting aggressive cancer (area under the curve [AUC] = 0.81 vs 0.71, $P <$ .01). Model validation in the Prostate Cancer Prevention Trial cohort accurately identified men at low (<10%) risk of aggressive cancer for whom biopsy could be averted (AUC = 0.78; 95% confidence interval, 0.75-0.80). Under criteria from the Early Detection Research Network model, prostate biopsy can be restricted to men with PSAD >0.1 ng/mL/cc or abnormal DRE. When PSAD is <0.1 ng/mL/cc, family history or obesity can identify biopsy candidates. **CONCLUSIONS:** A predictive model incorporating age, family history, obesity, PSAD, and DRE elucidates criteria whereby ¼ of prostate biopsies can be averted while retaining high sensitivity in detecting aggressive prostate cancer. ***Cancer* 2012;118:2651-58.** *© 2011 American Cancer Society.*

KEYWORDS: prostate cancer, biopsy, clinically significant, indolent.

INTRODUCTION

Prostate -specific antigen (PSA) screening has led to a significant increase in detection of clinically localized T1c prostate cancer with concomitant stage migration,[1,2] and results from randomized trials of PSA screening have revealed limited to no survival benefit when simple PSA cutoffs were used for recommendation for or against prostate biopsy.[3,4] These findings have raised questions as to whether strategies based simply on PSA and age cutoffs are sufficient for identifying suitable candidates for prostate biopsy when the ultimate goal of early detection is to identify aggressive disease that harbors lethal potential and yet is amenable to definitive treatment.

The ability to discern aggressive from indolent prostate cancer is a centerpiece of current efforts underway to refine prostate cancer detection, decision making, and care. Epstein et al identified histological criteria in prostate biopsy specimens that discriminate indolent from clinically significant prostate cancer.[5] As originally described, the histological criteria that define indolent disease on prostate biopsy include absence of Gleason pattern 4 or 5, cancer limited to 3 or fewer biopsy cores, and <50% tumor involvement in any individual core. Prospective studies have used these criteria to define eligibility for active surveillance.[6-8]

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Prior studies have used findings from biopsy to assess risk of indolent cancer at prostatectomy,[9-11] but predictive tools to discern risk of aggressive versus indolent cancer before a patient undergoes prostate biopsy have not been extensively characterized. The Prostate Cancer Prevention Trial calculator facilitates individual assessment of prostate cancer risk in general and specific risk of high-grade disease for men who undergo a prostate biopsy,[12] but does not discern the possibility of aggressive Gleason score 6 cancers, a limitation also inherent in a separate predictive nomogram developed based on a single-institution study.[13]

We sought to develop a predictive model to identify candidates for prostate biopsy based on multicenter data using prebiopsy parameters to selectively discriminate risk of histologically aggressive prostate cancer from no cancer or histopathologically indolent cancer.

MATERIALS AND METHODS

The multicenter National Cancer Institute/Early Detection Research Network prostate cancer detection cohort is a collaboration of several Early Detection Research Network clinical validation centers that prospectively enroll and follow men without prior diagnosis of prostate cancer. Men enrolled at 6 clinical practice sites at Harvard, Michigan, and Cornell universities who had undergone their first prostate biopsy were identified. As part of participation in the Early Detection Research Network cohort, all men had provided written informed consent, and all prostate biopsies had been offered according to National Comprehensive Cancer Network guidelines.[14] Demographic and prebiopsy clinical data, including PSA history, digital rectal examination (DRE) results, prostate volume, and all biopsy procedure details were ascertained on case report forms. All prostate biopsy results were reviewed, with reports confirmed by institutional pathologists. All pathology reports included confirmed histology, number of cores, percentage of each core involved with carcinoma, and primary and secondary Gleason patterns. At the time of this analysis, the Early Detection Research Network cohort database comprised 902 subjects who enrolled between June 2005 and December 2007, 635 of whom had enrolled immediately before their first prostate biopsy and had complete, quality-controlled demographic, clinical, and pathological data available. They are the subject of this analysis. Furthermore, 236 Early Detection Research Network patients, enrolled January 2008 through April 2009, were also used to discern how many biopsies could be avoided by using the proposed model.

Histologically aggressive prostate cancer was defined by Epstein's histopathologic criteria: Gleason score ≥ 7, or >3 cores positive, or $\geq 50\%$ tumor involvement in any individual core; all other cancers (Gleason score ≤ 6, ≤ 3 cores positive, and $<50\%$ tumor involvement in any core) were deemed indolent.[5]

In the Early Detection Research Network analysis cohort, demographic and prebiopsy clinical data were compared between men with histologically aggressive prostate cancer and men with indolent or no prostate cancer using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables. Multivariate logistic regression models were fit that considered age, body mass index (BMI), race/ethnicity, family history of prostate cancer, abnormal/suspicious DRE result, PSA, prostate volume, and PSA density (PSAD = PSA/[prostate volume]), the latter 3 risk factors with log-transformation to improve fit of the model. Model selection was performed to identify and include only statistically significant risk factors at the .05 level of statistical significance, in particular to identify the strongest predictor among the highly correlated measures of PSA, prostate volume, and PSAD. Individual risks of histologically aggressive prostate cancer were calculated using the inverse logistic function $(\exp[X'\beta]/[1 + \exp(X'\beta)])$, where X represents individual risk factors observed and β represents the associated log odds ratios for the individual risk factors estimated from the model. Discriminative performance of these predicted risks were then compared with 2 univariate models of PSA alone and PSAD alone using the difference in the area under the receiver operating characteristic (ROC) curve (AUC) with bootstrap 95% confidence intervals (CIs), which provides an optimistically biased internal validation because the same data set was used to build the model underlying predicted risks.

Data from 3833 of 4734 participants in the control arm of the Prostate Cancer Prevention Trial were used as a validating generalization set for the Early Detection Research Network prediction model. The Prostate Cancer Prevention Trial study served as a generalization set, because unlike the Early Detection Research Network cohort, the Prostate Cancer Prevention Trial study was a screening study of older healthy and primarily Caucasian men with PSA <3.0 ng/mL and normal DRE required at study entry, and Prostate Cancer Prevention Trial participants had a required end-of-study biopsy regardless of PSA or DRE. PSA and DRE results either on the day of, but before the biopsy, or within a maximum of 1 year

Table 1. Demographic and Prebiopsy Clinical Characteristics of Men Undergoing First Prostate Biopsy for Prostate Cancer Detection in the EDRN Analysis and PCPT Validation Cohorts, According to Biopsy Result

Characteristic	EDRN Analysis Cohort, N=635			PCPT Validation Cohort, N=3833		
	No Prostate Cancer	Indolent Prostate Cancer	Histologically Aggressive Prostate Cancer	No Prostate Cancer	Indolent Prostate Cancer	Histologically Aggressive Prostate Cancer
Patients, No. (%)	361 (57)	88 (14)	186 (29)	3176 (83)	333 (9)	324 (8)
Age, y [IQR][a]	60 [54-66]	61 [56-66]	64 [59-71]	69 [65-73]	69 [65-73]	69 [65-74]
BMI, kg/m^2 [IQR]	27 [25-31]	27 [25-31]	27 [25-32]	27 [25-30]	27 [25-30]	27 [25-30]
Non-Caucasian, No. (%)	57 (16)	13 (15)	21 (11)	86 (3)	8 (2)	19 (6)
Family history of prostate cancer, No. (%)	88 (24)	28 (32)	60 (32)	468 (15)	67 (20)	72 (22)
Abnormal DRE, No. (%)[a]	57 (16)	15 (17)	59 (32)	98 (3)	57 (17)	60 (15)
PSA, ng/mL [IQR][a]	4.6 [3.0-6.0]	4.5 [3.4-6.0]	6.6 [4.8-9.0]	1.2 [0.7-2.0]	1.8 [1.0-2.9]	2.4 [1.5-4.0]
Prostate volume by TRUS, cc [IQR][a]	47 [35-65]	44 [35-58]	40 [31-55]	34 [26-45]	32 [25-42]	33 [25-43]
PSA density, ng/mL/cc [IQR][a]	0.09 [0.06-0.12]	0.10 [0.07-0.16]	0.16 [0.10-0.25]	0.03 [.02-.05]	0.05 [0.03-0.09]	0.07 [0.04-0.11]

Abbreviations: BMI, body mass index; DRE, digital rectal examination; EDRN, Early Detection Research Network; IQR, interquartile range; PCPT, Prostate Cancer Prevention Trial; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
[a] $P < .01$ in univariate comparison of histologically aggressive prostate cancer versus others; No. (%) compared using Fisher exact tests; or median [IQR] compared using Kruskal-Wallis tests.

before biopsy were used. Because of missing details about biopsy cores, the definition of histologically aggressive prostate cancer was modified to include greatest linear extent of cancer (>5 mm as a surrogate for ≥50% tumor involvement in a core). In total, 901 patients were excluded because of missing BMI (0.9%), prostate volume (14%), or details about biopsy cores (5%). Sensitivity analyses assessed the impact of this exclusion by repeating the analysis using simple imputation of the median BMI or prostate volume, and by considering any patient with missing details about biopsy cores as having indolent cancer; the results were consistent and are not presented. Evaluation of the Early Detection Research Network prediction model was assessed by ROC AUC, with bootstrap 95% CIs, and by calibration comparing average model risk and observed percentage with histologically aggressive prostate cancer. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Demographic and preclinical data of the 635 men undergoing first prostate biopsy as part of the Early Detection Research Network analysis cohort are summarized in Table 1. Three hundred sixty-one (57%) men had no cancer, whereas 88 (14%) and 186 (29%) patients were identified with indolent and histologically aggressive cancer, respectively. Only 22 of 186 men diagnosed with histologically aggressive prostate cancer had Gleason score 6 cancer with >3 cores positive or with at least 1 core containing ≥50% cancer; all others had Gleason score ≥7 disease. In univariate analyses, men diagnosed with histologically aggressive prostate cancer were significantly older, had significantly higher PSA, smaller gland volume, and higher PSAD, and more often had abnormal DRE than men with indolent disease or no prostate cancer (each $P < .01$).

In multivariate modeling, age, BMI, family history of prostate cancer, abnormal DRE, and log of PSAD were significant predictors of histologically aggressive cancer (each $P < .05$) (Table 2). The AUC for model-predicted risks was 0.81 (95% CI, 0.77-0.84) (Fig. 1). In contrast, the AUCs for PSA only or PSAD only were 0.71 (95% CI, 0.67-0.75) and 0.75 (95% CI, 0.71-0.80), respectively. When compared with PSA alone, at a sensitivity level of 90%, the multivariate model improved specificity from 32% to 42%. The predicted probabilities of histologically aggressive prostate cancer for a range of risk factor values are presented in Table 3. By using our model, of the 236 Early Detection Research Network patients enrolled from January 2008 through April 2009, 24.6% of biopsies could be avoided.

To assess the performance of the Early Detection Research Network prediction model in identifying men with histologically aggressive prostate cancer in the general population, we applied the prediction model to the

Table 2. Multivariate Model of Demographic and Prebiopsy Clinical Characteristics for the Presence of Histologically Aggressive Prostate Cancer on First Prostate Biopsy in the Early Detection Research Network Analysis Cohort

Parameter	Estimate	Standard Error	Odds Ratio (95% CI)	*P*
Intercept	−3.28	1.04	—	—
Age per 10 years	0.54	0.12	1.72 (1.35-2.18)	<.0001
BMI per 1 kg/m^2	0.06	0.02	1.07 (1.02-1.11)	.002
Family history of prostate cancer	0.82	0.23	2.27 (1.45-3.54)	.0003
Abnormal DRE	1.08	0.25	2.95 (1.81-4.80)	<.0001
Log PSA density per 1 U	1.51	0.17	4.51 (3.25-6.27)	<.0001

Abbreviations: BMI, body mass index; CI, confidence interval; DRE, digital rectal examination; PSA, prostate-specific antigen.

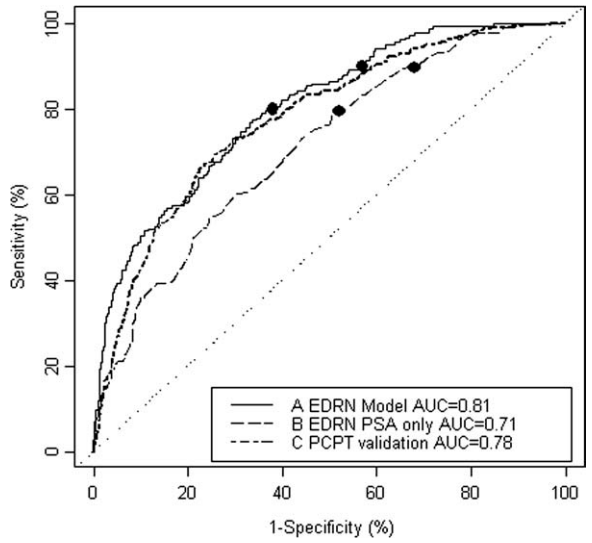

Figure 1. Receiver operating characteristic curves are shown for the multivariate prediction model (A) versus prostate-specific antigen (PSA) alone (B) for predicting histologically aggressive prostate cancer in the Early Detection Research Network (EDRN) analysis cohort (n = 635), and for the model-predicted risks in the Prostate Cancer Prevention Trial (PCPT) validation cohort (C; n = 3833). In the EDRN cohort, for a sensitivity of 90%, specificity was 42% versus 32% for PSA; for a sensitivity of 80%, specificity was 60% versus 48% for PSA (denoted by closed circles). AUC, area under the ROC curve.

control arm of the Prostate Cancer Prevention Trial study. Among 3833 Prostate Cancer Prevention Trial subjects, 324 (8%) had aggressive cancer on biopsy, 333 (9%) had indolent cancer, and the remainder had no cancer. The model performed well in predicting aggressive cancer (AUC, 0.78; 95% CI, 0.75-0.80). Although predicted and observed probabilities of prostate cancer diverged by overpredicting risk among patients at higher risk for aggressive cancer, the model performance was robust at lower levels of cancer risk (ie, risk <10%; Table 4) and across most subgroups of the population (Table 5), confirming the predictive accuracy of this model in identifying men who can forego prostate biopsy while retaining 90% sensitivity in detection of aggressive cancer.

DISCUSSION

Stage migration related to widespread use of PSA screening has raised concerns regarding possible overdiagnosis and overtreatment of prostate cancer.[1,2,15] In the Early Detection Research Network cohort, nearly 1/3 of biopsy-detected cancers had histological features of indolent disease. Overtreatment of cancers that are diagnosed during an indolent phase early in the course of the disease could be averted by selective use of active surveillance.[6-8,16-19] However, the use of active surveillance remains underused; definitive primary treatments are more commonly being used, sometimes with adverse effects on quality of life.[2,20] Conversely, use of routine PSA cutoffs alone as a decision point for identifying prostate biopsy can also lead to underdiagnosis or nondiagnosis of cancers that are histologically aggressive but have PSA levels below routine thresholds. The use of simple PSA cutoffs as a sole focal decision point for identifying candidates for prostate biopsy has therefore been challenged by recent changes in American Urological Association best practice recommendations regarding prostate cancer screening and early detection.[21]

Prostate biopsy does not come without inherent risks, which include physical morbidity, emotional uncertainty regarding being diagnosed with indolent cancer, and cost to the health care system. Up to 2% of patients undergoing prostate biopsy develop a febrile urinary tract infection, bacteremia, or acute prostatitis requiring hospitalization, complicated by recent emergence of fluoroquinolone resistance, among other possible biopsy-related complications.[22,23] The emotional sequelae of identifying indolent cancer and the decision to undergo treatment or active surveillance, as well as the cost of biopsy (approximately $347.24/man in the United States)[24]—together with the unmeasured cost of cancers missed because of

Table 3. Predicted Probabilities for the Presence of Histologically Aggressive Prostate Cancer on First Prostate Biopsy Based on the Early Detection Research Network Analysis Cohort, for a Range of Demographic and Prebiopsy Clinical Factors

Age, y	Family History of Prostate Cancer	BMI, kg/m^2	Normal DRE, PSA Density, ng/mL/cc			Abnormal DRE, PSA Density, ng/mL/cc		
			0.066	0.102	0.157	0.066	0.102	0.157
55	No	25	5.6 (3.6-8.6)	10.3 (7.2-14.6)	18.0 (13.1-24.3)	15.0 (9.2-23.3)	25.3 (16.9-36.1)	39.3 (27.9-52.0)
		30	7.5 (5.1-11.0)	13.6 (9.9-18.3)	23.1 (17.5-29.8)	19.4 (12.4-29.0)	31.7 (21.9-43.3)	47.0 (34.7-59.7)
	Yes	25	11.9 (7.8-17.7)	20.7 (14.6-28.4)	33.3 (24.6-43.2)	28.5 (18.3-41.5)	43.5 (30.6-57.3)	59.5 (45.3-72.3)
		30	15.6 (10.9-21.9)	26.3 (19.6-34.2)	40.6 (31.5-50.3)	35.3 (23.8-48.8)	51.3 (37.8-64.6)	66.8 (53.1-78.2)
60	No	25	7.2 (4.9-10.6)	13.1 (9.7-17.5)	22.4 (17.3-28.4)	18.7 (12.3-27.6)	30.8 (21.8-41.4)	45.9 (34.7-57.6)
		30	9.7 (6.9-13.3)	17.1 (13.3-21.7)	28.3 (22.7-34.6)	24.0 (16.2-33.9)	37.8 (22.7-49.0)	53.8 (42.0-65.2)
	Yes	25	15.1 (10.2-21.7)	25.4 (18.6-33.8)	39.5 (30.3-49.5)	34.4 (23.1-47.8)	50.2 (37.0-63.4)	65.9 (52.4-77.2)
		30	19.5 (14.0-26.6)	31.8 (24.5-40.2)	47.2 (37.9-56.8)	41.7 (29.3-55.3)	58.0 (44.6-70.2)	72.5 (60.0-82.3)
65	No	25	9.3 (6.4-13.2)	16.5 (12.5-21.4)	27.4 (21.8-33.9)	23.2 (15.7-32.9)	36.8 (27.1-47.7)	52.7 (41.4-63.7)
		30	12.3 (9.0-16.6)	21.3 (16.9-26.4)	34.1 (28.0-40.7)	29.3 (20.5-39.9)	44.3 (33.7-55.5)	60.4 (48.9-70.8)
	Yes	25	18.9 (12.8-26.9)	30.9 (22.7-40.5)	46.1 (35.9-56.7)	40.7 (28.0-54.7)	56.9 (43.3-69.6)	71.7 (58.8-81.7)
		30	24.1 (17.3-32.7)	38.0 (29.3-47.5)	54.0 (43.8-63.9)	48.4 (35.0-62.1)	64.4 (51.0-75.8)	77.6 (66.0-86.1)

Abbreviations: BMI, body mass index; DRE, digital rectal examination; PSA, prostate-specific antigen.
The values are presented as percentages with 95% confidence intervals.
Values of age are approximately the 25th, 50th, and 75th percentiles of the distribution; values of BMI are approximately the 25th and 75th percentiles of the distribution. Values of PSA density are the 25th, 50th, and 75th percentiles of the distribution.

Table 4. Comparison of Model-Predicted Risks With Observed Risks of Histologically Aggressive Prostate Cancer in an Initial Prostate Biopsy in the Prostate Cancer Prevention Trial Validation Cohort

Model-Predicted Risk Range, %		Patients, No.	Risk of Histologically Aggressive Prostate Cancer	
			Mean Model-Predicted Risk, %	Observed Percentage of Patients
0.18	1.86	383	1.3	0.5
1.87	2.92	383	2.4	1.8
2.92	4.16	384	3.5	2.6
4.16	5.57	383	4.8	5.0
5.57	7.33	383	6.4	4.2
7.34	9.52	384	8.3	5.5
9.53	12.83	383	11.0	6.0
12.86	17.91	384	15.2	12.8
17.91	27.50	383	22.2	15.1
27.56	99.98	383	45.0	31.1
0.18	99.98	3833[a]	12.0	8.5

[a] All patients.

underdiagnosis among some men with normal PSA levels—further elevate societal costs of poorly discriminant algorithms to identify candidates for prostate biopsy. Urological practice, patient outcomes, and cost effectiveness of health care would each benefit from new targeted strategies, such as nomograms that improve prediction of aggressive cancers, to enable selective identification of candidates for prostate biopsy that would improve the yield of clinically significant, histologically aggressive cancers warranting subsequent definitive treatment.

Recognizing the value of avoiding unnecessary biopsy by predicting individual probability of a prostate cancer diagnosis, Thompson et al used data from the control arm of the Prostate Cancer Prevention Trial to develop a prostate cancer risk calculator.[12] The Prostate Cancer Prevention Trial calculator uses a combination of other risk factors with PSA (age, family history, and DRE) to specify risk of prostate cancer before biopsy. The Prostate Cancer Prevention Trial risk calculator was also used for predicting high-grade cancers. However, the Prostate Cancer Prevention Trial calculator has not been optimized and validated specifically for the measurement of risk of histologically aggressive disease as defined by the Epstein criteria (which include amount of cancer on

Table 5. Comparison of Average Model-Predicted Risks With Observed Risks of Histologically Aggressive Prostate Cancer in an Initial Prostate Biopsy Among Subgroups of the Prostate Cancer Prevention Trial Validation Cohort

Group	Patients, No.	Risk of Histologically Aggressive Prostate Cancer		AUC (95% CI)
		Mean Model-Predicted Risk, %	Observed Percentage of Patients	
All	3833	12.0	8.5	0.78 (0.75-0.80)
Age <65 years	808	10.4	8.5	0.79 (0.74-0.84)
Age ≥65 years	3025	12.4	8.4	0.77 (0.75-0.80)
Caucasian	3720	12.0	8.2	0.77 (0.74-0.80)
Non-Caucasian	113	13.7	16.8	0.85 (0.75-0.94)
BMI <30 kg/m^2	2827	11.4	8.4	0.77 (0.74-0.80)
BMI ≥30 kg/m^2	1006	13.8	8.6	0.80 (0.75-0.85)
No family history	3226	10.3	7.8	0.79 (0.75-0.82)
Family history	607	21.2	11.9	0.73 (0.67-0.80)
Normal DRE	3628	10.9	7.6	0.77 (0.74-0.80)
Abnormal DRE	205	31.9	24.4	0.65 (0.56-0.73)
PSA density <0.102 ng/mL/cc	3518	9.3	6.5	0.74 (0.70-0.77)
PSA density ≥0.102 ng/mL/cc	315	42.7	30.8	0.58 (0.51-0.65)

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; DRE, digital rectal examination; PSA, prostate-specific antigen.

biopsy), and does not provide the capability of considering high-volume Gleason score 6 cancers as aggressive tumors, together with higher Gleason score cancers, as proposed and validated by the model that we have developed in this study.

Postbiopsy, preprostatectomy nomograms have been developed that used pathology findings at biopsy to predict the probability of indolent prostate cancer at prostatectomy.[9,10] The Kattan postbiopsy nomogram used studied sextant biopsy results in radical prostatectomy patients to predict indolent disease at prostatectomy and was recalibrated in a screening population from the European Randomized Study on Screening for Prostate Cancer and in a single-practice tertiary care US setting.[9,10,25] Although both nomograms predict indolent disease with adequate discrimination, they require pathology results of prostate biopsy to predict prostatectomy endpoints, and therefore have limited utility in decision making regarding which patients should undergo prostate biopsy in the first place. With our predictive model, we propose bringing the strategy of a predictive model upstream in the urological care process, to help improve selection for men for prostate biopsy.

Nam et al previously demonstrated a multivariate model of known prostate cancer risk factors to significantly improve the positive predictive value of PSA.[13] In an attempt to individualize prostate cancer risk at the time of first PSA and DRE, Nam et al developed a predictive nomogram from men who underwent prostate biopsy.[26] The nomogram incorporated age, ethnicity, family history of prostate cancer, presence of urinary symptoms, total PSA, free:total PSA, and DRE to identify risk of prostate cancer at first biopsy. The AUC for the nomogram in predicting overall (0.74 vs 0.62) and specifically high-grade cancer (0.77 vs 0.69) was significantly greater than the AUC using PSA and DRE alone. Although the nomogram proposed by Nam et al was an improved predictor for high-grade prostate cancer (Gleason score ≥7), this criteria for identifying clinically significant disease does not conform to the criteria previously identified by Epstein. Moreover, the Prostate Cancer Prevention Trial and Nam nomograms did not elucidate practical cutpoints or criteria based on the predictive models to guide a specific decision as to when a biopsy may be averted. Roobol et al have proposed an individualized screening algorithm based on prebiopsy information by which applying an additional biopsy cutoff of 12.5% would lead to a 33% reduction in unnecessary biopsies.[27]

We found age, obesity (as measured by BMI), family history, abnormal DRE, and PSAD as the principal factors associated with histologically aggressive cancer (all $P < .001$). By using model-defined parameters at 90% sensitivity to evaluate a subsequent cohort of 236 consecutively enrolled men in the Early Detection Research Network study, we found that 58 of 236 (24.6%) biopsies would have been avoided. Averting 1/4 of prostate biopsies while retaining 90% sensitivity for detecting aggressive cancers as could be guided by this Early Detection Research Network model would have the potential to significantly reduce the burden of excess detection and treatment of indolent prostate cancers.

The association of the factors identified in the current study with prostate cancer severity has been previously established in other settings, and supports the external validity of our findings. Age, family history, and DRE had also been found to be significant determinants for presence or absence of cancer in the Prostate Cancer Prevention Trial calculator.[12] Of note, obesity as measured by BMI was a significant predictor for clinically significant cancer, and this factor has not been included in other tools used to discern indolent from aggressive cancers.[5,9,10,12,25] The relationship of obesity with aggressiveness of treated prostate cancers, however, is well established, and with the increasing prevalence of obesity worldwide, this variable may become ever more meaningful in decision making during routine urological practice.

The biological basis for PSAD as predictive of cancer severity is reflected by larger prostate being associated with higher serum PSA because of PSA produced by benign prostatic hyperplasia in the absence of any cancer.[28-31] PSAD has previously been found to be superior to PSA alone in discerning cancer from benign pathology in patients with PSA between 4 and 10 ng/mL,[29,30] and has also been found to be associated with probability of recurrence-free survival after prostatectomy.[29,30] Indeed, in his initial report defining indolent cancers, Epstein determined that PSAD <0.1 ng/mL/g complemented histological criteria in predicting indolent cancer at prostatectomy. Our observed association of PSAD with detection of histologically aggressive cancer validates this component of Epstein's original findings and extends its use, when combined with family history, age, DRE findings, and BMI, to the identification of patients who are candidates for initial prostate biopsy.

There are several limitations to our study. We used Epstein's original histological criteria to discern indolent from aggressive cancers, and long-term clinical outcomes of these patients to verify indolent behavior are limited.[5,7] We used <5-mm tumor involvement per core in the Prostate Cancer Prevention Trial cohort because actual percentage tumor involvement per core was not recorded, and therefore we could not extrapolate percentage tumor involvement per core. Prior studies have suggested the role of percentage and tumor length in prostate biopsy cores as predictors of more aggressive disease at radical prostatectomy and hence clinically significant disease.[32] Although our predictive model has not been externally validated by others, the model was derived from multiple institutions to avoid single-institution, practice-specific, or regional biases, and was validated in the Prostate Cancer Prevention Trial study representing the general population. Nevertheless, further external validation is warranted to determine whether the model can be applied to other clinical populations. Selection bias may be inherent in our cohort, as enrollment focused on patients who had been referred to a urology practice; therefore, our findings are more relevant to decision making by urologists in evaluating patients referred from a primary care provider than decision making in the primary care setting. Our study did not include percentage free PSA, which has been found to be associated with prostate cancer aggressiveness,[11] because percentage free PSA is validated for use only when total serum PSA is between 4 and 10 ng/mL, whereas our model targets cancer detection across an unrestricted spectrum of total PSA results. The patient population has limited racial diversity, with 14% of men self-reporting as non-Caucasian comprised of 7% African American and 7% a mix of Hispanic, Asian, middle or southeast Asian, and Cape Verdean, and an association of race with aggressive cancer, independent of the other model factors, was not detected; it is possible that racial effects may be significant in more diverse study cohorts or clinical settings. Overdiagnosis is a problem in prostate cancer, and this could be addressed either by refining who we biopsy or by better selection of patients for active surveillance. The purpose of our study is to better identify patients who may be harboring clinically significant prostate cancer who may benefit from earlier intervention and to improve current active surveillance selection protocols. Finally, accepting a false-negative rate of 10%, thereby avoiding 25% of biopsies, may be viewed as excessively high. Up to 30% of men with insignificant cancer at first biopsy ultimately are discovered to have significant cancer (either at subsequent biopsy or surgery); thus, the real false-negative rate could be much higher for the predictive model. However, the strategy of avoiding biopsy at initial evaluation does not preclude the possibility that patients with false-negative initial screening results could be detected during follow-up screening in subsequent years. In light of these limitations, more extensive evaluation of our model may be warranted to justify further broader acceptance of averting biopsy.

Conclusions

Prior predictive nomograms or risk calculators have not sought to identify men who should undergo prostate biopsy with the goal of improving selective detection of significantly aggressive prostate cancer, while avoiding biopsy that would detect indolent disease. Our

multivariate, predictive model improved the specificity of PSA alone in detecting such histologically aggressive cancers and elucidated practical cutpoints or criteria to guide specific decision as to when a biopsy may be averted while retaining 90% sensitivity for detection of histologically aggressive prostate cancer. Generalizability of these findings was verified in the control arm of the Prostate Cancer Prevention Trial cohort. Our findings suggest that 90% sensitivity for detecting significant cancer can be retained while averting prostate biopsy in men who meet each of the following criteria: normal DRE, no family history of prostate cancer, PSAD <0.1 ng/mL/cc, and BMI <25 kg/m^2. These criteria would avoid biopsy in approximately $^1/_4$ of biopsy-eligible men.

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CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. Potosky AL, Miller BA, Albertsen PC, et al. The role of increasing detection in the rising incidence of prostate cancer. *JAMA.* 1995; 273:548.
2. Cooperberg MR, Park S, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol.* 2004;22:2141-2149.
3. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009;360:1320-1328.
4. Andriole GL, Crawford ED, Grubb RL III, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360:1310-1319; erratum 1797.
5. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of non-palpable (stage T1c) prostate cancer. *JAMA.* 1994;271:368.
6. Klotz L. Active surveillance with selective delayed intervention: using natural history to guide treatment in good risk prostate cancer. *J Urol.* 2004;172:S48-S50; discussion S50-S51.
7. Warlick C, Trock BJ, Landis P, et al. Delayed versus immediate surgical intervention and prostate cancer outcome. *J Natl Cancer Inst.* 2006;98:355.
8. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer.* 2008;112:2664-2670.
9. Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. *J Urol.* 2003;170: 1792.
10. Steyerberg EW, Roobol MJ, Kattan MW, et al. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. *J Urol.* 2007;177:107.
11. Epstein JI, Chan DW, Sokoll LJ, et al. Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. *J Urol.* 1998;160(pt 2):2407-2411.
12. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst.* 2006;98:529-534.
13. Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. *J Clin Oncol.* 2007;25:3582-3588.
14. Kawachi MH, Bahnson RR, Barry M, et al. NCCN. Prostate cancer early detection. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2007;5:714-736.
15. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer screening trends. *J Natl Cancer Inst.* 2002;94:981-990.
16. Zietman AL, Thakral H, Wilson L, Schellhammer P. Conservative management of prostate cancer in the prostate specific antigen era: the incidence and time course of subsequent therapy. *J Urol.* 2001; 166:1702-1706.
17. Carter HB, Walsh PC, Landis P, et al. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol.* 2002;167:1231-1234.
18. Carter CA, Donahue T, Sun L, et al. Temporary deferred therapy (watchful waiting) for men younger than 70 years with low-risk localized prostate cancer in the prostate specific antigen era. *J Clin Oncol.* 2003;21:4001-4008.
19. Patel MI, DeConcini DT, Lopez-Corona E, et al. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. *J Urol.* 2004;171:1520-1524.
20. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate cancer survivors. *N Engl J Med.* 2008;358:1250-1261.
21. Carroll P, Albertsen PC, Greene K, et al. Prostate-Specific Antigen Best Practice Statement: 2009 Update. Linthicum, MD: American Urological Association Office of Education and Research; 2009.
22. Kapoor DA, Klimberg IW, Malek JH, et al. Single dose ciprofloxacin versus placebo for prophylaxis during transrectal ultrasound prostate biopsy. *Urology.* 1998;52:552-558.
23. Feliciano J, Teper E, Ferrandino M, et al. The incidence of flouroquinolone resistant infections after prostate biopsy—are flouroquinolones still effective prophylaxis? *J Urol.* 2008;179:952-955.
24. Ekwueme DU, Stroud LA, Chen Y. Cost analysis for screening, diagnosing and staging prostate cancer based on a systematic review of published studies. *Prev Chron Dis.* 2007;4:A100.
25. Dong F, Kattan MW, Steyerberg EW, et al. Validation of pretreatment nomograms for predicting indolent prostate cancer: efficacy in contemporary urological practice. *J Urol.* 2008;180:150-154.
26. Nam RK, Toi A, Trachtenberg J, et al. Making sense of prostate specific antigen: improving its predictive value in patients undergoing prostate biopsy. *J Urol.* 2006;175:489-494.
27. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Euro Urol.* 2010;57:79-85.
28. Benson MC, Olsson CA. Prostate specific antigen and prostate specific antigen density: roles in patient evaluation and treatment. *Cancer.* 1994;74:1667-1673.
29. Bretton PR, Evans WP, Borden JD, et al. The use of prostate specific antigen density to improve the sensitivity of prostate specific antigen in detecting prostate carcinoma. *Cancer.* 1994;74:2991-2995.
30. Seaman EK, Wang IS, Cooner W, et al. Predictive value of prostate specific antigen density for the presence of micrometastatic carcinoma of the prostate. *Urology.* 1994;43:645-648.
31. Brassell SA, Tzu-Cheg K, Sun L, et al. Prostate specific antigen versus prostate specific antigen density as predictor of tumor volume, margin status, pathologic stage, and biochemical recurrence of prostate cancer. *Urology.* 2005;66:1229-1233.
32. Naya Y, Slaton JW, Troncoso P, Okihara K, Babaian RJ. Tumor length and location of cancer on biopsy predict for side specific extraprostatic cancer extension. *J Urol.* 2004;171:1093-1097.