

Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial

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Background: Prostate-specific antigen (PSA) testing is the primary method used to diagnose prostate cancer in the United States. Methods to integrate other risk factors associated with prostate cancer into individualized risk prediction are needed. We used prostate biopsy data from men who participated in the Prostate Cancer Prevention Trial (PCPT) to develop a predictive model of prostate cancer. **Methods:** We included 5519 men from the placebo group of the PCPT who underwent prostate biopsy, had at least one PSA measurement and a digital rectal examination (DRE) performed during the year before the biopsy, and had at least two PSA measurements performed during the 3 years before the prostate biopsy. Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy. Risk equations were created from the estimated logistic regression models. All statistical tests were two-sided. **Results:** A total of 1211 (21.9%) men were diagnosed with prostate cancer by prostate biopsy. Variables that predicted prostate cancer included higher PSA level, positive family history of prostate cancer, and abnormal DRE result, whereas a previous negative prostate biopsy was associated with reduced risk. Neither age at biopsy nor PSA velocity contributed independent prognostic information. Higher PSA level, abnormal DRE result, older age at biopsy,

and African American race were predictive for high-grade disease (Gleason score ≥ 7) whereas a previous negative prostate biopsy reduced this risk. **Conclusions:** This predictive model allows an individualized assessment of prostate cancer risk and risk of high-grade disease for men who undergo a prostate biopsy. [J Natl Cancer Inst 2006;98:529–34]

Since the advent of prostate-specific antigen (PSA) screening in the late 1980s, approximately 50% of U.S. men have had a PSA test performed regularly (1). Early large-scale prostate cancer screening studies used 4.0 ng/mL PSA as a threshold value to prompt a recommendation for prostate biopsy (2,3). Subsequent studies suggested that the risk of prostate cancer, as determined

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at prostate biopsy, among men who have PSA levels between 2.5 ng/mL and 4.0 ng/mL is similar to that among men with PSA levels greater than 4.0 ng/mL (4,5). Nevertheless, PSA level has, in general, been treated as a dichotomous biomarker. That is, a PSA level greater than 4.0 ng/mL has been considered “abnormal” and a prostate biopsy has been recommended, whereas a PSA level at or below 4.0 ng/mL has been considered “normal,” with no action necessary. The completion of the Prostate Cancer Prevention Trial (PCPT), a phase III randomized, double-blind, placebo-controlled trial of finasteride for the prevention of carcinoma of the prostate (6), provided the first opportunity to examine the risk of prostate cancer among men who had a broad range of PSA values, including many below 4.0 ng/mL. By examining the end-of-study biopsy samples from men who had a normal PSA level, we recognized that prostate cancer could be found at all levels of PSA and that, in this group of men with normal PSA levels, 15% had prostate cancer (1).

PSA level is only one of several determinants of prostate cancer risk. Family history of prostate cancer, age, race, and digital rectal examination (DRE) findings also play a role in the assessment of prostate cancer risk (2,3). However, possible interactions between these and other variables that are associated with the risk of prostate cancer are not known. Here we used prostate biopsy data from 5519 participants in the PCPT to examine whether interactions among these variables can be used to predict prostate cancer risk in an individual patient.

SUBJECTS AND METHODS

The PCPT randomly assigned 18882 men who were 55 years old or older and had a normal DRE and a PSA level less than or equal to 3 ng/mL to either finasteride or placebo for 7 years (4). A PSA test and DRE were performed annually. Study participants assigned to placebo were recommended to undergo a prostate biopsy if any DRE result was abnormal or if their PSA value exceeded 4.0 ng/mL. At the end of the 7 years on study, all men who had not been diagnosed with prostate cancer were asked to undergo an end-of-study prostate biopsy. The PCPT was approved by the institutional review boards at all study sites, and all participants provided written informed consent.

This analysis included all participants in the placebo group who underwent a prostate biopsy after any of the six annual visits or at the seventh year visit, when an end-of-study biopsy was recommended. Inclusion criteria for this analysis were a PSA test and DRE within 1 year of the biopsy as well as an additional PSA measurement during the 3 years before the biopsy to compute PSA velocity. For participants with multiple biopsies, the most recent study biopsy was used to assess the effect of a prior negative biopsy on prostate cancer risk; qualitatively similar risk estimates were obtained when the first study biopsy was used instead of the most recent study biopsy.

For purposes of prostate cancer risk modeling, a family history of prostate cancer was coded as 0 (no) or 1 (yes); race as 0 (not African American) or 1 (African American); most recent DRE result at time of biopsy as 0 (negative or normal) or 1 (positive or suspicious for cancer); and previous biopsy history as 0 (no previous biopsy) or 1 (one or more previous biopsies, all negative for prostate cancer). The value for age was the participant's age at prostate biopsy. To improve the goodness-of-fit of the models to the observed data, all models used PSA values that were transformed using the natural logarithm [$\log(\text{PSA})$]. All

previous PSA measurements obtained within 3 years of a participant's prostate biopsy were used to compute his PSA velocity, which was defined as the slope of $\log(\text{PSA})$ per year as obtained by linear regression. There are many ways to define a change in the level of PSA over 3 years of follow-up, and there is no consensus on the optimal definition. Table 1 lists the 19 alternative definitions of PSA velocity that we evaluated in addition to the definition used in the analysis. We chose the first definition because it considers all PSA values obtained within the 3 years before the prostate biopsy and, hence, allows a more precise measurement of PSA velocity. PSA doubling times (i.e., the time required for a PSA level to double in value) were not considered in this analysis because the PSA values for many participants declined over time, which prevented a calculation of the doubling time.

We used multivariable logistic regression to model the risk of prostate cancer by considering all possible combinations of main effects and interactions; the models chosen were those that minimized the Bayesian information criterion (BIC) and maximized the average out-of-sample area under the receiver operating characteristic curve (AUC) (7). The BIC was defined as follows: $(-2) \times \text{maximized log likelihood} + (\text{number of parameters in the model}) \times \log n$, where $n = 5519$, the sample size. The out-of-sample AUC was calculated using fourfold cross-validation. To calculate the average out-of-sample AUC, the sample of 5519 participants was randomly partitioned into four subsets of approximately equal size ($n = 1380, 1380, 1380, \text{ and } 1379$); the percentage of prostate cancer cases in each subsample ranged from 20% to 23%, and the percentage of high-grade cases of prostate cancer in each subsample ranged from 5.0% to 5.7%. The model was fit to each three-quarter subset of the data and tested on the remaining quarter subset of data, yielding four out-of-sample AUCs. The mean of these four AUCs was defined as the average out-of-sample AUC. We used a similar approach to model the risk of high-grade disease, which was defined as Gleason score of 7 or higher, versus no cancer or low-grade disease (i.e., a Gleason score <7). Five models were selected that had the lowest BIC values and the highest AUC values. Because the AUC value was the same for each of these five models, the model among these five with the lowest BIC was selected as the optimal model for analysis. For assessing the statistical significance of predictors in the optimal

Table 1. Definitions of PSA velocity considered in the risk models*

Number	Definition
1†	Slope of $\log(\text{PSA})$ per year obtained by linear regression using all PSA values obtained within the previous 3 years
2–3	Slope of $\log(\text{PSA})$ per year obtained by linear regression using all PSA values obtained within the previous 1 year and 2 years, respectively
4–6	Slope of PSA level per year obtained by linear regression using all PSA values obtained within the previous 1 year, 2 years, and 3 years, respectively
7–16	Indicator for whether the percent increase in PSA level exceeded X percent over the previous year's PSA level for $X = 5\%, 10\%, 20\%, 30\%, 40\%, 50\%, 60\%, 70\%, 80\%$, and 90% , respectively
17	Indicator of whether the change in PSA level from the previous year was $\leq 0\%, 0\%–10\%, 10\%–100\%$, or $>100\%$
18 and 19	Same as definition 17, except that 10% was replaced with 20% and 25% , respectively
20	PSA level for current year minus PSA level for previous year

*PSA = prostate-specific antigen.

†Definition 1 was used in the final analysis.

logistic regression model for prostate cancer risk and high-grade disease, two-sided Wald tests at the .05 level were used.

Estimates of risks were computed using the inverse logistic function, with β coefficients from the logistic model assembled into a vector, and the risk factors assembled into a vector, \mathbf{X} . The inverse logistic function was $\exp(\mathbf{X}'\beta)/(1 + \exp(\mathbf{X}'\beta))$, where $\mathbf{X}'\beta$ indicates the summation of component-wise multiplication of the elements of \mathbf{X} by the elements of β , and $\exp(\mathbf{X}'\beta)$ denotes the natural exponential function ($e = 2.718282$) raised to the power $\mathbf{X}'\beta$. Standard estimates of risks were obtained by applying the delta rule using the estimated asymptotic variance covariance matrix of the β parameters from the logistic regression (8).

RESULTS

Characteristics of the 5519 participants included in this study are displayed in Table 2. Among the men who had one or more previous biopsies, the median time between the biopsy used for the analysis and the previous biopsy was 976 days (range = 14–2466 days).

The median PSA level (for PSA levels measured within 1 year of the analysis biopsy) for the 5519 men included in the analysis was 1.5 ng/mL (range = 0.3–287.0 ng/mL), and 4888 men (88.6%) had a PSA level that was less than or equal to 4.0 ng/mL. Table 3 shows the distributions of prostate cancer cases and high-grade disease cases by PSA level. Of the 5519 men in this analysis, 1211 (21.9%) developed prostate cancer and 257 (4.7%) developed high-grade disease, and the risk of each increased more or less steadily with increasing PSA level.

In a multivariable analysis, the following variables were statistically significantly associated with an increased risk of prostate cancer: increasing log(PSA) (odds ratio [OR] = 2.34, 95% confidence interval [CI] = 2.13 to 2.56, $P < .001$), positive family history of prostate cancer (OR = 1.31, 95% CI = 1.11 to 1.55, $P = .002$), and abnormal DRE result (OR = 2.47, 95% CI = 2.03

Table 3. Numbers (percentages) of prostate cancers and high-grade prostate cancers by PSA level*

PSA level, ng/mL	N	No. of prostate cancers (%)	No. of high-grade prostate cancers† (%)
0–1	1963	217 (11.1)	19 (1.0)
1.1–2	1640	337 (20.5)	43 (2.6)
2.1–3	775	205 (26.5)	44 (5.7)
3.1–4	510	153 (30.0)	48 (9.4)
4.1–6	481	234 (48.6)	70 (14.6)
>6	150	65 (43.3)	33 (22.0)
Total	5519	1211 (21.9)	257 (4.7)

*PSA = prostate-specific antigen.

†Gleason score of 7 or higher.

to 3.01, $P < .001$). Having had one or more previous negative biopsies was statistically significantly associated with a decreased risk of prostate cancer (OR = 0.64, 95% CI = 0.53 to 0.78, $P < .001$).

When evaluated in the absence of other factors, PSA velocity was statistically significantly associated with a nearly sixfold increase in the risk of prostate cancer per unit increase in velocity (OR = 5.65, 95% CI = 4.13 to 7.74, $P < .001$). However, when the statistically significant factors described above were included in the model, the association was no longer statistically significant (OR = 1.18 [95% CI = 0.82 to 1.69], $P = .38$), and inclusion of PSA velocity did not improve the out-of-sample prediction of prostate cancer risk. In other words, PSA velocity did not add independent prognostic information to that provided by PSA level, family history of prostate cancer, DRE result, and result of previous prostate biopsies. In fact, in a prostate cancer risk model containing only PSA and PSA velocity, PSA velocity was not statistically significant (data not shown), meaning that PSA velocity does not add independent prognostic information to PSA value alone, regardless of the other risk factors. As a single predictor with strength measured by the maximized log likelihood value, PSA level was a stronger predictor than PSA velocity. The 19 alternative definitions of velocity listed in Table 1 did not outperform definition 1 in the model described here in that none added independent prognostic information to PSA level.

We evaluated race in combination with these factors and found that, compared with non-African Americans, African Americans had an approximately 40% increased risk of prostate cancer that was marginally statistically significant (OR = 1.42 [95% CI = 1.0 to 2.01]; $P = .051$). The addition of race did not improve the BIC above the optimal model. Age was not significant in combination with factors in the optimal model and the addition of age to the optimal model also did not improve the BIC (data not shown).

We used the inverse logistic function to estimate the risk of prostate cancer based on all factors that contributed independent prognostic information. β coefficients used in the risk equation included -1.80 (95% CI = -1.89 to -1.70) for the intercept, 0.85 (95% CI = 0.76 to 0.94) for log(PSA), 0.27 (95% CI = 0.10 to 0.44) for family history, 0.91 (95% CI = 0.71 to 1.10) for DRE, and -0.45 (95% CI = -0.65 to -0.25) for prior biopsy. Risk curves as a function of PSA level for men who did not have a previous prostate biopsy are shown in Fig. 1.

The average out-of-sample AUC for the prediction given by the risk equation was 70.2% (standard deviation = 0.57%). It is noteworthy that this out-of-sample estimate of the AUC is only slightly higher than the in-sample AUC for PSA level alone

Table 2. Characteristics of study participants included in the analysis (N = 5519)*

Characteristic	N	(%)
Age at biopsy, y		
55–60	38	(0.7)
60–64	1143	(20.7)
65–69	1741	(31.5)
70 or older	2597	(47.1)
Family history of prostate cancer		
No	4599	(83.3)
Yes	920	(16.7)
Race		
White†	5276	(95.6)
African American‡	175	(3.2)
Other	68	(1.2)
No. of previous negative biopsies		
0	4873	(88.3)
≥1	646	(11.7)
≥2	107	(1.9)
No. of previous PSA screens		
1–2	230	(4.2)
3–4	248	(4.5)
5–7	5041	(91.3)

*PSA = prostate-specific antigen.

†Includes both Hispanics and non-Hispanic whites.

‡Includes three Hispanic African-Americans.

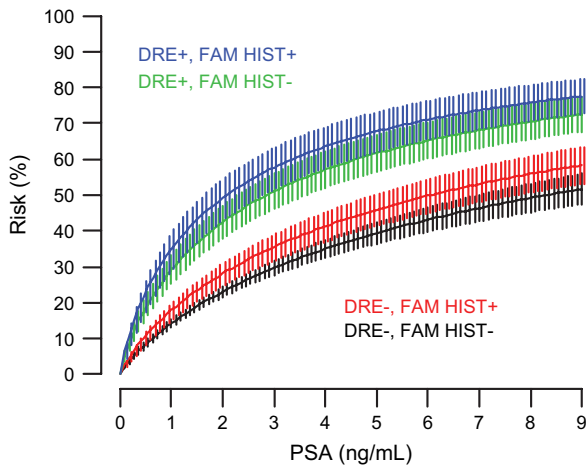


Fig. 1. Risk of prostate cancer as a function of prostate-specific antigen (PSA) level, digital rectal examination result, and family history of prostate cancer for men who did not have a previous prostate biopsy. **Vertical lines** indicate pointwise 95% confidence intervals for the risk at each PSA level. **DRE+** = an abnormal digital rectal examination that is suggestive of prostate cancer; **DRE-** = a normal digital rectal examination; **FAM HIST+** = family history of prostate cancer; **FAM HIST-** = no family history of prostate cancer.

(AUC = 67.8%) reported by Thompson et al. (9) that was based on essentially the same set of participants, indicating that the independent risk factors of family history, DRE result, and previous prostate biopsy did not appreciably improve the sensitivity and specificity of PSA level. This latter estimate, which may be considered an approximation of the out-of-sample AUC for PSA level alone because a training set was not required for model building in our earlier analysis, indicates that the independent risk factors of family history, DRE result, and previous prostate biopsy did not appreciably improve the sensitivity and specificity of PSA level. Figure 1 shows that family history of prostate cancer and DRE result led to substantial differences in predictive value beyond use of the PSA level alone for an individual patient.

Statistically significant predictors of high-grade disease included the logarithm of the PSA level (OR = 3.64, 95% CI = 3.04 to 4.37, $P < .001$), the DRE result (OR = 2.72, 95% CI = 1.96 to 3.77, $P < .001$), and previous prostate biopsy (OR = 0.70, 95% CI = 0.49 to 0.99, $P = .04$), but not family history ($P > .05$). Race was a statistically significant predictor of high-grade disease: African Americans had a higher risk of high-grade disease than non-African Americans (OR = 2.61, 95% CI = 1.55 to 4.41, $P < .001$). Although age at biopsy was statistically significantly associated with an increased risk of high-grade disease, the odds ratio for each 1-year increase in age was only 1.03 (95% CI = 1.01 to 1.06, $P = .01$). When considered alone, an increase in PSA velocity was strongly and statistically significantly associated with an increased risk of high-grade disease (OR = 8.93, 95% CI = 5.71 to 13.97, $P < .001$); however, when considered in combination with PSA level, DRE result, age, and previous prostate biopsy, an increase in PSA velocity was non-statistically significantly associated with a decreased risk of high-grade disease (OR = 0.82, 95% CI = 0.44 to 1.53, $P = .54$). By using only factors that contribute independent prognostic information to the risk of high-grade disease, the inverse logistic function was obtained with β coefficients of -6.25 (95% CI = -7.91 to -4.58) for the intercept, 1.29 (95% CI = 1.11 to 1.47) for the logarithm of PSA, 1.00 (95% CI = 0.67 to 1.33) for DRE, 0.03 (95% CI =

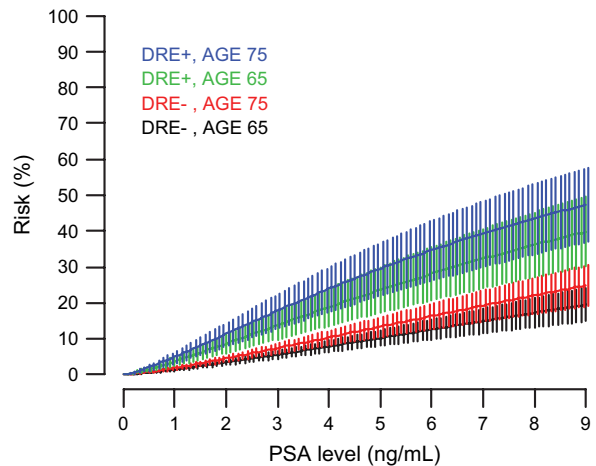


Fig. 2. Risk of high-grade prostate cancer as a function of prostate-specific antigen (PSA) level and digital rectal examination result for white men aged 65 years or 75 years who had no previous prostate biopsy. **Vertical lines** indicate pointwise 95% confidence intervals for the risk at each PSA level. **DRE+** = an abnormal digital rectal examination that is suggestive of prostate cancer; **DRE-** = a normal digital rectal examination.

0.01 to 0.05) for age, 0.96 (95% CI = 0.44 to 1.48) for race, and -0.36 (95% CI = -0.72 to -0.01) for prior biopsy. Estimates of risk of high-grade disease based on DRE result and PSA level for men of age 65 and 75 are shown in Fig. 2. The out-of-sample AUC for the risk of high-grade disease was 69.8% (standard deviation = 1.03%).

Rather than providing prostate cancer risk by level of PSA as shown in Fig. 1, the risk model may be inverted to show PSA level as related to level of risk of cancer as in Fig. 3. For example, instead of referring patients to biopsy by level of PSA, a physician may opt to refer to biopsy by a threshold of risk, such as a 25% risk of prostate cancer. Fig. 3 then allows individualized cutpoints of PSA obtaining the specified risk. At any specified level of risk, a man with other risk factors for prostate cancer will be referred to biopsy at a lower PSA level than a man without the

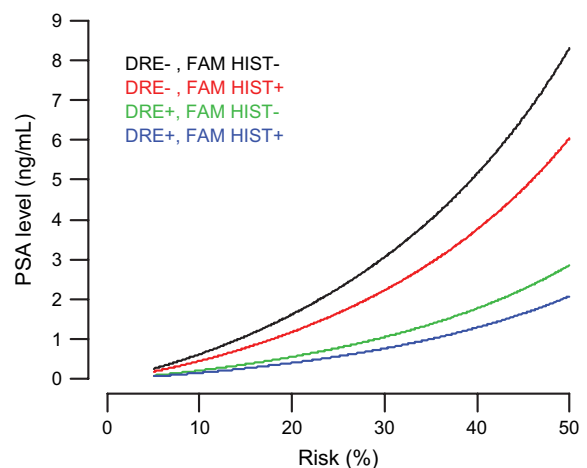


Fig. 3. Prostate-specific antigen (PSA) levels achieving specified risks of prostate cancer ranging from 5% to 50% by digital rectal examination result and family history for men who had no previous prostate biopsy. **DRE+** = an abnormal digital rectal examination that is suggestive of prostate cancer; **DRE-** = a normal digital rectal examination; **FAM HIST+** = family history of prostate cancer; **FAM HIST-** = no family history of prostate cancer.

other risk factors. Fig. 3 shows how the other risk factors lower the PSA threshold.

DISCUSSION

In addition to the central finding of the PCPT—a 25% reduction in prostate cancer risk in men who received finasteride—a major observation was the 24.4% prevalence of prostate cancer diagnosed in the placebo group of this generally low-risk study population (1,6). With the subsequent recognition that PSA is associated with a range of risk and that there is no lower limit at which there was no risk of prostate cancer, men and their physicians have struggled with how to interpret their PSA value. In a previous analysis (9) of the operating characteristics of PSA levels across the range of PSA values, we concluded that a PSA threshold of less than 1.0 ng/mL was required to achieve sensitivity greater than 80%, but at the price of a false-positive rate near 60%.

Several other factors have been found to be associated with prostate cancer risk independent of PSA level. The factors that appear to have the strongest association with risk include race/ethnicity (higher risk among African Americans, lower among Hispanics), family history of prostate cancer (higher risk with a positive family history), age (risk increases with age), DRE result (higher risk with an abnormal examination), and a previous prostate biopsy (decreased risk with negative biopsy). Our analysis of 5519 men who underwent a prostate biopsy has demonstrated that it is possible to incorporate these factors into an individualized risk assessment for prostate cancer.

A central limitation of this analysis is that, despite the relative large number of men studied, the characteristics of these men do not reflect those of the general U.S. population. For example, the average age of PCPT participants at study entry was 62 years, and the average age of participants after 7 years on study at the end-of-study biopsy was 70 years. Nevertheless, because this analysis included end-of-study biopsies as well as those performed because of an elevated PSA level or an abnormal DRE result, the age range, as described in Table 2, was reasonably reflective of a large population of men undergoing PSA screening in the U.S. An additional limitation was that all study participants had a PSA level of 3.0 ng/mL or less at study entry; thus, the precision of the risk estimates for men whose first PSA measures are above this value is uncertain. Nonetheless, in the group of men in this analysis, 631 (11.4%) had PSA levels above 4.0 ng/mL at the time of biopsy. A final limitation of this analysis was that 95.6% of the study population was white.

In collaboration with the Early Detection Research Network of the National Cancer Institute, we used the risk equations generated here to develop a prostate cancer risk calculator (available at <http://www.compass.fhrc.org/edrnnci/bin/calculator/main.asp>) that is applicable to men who are at least 50 years old, have no previous diagnosis of prostate cancer, and have DRE and PSA results that are less than 1 year old. The calculator allows a physician or patient to enter the values for variables that were determined to have a significant impact on the risk of cancer to obtain estimates of the risks of prostate cancer and high-grade prostate cancer on prostate biopsy. The uncertainty in estimates of risk, as indicated by the pointwise 95% confidence intervals in Figs. 1 and 2, are reported in addition to the risk estimate in the online calculator. The disclaimer page for the calculator emphasizes the population of men from which the risk estimates were derived and the uncertainty of estimates for other populations.

For example, the risk model may not be applicable for a man 35 years of age because the minimum age in the PCPT population was 55 or for a man with a PSA level exceeding 10 ng/mL because fewer than 1% of participants had a PSA level exceeding this value.

The two-decade public experience with PSA levels presents a challenge for the application of this prediction model because this biomarker has been viewed by both physicians and patients as a dichotomous biomarker whose level is either normal or elevated. On the basis of the results of this analysis and of our previous analyses of data from the PCPT (1,9), we suggest that PSA level should be thought of as a continuous biomarker rather than as a dichotomous biomarker, such that the risk of prostate cancer increases as the PSA level increases. Although these data will certainly prompt further investigations regarding patient decision-making vis-à-vis the PSA level at which a prostate biopsy is elected, there are two reasonable initial approaches for the use of these data in the clinical setting. The first approach is based on the historical use of the PSA level. Before these analyses, a PSA level greater than 4.0 ng/mL usually led to a recommendation for a prostate biopsy because it was generally found that above this level, the risk of a positive biopsy was approximately 25% (positive predictive value [PPV] = 25%). If it is presumed that a PPV of 25% would be a reasonable threshold for a prostate biopsy recommendation, an individual patient's characteristics could be entered into the risk calculator and if the risk exceeded 25%, a biopsy could be recommended. For example, a 65-year-old man who had a normal DRE and no family history of prostate cancer would have a 25% risk of having a positive biopsy if his PSA level was 2.27 ng/mL; a 65-year-old man who had a normal DRE and positive family history of prostate cancer would have 25% risk of having a positive biopsy if his PSA level was only 1.66 ng/mL; and a 65-year-old man who had an abnormal DRE and a positive family history of prostate cancer would have a 25% risk of having a positive biopsy if his PSA level was even lower, 0.57 ng/mL.

A second approach to the use of these data would be to allow an individual man to determine his own prostate cancer risk threshold that would prompt a prostate biopsy recommendation. Thus, a 60-year-old man who had a normal DRE but whose father died of prostate cancer may opt for a prostate biopsy at a PSA level of 1.9 ng/mL given that his estimated risk of prostate cancer would be 27.2%. If that biopsy was negative and his PSA level had increased by 0.1 ng/mL to 2.0 ng/mL the following year, that previous negative biopsy would then reduce his risk of prostate cancer to 19.9%, a level at which a prostate biopsy might be deferred.

We anticipate that other groups will validate this model and in so doing may consider adding other variables to the risk prediction. However, considering the fact that Pepe et al. (10) have demonstrated that the AUC does not change substantially unless risk variables with odds ratios of 10 or more are included, it is unlikely that additional risk factors (such as body mass index or ethnicity) will substantially affect the risk assessment.

Although this prostate cancer risk calculator, which is based on results of a sample of men who had a prostate biopsy across the range of PSA values, represents a major step forward in prostate cancer screening, it is important to acknowledge the distinction between the accuracy and the efficacy of a screening test; whereas risk models can improve the former, their effect on the latter remains an open question. Therefore, a better tool would be one that predicts the risk of a prostate tumor that would cause

morbidity or mortality during the person's lifetime. Although it is possible to identify the most potentially aggressive prostate tumors (in general, those with Gleason scores of 8–10), it is not yet possible to distinguish clinically significant from clinically insignificant cancers with a high degree of certainty. This is because assessments of the relative clinical significance of screen-detected tumors are not based on studies that included lifetime follow-up to determine whether morbidity and mortality developed.

This risk calculator model uses variables that go beyond only PSA level to help patients and physicians decide whether a prostate biopsy should be performed. We anticipate that the area of cancer risk modeling—including the incorporation of new risk variables and the understanding of patient decision-making—will have a measurable clinical impact over the next few years.

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NOTES

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